



SJMLS-4(1)-010

Oropharyngeal Candidiasis among HIV Infected Individuals in Africa: A Systematic Review
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Oropharyngeal candidiasis in HIV patients is a common occurrence all over the world and Africa is not an exception. It can affect any part of the oral cavity in respect of the age or gender of the affected patient and cause disturbing consequences. The aim of the study was to determine the burden of *Candida* species among HIV patients in some African countries. Some different articles from different countries of the continent of Africa were drawn as published by various authors across region, using different search engines like Google, Bing, Duck Duck Go and Ask.com. Spectrum of the disease as it affects many patients infected with HIV in different African countries like Nigeria, South Africa, and Ghana among others, were observed. The disease was shown to have affect different ages across the genders, among all the affected individuals infected with HIV in the countries studied. *Candida* species plays a major role as group of most frequent mycotic agents that manifest in many cases of HIV infections worldwide and this poses threat to public health the world over.

Keywords: *Candidiasis, Oropharyngeal, HIV, Africa*

Introduction

Oropharyngeal candidiasis, is a common opportunistic mycotic infection occurring among human being, more especially among immune deficient individuals, like in the case of HIV infected patients across the globe, most importantly in the resource poor-settings. Human Immunodeficiency Virus (HIV) and

AIDS remain a global emergency and continue to spread over decades as an epidemic despite global efforts to tackle the problems associated with it (Das and Horton, 2012). The spread still continues exponentially in countries, globally, irrespective of their income rates, but with a greater impact on the more vulnerable developing regions of the world and has emerged as a global crisis since its discovery in 1981 (Shetti *et al.*, 2011).

It was found all over the world that, an estimated 35.3 million people happen to be HIV seropositive, 2.3 million people become newly infected, and 1.6 million occurred as recorded deaths in the year 2012 (UNAID, 2013). Owing to a weakened immune system, the infected person is placed at an increased risk of a wide variety of opportunistic infections including that due to mycotic agents (Shahapur and Rbidri, 2014; Damtie *et al.*, 2013).

Diseases due to mycotic agents serving as opportunistic pathogens in HIV patients are a major cause of morbidity and mortality in such group of ill individuals (Durdan and Elewski, 1997) and compromise the quality of life of such affected subjects. Oral candidiasis has since been reported among the most common fungal opportunistic infections by some previous researches (Wadhwa *et al.*, 2007; Chakravarty *et al.*, 2006). Among the mycotic opportunistic pathogens are *Candida* spp whose spectrum of infections range from asymptomatic colonization to oropharyngeal candidiasis (OPC), esophagitis, onychomycosis, vulvovaginitis, cutaneous candidiasis, and

systemic candidiasis or invasive candidiasis like candidemia (Anwar *et al.*, 2012). It has been established that majority of HIV infected individuals are colonized by *Candida species* and up to 90–95% develop clinical lesions as the viral disease progresses (Dupont *et al.*, 1992). Oral candida carriage and oral candidiasis has been shown to have positive correlation with low

CD4 counts and high plasma HIV RNA levels among HIV infected patients (Liu *et al.*, 2006; Nicolatou-Galitis *et al.*, 2004; Gottfredsson *et al.*, 1999). Figure 1 shows the different presentations of Esophagitis due to candida spp (esophageal candidiasis) active infection (A) and ulcerated mucosal surface (B).

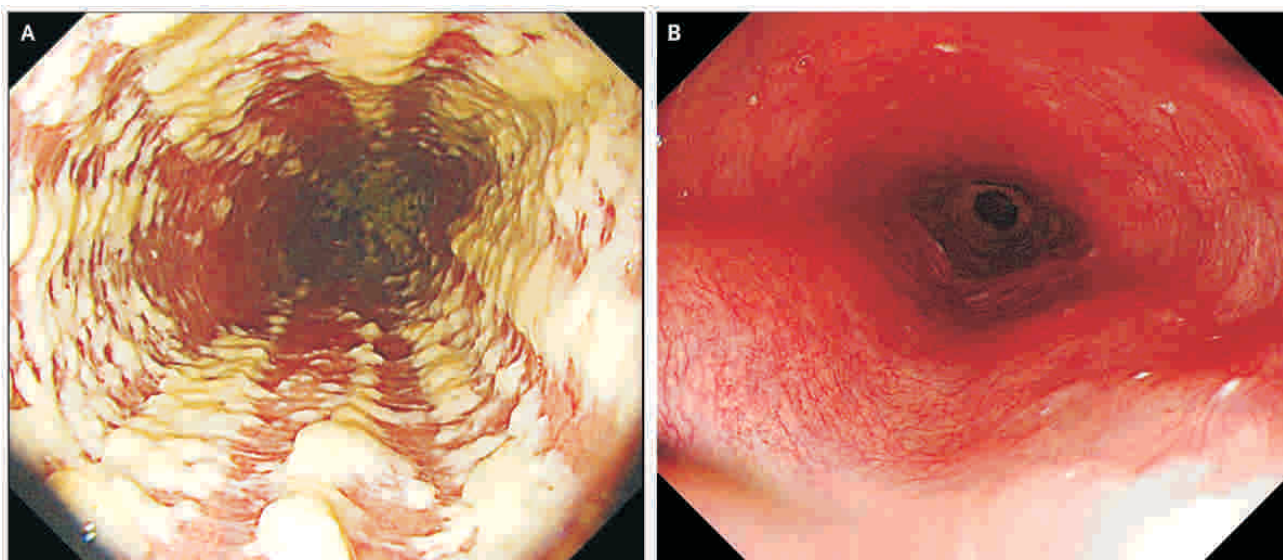


Figure 1: Different presentations of Esophagitis due to candida spp (esophageal candidiasis) active infection (A) and ulcerated mucosal surface (B)

Although traditionally, *Candida albicans* is believed to be the most frequently isolated candida species as a colonizer and as a pathogen of the oral mucosa, other *Candida* species, such as *C. guilliermondii*, *C. parapsilosis*, *C. kefyr*, *C. tropicalis*, *C. krusei*, *C. glabrata*, *C. dubliniensis*, and *C. pelliculosa*, have become a significant cause of infection in patients with HIV infection (Mane *et al.*, 2010; Costa *et al.*, 2006; Gughani *et al.*, 2003).

The non-albican spp owed their clinical importance due to the fact that they are in most cases less susceptible to the more commonly used azole antifungal drugs, these attributes pose significant threat to effective treatment of the affected patients (Mane *et al.*, 2010). These poses a serious challenge to modern mycology laboratory in several aspects, relating to these organisms, as it affects detection, identification, epidemiological analysis and therapy particularly in an attempt to better understand these pathogens and provide an effective cure (Coleman *et al.*, 1998).

It has been documented that, Oropharyngeal candidiasis (OPC) is one of the common opportunistic fungal infections among HIV-infected individuals. It has been estimated that more than 90% of HIV patients come up with it, at some time during progression of their disease. Although the introduction of highly active antiretroviral therapy (HAART) has significantly reduced the incidence of the disease, it remains among the most frequent opportunistic infection in HIV-infected patients. Clinically, OPC in HIV patients are classified as exhibiting pseudomembranous and erythematous variants, or angular cheilitis (Abi *et al.*, 1997). The pseudomembranous form of HIV-associated oropharyngeal candidiasis is characterized as having multifocal smooth white papular lesions known to be easily rubbed away, leaving a mark of red surface, in which surface pseudohyphae can be readily detected. The erythematous form of OPC appears to be diffuse with multiple foci of macular erythema that affects the buccal mucosa, oropharynx, palate, and dorsal tongue, but usually hyphae are

frequently absent. Oropharyngeal candidiasis is in most cases complicated by esophageal candidiasis, which may limit food intake and that leads to weight loss, putting the general health of

HIV-infected individuals at greater risk (Farah *et al.*, 2002). Figure 2 shows the Pseudomembranous form of HIV-associated Oropharyngeal candidiasis.

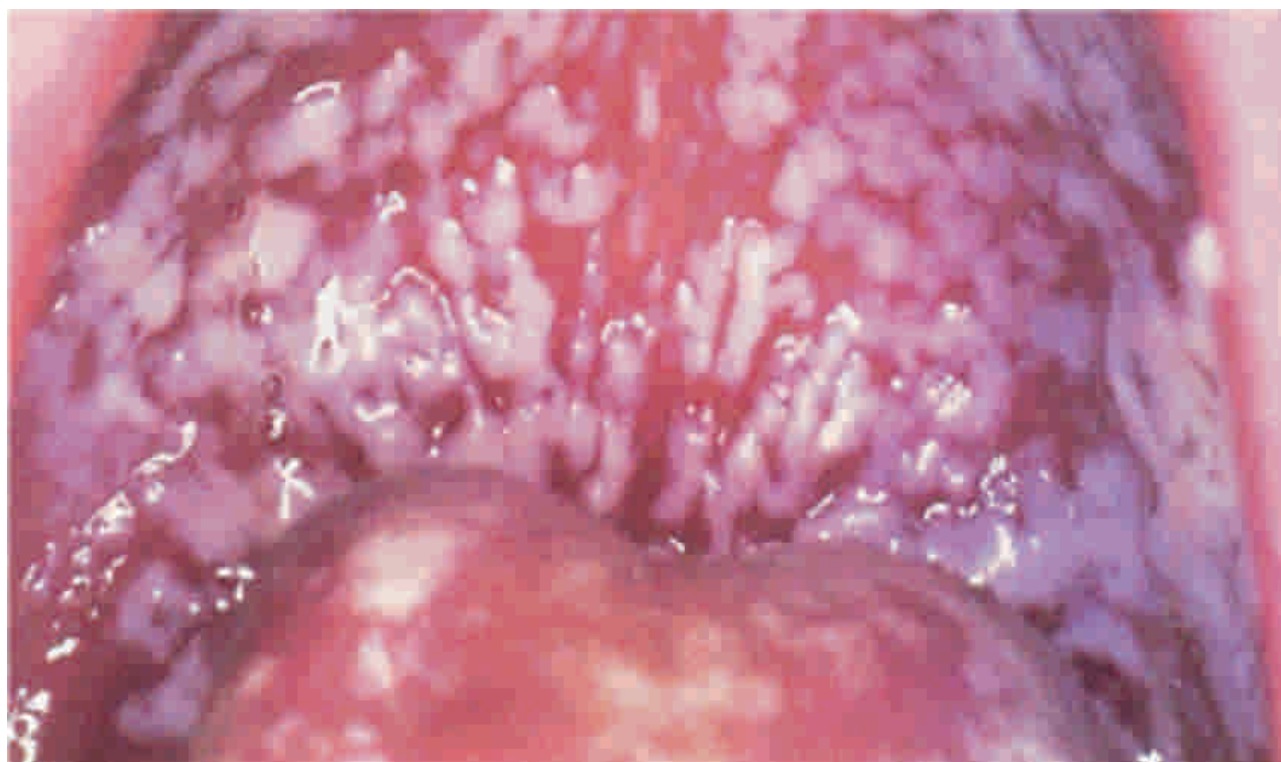


Figure 2: Pseudomembranous form of HIV-associated Oropharyngeal candidiasis

As highly active antiretroviral therapy (HAART) came into being in 1996, including protease inhibitors, such discovery dramatically reduced the prevalence of Oropharyngeal candidiasis and esophageal candidiasis EC in HIV-infected patients (Detels *et al.*, 2001).

After monitoring treatment for over 12 months after starting antiretroviral therapy, including a protease inhibitor, significant reduction was observed in the prevalence of OPC (from 30–56% to 1–9%), the number of relapses of OPC, the rate of asymptomatic oral carriage of *C. albicans*, and oral candida burdens were reduced as well (Arribas *et al.*, 2000).

The risk of systemic fungal infections has increased markedly over decades. This has been as a consequence of wider use of broad-spectrum antibiotics, hyper alimentation products, central venous catheters, and immunosuppressive agents, greater survival of low birth weight infants, organ transplantation, and the acquired

immunodeficiency syndrome (AIDS) epidemic (Krcmery and Barnes, 2002).

According to some studies, Candidiasis is among the most common fungal infection amongst immunocompromised patients, accounting for up to 80% of fungal infections in these individuals and systemic candidiasis has also been documented to occur in up to 10% of infants with low birth weight (Benjamin *et al.*, 2013).

As against many other opportunistic fungi, *Candida* spp in human, are part of endogenous microbial flora, as it is on record that, it has been isolated from the oropharynx of 20%-50% of healthy individuals and from the gastrointestinal tract of up to about 60% of human (Bodey *et al.*, 2002).

The nature of the lesion associated with candida infection in HIV patients largely depends on their clinical status and it normally manifest in the form of oral lesions in this category of

patients, risk behavior and other factors like access to health care, race, education, and social or economic class are other attributes associated with this disease in HIV patients (Frezza *et al.*, 2005; Ceballos-Salobrena *et al.*, 2000; Schoofs *et al.*, 1998), innate, cellular and humoral factors of the immune system play a major role in host defenses against *Candida* infection which appear to be complex in nature. Local infection can be facilitated by the disruption of the mucocutaneous barrier, therefore, intravascular catheters and chemotherapy-induced mucositis can predispose these HIV patients to candida infection. HIV and AIDS patients that were proved to be having low CD4 lymphocyte counts are shown to especially be susceptible to *Candida* infections because CD4 lymphocytes have a major role in suppression of candidiasis (Ashman and Papadimitriou, 1995).

It has been documented (Li *et al.*, 2012), that, Oropharyngeal candidiasis (OPC) is highly prevalent and recurrent opportunistic infection in acquired immune deficiency syndrome (AIDS) patients sometimes serves as a pointer to the presence of human immunodeficiency virus (HIV) infection and its progression. A previous study (Flint *et al.*, 2006), reported that,

oropharyngeal candidiasis meets the criteria to serve as a useful marker for both the restoration of immune functions and HIV disease progression in the event of highly active antiretroviral therapy (HAART) failure, as it appears non- gender- or race-specific. It has also been shown to occurs early in immune dysfunction in the erythematous form and its prevalence correlates with the HIV viral load. Even though the occurrence of OPC has declined due to the advent of anti-retroviral therapy (ART), its presence still poses significant problem for patients in resource-limited settings and/or among individuals who develop mycological resistance or have a poor immunologic response (Thompson *et al.*, 2010). The presence of OPC in HIV/non -HIV patients denotes candidiasis of the mouth and throat. When the disease affects the esophagus, it is called esophageal candidiasis or candida esophagitis (Centers for Disease Control and Prevention, 2017). OPC inevitably occurs in 80–90% of HIV patients in the primary, asymptomatic, or overt phases of the disease (Vazquez, 2000). It normally manifests as a superficial mucosal infection appearing as pseudomembranous, erythematous, or angular cheilitis in HIV-infected patients.



Candida Angular cheilitis

Candida infection in human has a diverse spectrum, which starts from asymptomatic colonization to Oropharyngeal Candidiasis (OPC), cutaneous Candidiasis, esophagitis, vulvovaginitis, onychomycosis and systemic candidiasis or invasive candidiasis including candidemia (Calderone, 2000; U.S. Public Health Service, 2002; Armstrong, 1989). Oropharyngeal candidiasis, mostly appears as one of the first signs of HIV infection, and as one of the most frequent fungal opportunistic infection in HIV-infected patients (Barr, 1992). Prior to the availability of active antiretroviral therapy, oropharyngeal Candidiasis was in the fore front among patients with HIV/AIDS. However, with the discovery of effective anti-retroviral drugs, frequency of oral Candidiasis is shown to have been decreased (Cameron, *et al.*, 1998; Hood, *et al.*, 1998; Revankar, *et al.*, 1998). Immunity-wise, a low absolute CD4⁺ T-lymphocyte count is a pointer to greatest risk factor for Oropharyngeal candidiasis to ensue and current guidelines suggest increased risk, once CD4⁺ T-lymphocyte counts fall below the minimum level required. It has been observed that OPC is more common among HIV infected individuals than those with other forms of immunosuppression, like those with bone marrow transplant or patients receiving chemotherapy. This is suggestive of the role that HIV itself might play in host susceptibility (Calderone, *et al.*, 2001).

Inefficiency in cellular immunity which characterizes HIV infected patients predisposes them to Candida infections. Also, the role of lymphocytes and polymorphonuclear leukocytes in protection against colonization leading to infection with Candida is of paramount importance, as shown by the relatively frequent occurrence of disseminated candidiasis in neutropenic patients that has no deficiency in cellular immunity (Armstrong, 1989).

According to White and Zaman, (1992), the clinical status of AIDS in India appears to be different from what is attainable in developed world, because the HIV patients in India lives in an environment with high rate of infectious diseases (White and Zaman, 1992). The predominant causes of morbidity and mortality

in people living with HIV are the opportunistic infections (OIs). This is usually due to the decreased immunity in such group of patients due to destruction of CD4⁺ cells. As such, the patients are rendered vulnerable to various opportunistic infections, most especially those caused by fungi (Gradon *et al.*, 1992; Jain *et al.*, 1992).

The forms of mycotic infection (oropharyngeal candidiasis and esophageal candidiasis), can occur at any time during the course of HIV infection, including primary HIV infection, the chronic asymptomatic phase and overt AIDS (Abgrall *et al.*, 2001; Chiou *et al.*, 2000). In HIV patients, during the chronic asymptomatic phase, both erythematous and pseudomembranous candidiasis are predictive of progressive immunodeficiency and onset of AIDS, independent of the CD4-cell count. The burdens of *C. albicans orally*, are augmented in HIV-infected individuals even before the onset of the first episode of oropharyngeal candidiasis (Vargas and Joly, 2002), it has been observed also that, the intensity of carriage becomes significantly higher during the progression from asymptomatic *Candida* carrier to full blown episode of OPC. This signifies that, normal defenses against *Candida* are disturbed in the early stages of progression of HIV infection prior to any marked depletion of CD4-cells. However, there are evidence of increased prevalence of the pseudomembranous form of OPC and esophageal candidiasis dramatically in advanced form of HIV infection associated with low CD4-cell counts (Vargas and Joly, 2002), while erythematous candidiasis and angular cheilitis are less commonly associated with late form of the disease.

Close association has been established between lower CD4-cell counts and OPC in HIV-infected women and children (Greenspan *et al.*, 2000). It has also been established that, enhanced risk of OPC and esophageal candidiasis are associated with higher HIV RNA burdens but inversely correlated with CD4-cell counts, especially in the absence of treatment with HAART.

To further understand the relation of candida infection in the oral cavity in human, identical

studies are needed in animal model like study on **Oroesophageal Candidiasis in CD4C/HIV Transgenic Mice which could help to study the candida pathogenesis and serve as a new tool to study pathogenesis.**

According to, **de Repentigny et al. (2002)**, controlled studies of the pathogenesis concerning mucosal candidiasis as it affects HIV infection have been hampered by the inability to get suitable animal model. It was observed that, having CD4C/HIV Tg mice expressing HIV-1 in immune cells and developing an AIDS-like disease has provided a rare and unique opportunity to devise a novel model of mucosal candidiasis that closely mimics the clinical and pathological features of candidal infection in human HIV infection (**de Repentigny et al., 2002**).

There were observations that some important features of mucosal candidiasis observed in Tg mice which were found to be identical to those in patients with HIV infection, this includes a sustained enhancement of oral burdens of *C. albicans*, becoming more manifest in the later stage of HIV disease (**Fong et al., 1997**), penetration of stratified squamous epithelium of the oral cavity and esophagus, limited to the superficial epithelial layer by *Candida species* hyphae a low occurrence of systemic dissemination of *C. albicans* and an infiltration of the mucosa by the mononuclear inflammatory cells (**Eversole et al., 1997**).

The burden in some African Countries

Iriagbonse et al. (2017) in the University of Benin Teaching Hospital (UBTH), Nigeria, worked on oral swabs from 72 participants. They were able to get an isolation rate for *Candida* species of 20.6%. Of these, 55 were colonized, but asymptomatic (76.4%), while 17 had oropharyngeal candidiasis OPC (23.6%). *Candida* species were isolated from all the patients with clinical lesions. Seventy-five *Candida* isolates were recovered. The most frequently isolated species was *Candida albicans*, numbering 61 (81.3%). Among the non-*albicans candida* spp (NAC), there were some close ties, with *C. parapsilosis* as the most common according to the study, 5 (6.7%);

followed closely by *C. glabrata*, 4(5.3%); *C. tropicalis*, 2(2.7%); *C. krusei*, 2(2.7%) and *C. famata*, 1(1.3%). Three participants had mixed growth of *Candida* (4.2%); each had *C. albicans* in addition to a NAC species.

Nweze et al. (2011) in Ebonyi State University Teaching Hospital, Abakiliki, South Eastern Nigeria studied a total of 200 oropharyngeal swabs obtained from HIV-infected patients (108 males and 92 females). Of the 200 patients investigated, 120 of them (90 treated with HAART) were colonized with different kinds of yeast. Detectable growths were produced by all isolates after incubation for 24-48 hours. *C. albicans* had the highest frequency among all the species with a total number of 54 (45%). For the non-*albicans* species and their frequencies, *C. tropicalis* 22 (18.3%), *C. parapsilosis* 18 (15%), *C. guilliermondii* 11 (9.2%), *C. dubliniensis* 9 (7.5%), *C. lusitaniae* 2 (1.7%), *C. krusei* 2 (1.7%), and *C. kefyr* 2 (1.7%). *C. albicans* was isolated in 50 (55.6%) patients treated with HAART and in 23 (76.7%) patients who were not on HAART. In the age-matched control subjects, *C. albicans* was the major species recovered and comprised 13 and 12 isolates from male and female subjects, respectively. *C. tropicalis* and *C. parapsilosis* were also recovered from the control participants. Similarly, for the non-*albicans Candida*, 40 (44.4%) were isolated from patients treated with HAART, whereas 7 (23.3%) isolates were from patients who were not on HAART.

An investigative study by **Foluso et al. (2013)**, on the factors associated with oral colonization of *Candida* spp. in a cohort of HIV-positive women in South Africa, discovered clearly that, out of 197 women investigated, 117 (59.4 %) were found colonized by yeasts, and 18 (9.14 %) discovered with active *Candida* infection. Among the patients, colonization rate was found to be significantly higher (77.4 %) in those patients with concurrent or recent infection with tuberculosis (TB) apart from the HIV compared with 56% colonization in those without TB.

A 10-year study on systematic review in sub-Saharan Africa revealed that, majority of the articles they worked on, reported on oral

candidiasis (OC), twenty-eight point six per cent (28.6%) reported on both OC and *Candida* colonization (CC), fourteen point three per cent (14.3%) had their reports on oral *Candida* species colonization only (Mushi, *et al.*, 2017). In those that reported on oral *Candida* species colonization among HIV-infected individuals, the prevalence ranged from 0.25% in Nigeria (Esebelahie *et al.*, 2013), to 82.3% in Ethiopia (Mulu *et al.*, 2013). With the exception of one article from Tanzania that did not report on OC prevalence (Hamza *et al.*, 2008), prevalence of oral *Candida* infection was reported to range from 7.6% in Nigeria to 75.3% in Ghana among HIV-infected individuals. The pooled prevalence of OC among HIV-infected Africans was 50.6%.

In a study on HIV positive patients who were attending HIV clinic in Charlotte Maxeke Johannesburg, South Africa, Academic Hospital, the carriage rate of *C. albicans* was 73.16%, 44.95% and 42.86% in patients with HIV, with cancer, and in normal healthy individuals, respectively (Owotade *et al.*, 2016), but Patients with HIV and cancer carried a variety of *Candida* species other than *C. albicans* in their oral cavities.

In **Southwest Uganda**, disease pattern and identity of yeast species recovered from the oral cavity of 605 HIV-infected individuals with oral lesions was investigated (Agwu *et al.*, 2012). Pseudomembranous candidiasis was the most common lesion observed (51.4 %) followed by EC (13.9 %), Kaposi's sarcoma (4.6%), angular cheilitis (3.1%), recurrent aphthous ulceration (2.5%) and other unspecified lesions (24.5%), respectively. Out of the 605 individual patient samples taken, 316 (52.2%) yielded yeast growth following culture on SDA at 37 °C for 3–4 days.

Species distribution as observed (Agwu *et al.*, 2012), growth on CHROMagar *Candida* medium revealed that 138/316 (43.7%) isolates represented single yeast species, while 178/316 (56.3%) of samples yielded two or more yeast species. *Candida albicans* accounted for 120/138 (87%) of the monoculture yeast samples. The remaining samples were mainly

comprised of *C. glabrata* (5/138 (3.6%)), *C. tropicalis* (5/138 (3.6%)) and *C. norvegensis* (4/138 (2.9%)) isolates. Small numbers of samples yielded *Candida parapsilosis* and *Candida sake*. *Candida albicans* was also found in 154/178 (86.5%) of the samples comprised of more than one species.

In Northern Tanzania, Kajeguka, *et al.* (2016), in a study that involved 314 (male=111; females=203) HIV positive patients, it was found generally that, of the 314 HIV positive patients, 42.0% (132/314) were positive for oral candida infection while 58.0% (182/314) were negative. Fifty-two (46.8%) of the males and 80 (39.4%) of the females had candida infection as well.

Conclusion

Candida species plays a major role as group of most frequent mycotic agents that manifest in many cases of HIV infections worldwide and this poses threat to public health the world over. There is need to optimize the care offered to patients with HIV patients with *Candida* infection in Africa.

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Citation: Sule, H. and Kumurya, A.S. Oropharyngeal Candidiasis among HIV Infected Individuals in Africa: A Systematic Review. *Sokoto Journal of Medical Laboratory Science*; 4(1): 68 - 77.

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