Association of oral candidal species with human immunodeficiency virus patients of West Godavari district, Andhra Pradesh – An *in vitro* study

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Abstract

Introduction: Human immunodeficiency virus (HIV) infection is a major worldwide health problem characterized by progressive immunosuppression. The morbidity of HIV patients is due to its association with opportunistic infections among which oral candidiasis is common. Regardless of HIV status, candidiasis can prevail when their immune system is depressed. Oral candidiasis can thus serve as a useful marker for both restoration of immune functions and HIV disease progression. Routine identification of Candida species is laborious and time-consuming. HICHROM agar stains different species into different colors facilitating rapid reliable identification of candida species as they differ in their virulence and sensitivity to antifungal drugs.

Materials and Methods: This cross-sectional study includes a total of 200 HIV seropositive patients from Anti-Retroviral Therapy Centre, West Godavari District. Unstimulated saliva samples were collected in a screw-capped universal container. Five microliters of each sample using a sterile inoculating loop is streaked on the chromogenic agar culture media. The colonies formed are counted using a magnifying glass and LAPIZ colony counter. Candidal colony-forming units per milliliter were analyzed, compared and correlated among different study groups. Different candida species were also identified in the study.

Results: Nonalbicans *Candida* was the most common species isolated in our study accounting for 53% and *Candida albicans* accounting for 47%. Considering initial and final CD4 counts, there is improvement in patients on retroviral therapy.

Conclusion: Identification of the species is important for epidemiological reasons and for treatment purposes to ensure a better prognosis since some species present reduced susceptibility to azoles.

Keywords: *Candida*, CD4 count, highly active antiretroviral therapy, human immunodeficiency virus-positive patients, nonalbican candida

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INTRODUCTION

Human immunodeficiency virus (HIV) infection is one of the most devastating diseases leading to be a very serious health issue.[1] It drastically changes the life of the patient in terms of quality leading to Acquired Immunodeficiency syndrome (AIDS). AIDS declared an epidemic is affecting all sectors of people all over the globe.[2]

UNAIDS commitments by 2020 are 90-90-90 targets: 90% of people living with HIV know their status, 90% of people living with HIV who know their HIV-positive status are accessing treatment and 90% of people on treatment have suppressed viral loads. Globally, 2019, at its end, affirms 1.7 million became newly infected with HIV, 81% (38 million) people knew their HIV status, 67% (25.4 million) were on antiretroviral therapy (ART) and 59% had suppressed viral loads. Access to ART has averted an estimated 12.1 million AIDS-related deaths since 2010. The setbacks of 2020 targets disrupted by the pandemic COVID-19 impacted AIDS mortality levels. UNAIDS is urging countries to fight the colliding epidemics of HIV and COVID-19, as we cannot afford to lose the gains that took so much effort to win.[3]

HIV infection causes depletion of CD4 cells, low CD4 cells count of <200/mm^3 has considered being an indication of active disease progression, further which determines the immune status of patient. Hence the CD4 cell count is essential in monitoring the disease advancement as well as to plan a suitable therapy.[4] Such immunosuppressed patients are prone to opportunistic infections particularly pneumocystosis, oral candidiasis and neoplasms.[5]

Fungal infections play a greater clinical challenge in HIV patients in severe immunosuppressive conditions.[6] Currently, there are 200 species within the genus candida, in which six species; *C. albicans*, *C. glabrata, C. tropicalis, C. parapsilosis, Candida krusei* and *C. lusitaniae* are the most commonly associated with human infection.[7] Dentist plays a pivotal role in diagnosing AIDS, as oral lesions especially oral candidiasis manifest early in HIV infection. HIV patients with oral candidiasis have 2.5 times more progressive risk to AIDS than without oral candidiasis.[4,7,8] Routine identification of candida species is laborious and time-consuming. To overcome this, HICHROM agar is used which stains different species to different colors that facilitates a simple, rapid and reliable method for identification of *Candida* species.[9]

The literature revealed no studies on HIV patients residing in West Godavari district and their factors associated with the disease process. The present study thus made an attempt to determine species diversity among candida isolates and their associations in both symptomatic and asymptomatic HIV seropositive patients of West Godavari district population. It also correlates CD4 count with the predominant Candidal species which paves a path for investigators to unveil a better diagnostic checkpoint and facilitate an active ART.

MATERIALS AND METHODS

The cross-sectional study included a total of 200 HIV seropositive patients from ART Centre, West Godavari District. An informed consent was obtained from every subject for inclusion in the study and performing the test. A detailed clinical history was recorded for all cases from archives of the ART center. Unstimulated saliva sample was collected in screw-capped universal container and stored at 4°C. The samples were transported to the microbiology laboratory for further analysis.

Identification of Candida: Samples were centrifuged at 5000 rpm for half an hour. Five microliters of each sample using a sterile inoculating loop was streaked on to the chromogenic agar culture media and incubated at 37°C for 48–72 h. HICHROM agar, a yeast differential and selective medium, allows recognition of mixed yeast cultures collected from clinical specimen. This media differentiates candida population by colonial morphology and color generated by a chromophore in the agar.

Statistical analysis

The statistical analysis was performed using SPSS software, (IBM Inc, Chicago, Illinois, USA) version 16. Pearson's Chi-square test was used for comparing the different candidal species with demographics in study groups. $P < 0.05$ was considered statistically significant.

RESULTS

Out of 200 HIV seropositive patients**,** 99 were male and 101 were female. Majority of patients belong to the age group between 26 and 45 years with a mean age of 31 years. By occupation, 112 (56%) patients were daily wage laborers, 50 (25%) were housewives, 25 (12.5%) were farmers, 8 (4%) were students and 5 (2.5%) were teachers [Graph 1].

Based on CDC classification CD4 counts were recorded, 90 patients showed initial CD4 count <200, 76 patients were in the range of 200–500 and 34 patients at 500 count. After the administration of highly active ART (HAART) for a period of 2–3 years, 7 patients showed a final CD4 count below 200, 48 were in the range of 200–500, whereas 145 patients crossed the CD4 count over 500. Significant observations ($P = 0.00$) from our study revealed a drastic difference between the initial and final CD4 count among students (609), followed by teachers (429), housewives (398), farmers (373) and daily wage laborer (322) [Graph 2].

The association between the age, gender and occupation with *C. albicans, C. krusei and C. glabrata* was observed in the study. Out of 200 patients, 152 HIV patients in the age range of 26–45 years predominantly showed Non-albicans candida (NACs). However, there was no statistically significant difference in the prevalence of various candida species.

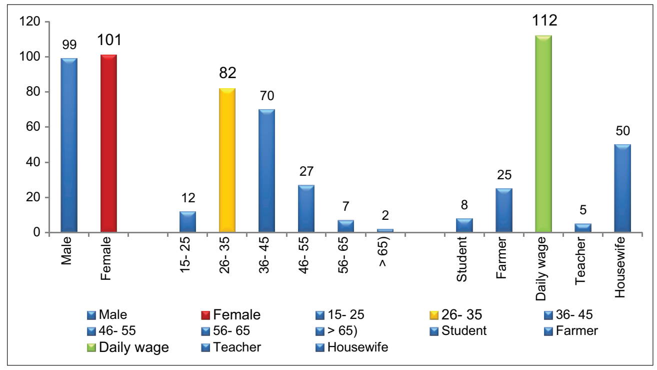
Qualitative assessment of Candida species was thus done in our study to differentiate the *Candida albicans* species from NACs using Hicrome agar media. Majorly three species were identified, among which *C. albicans* isolates appeared green in color, candida glabrata isolates in cream and candida krusei isolates in pale pink color [Figure 1]. Nonalbicans candida (106, 53%) was the species predominantly recovered in our study. *C. glabrata* (72, 36%) and *C. krusei* (34, 17%) were the two NACs that were persistently identified [Graph 3].

Quantitative assessment was performed by disclosing the number of candida colonies evolved in our study. *C. albicans* (3473) have shown a greater proportion of colonies followed by *C. glabrata* (2320) and *C. krusei* (961) [Graph 3 and Figure 2].

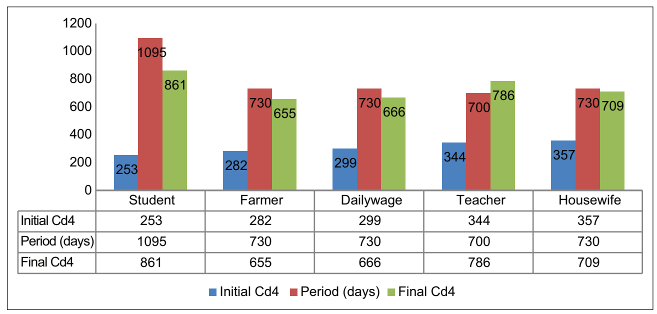
Colonization by more than one candida species has been reported in the literature. In our study, 104 (52%) of the patients were colonized by atleast 2 species and association was predominantly between *C. albicans and C. glabrata* 67 (64%). HIV patients with no clinical candidiasis also disclosed candidal colonization, emphasizing identification of asymptomatic candidal patients.

DISCUSSION

Oral microbiome and the immune system interplay encompass various strategic scuffles in health and disease.[10] The immune system, a double edge sword, congregate events in host defense on one hand while on other, aberrations ground to immunodeficiency.[11] Acquired immunodeficiency syndrome (AIDS) is a collection of symptoms or diseases caused by HIV. HIV infects and destroys immune cells resulting in person's vulnerability to infections. It invades various immune cells (e.g., CD4+ T cells, macrophages and monocytes) resulting in a decline in CD4+ T cell numbers below the critical level leading to AIDS.[12]

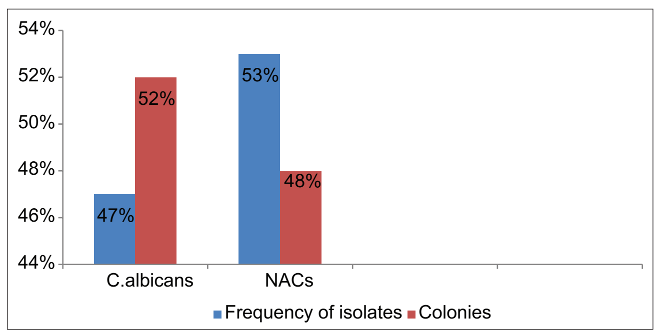


Graph 1: Distribution of demographic profile among study subjects – slight female predominance with prevalence in the age group of 26–35 and the most common social group affected being the daily wage laborers



	Student	Farmer	Dailywage	Teacher	Housewife
Initial Cd4	253	282	299	344	357
Period (days)	1095	730	730	700	730
Final Cd4	861	655	666	786	709

Graph 2: Immunological profiles of study subjects – influence of highly active antiretroviral therapy treatment on various occupations among which students have shown a drastic change between the initial and final CD4 count



Graph 3: Distribution of *Candida* isolates among study population – NACs are the predominant species isolated in the study. On comparing the number of colony-forming units, *Candida albicans* species are under greater proportion when compared to NACs

Our study revealed the mean age of HIV seropositive patients with both symptomatic and asymptomatic candidiasis as 31 years with a range of 26–45 years. Das *et al.* 2016, Maheswari *et al.* 2016, observed similar findings in their studies. They disclosed 26–40 years as the most commonly affected age, at which they are sexually active. In this study, the authors hypothesized that younger people are more commonly infected with HIV considering the fact that, this age group is at an edge of physical and emotional transformation which navigate

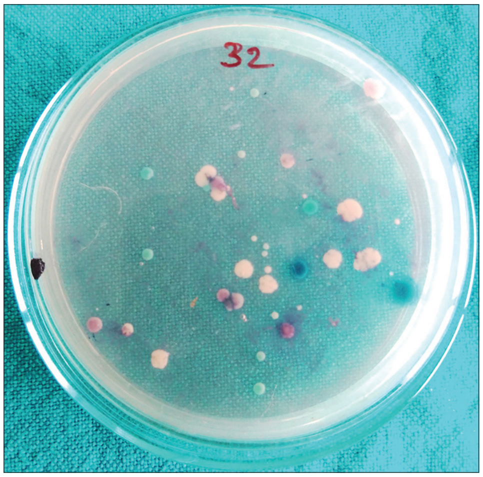


Figure 1: *Candida albicans* isolates show green colored colonies, candida glabrata isolates appearing cream color and candida krusei isolates in pale pink color

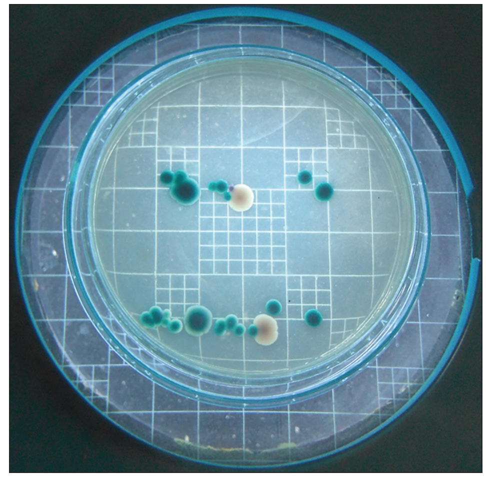


Figure 2: Number of colonies formed were more in *Candida albicans* species when compared to NACs

them toward the sexual urge. Authors also presumed that vertical transmission, intergeneration sex, transgender sex, homosexuality, intravenous drug abuse and blood transfusion are the possible risk zones encountered in the younger people.[13,14] This can be ascribed to their experimental nature and lack of knowledge that indulged them to infection. As seen in Sravya Kurapati 2012; Kothari and Goyal 2001; Kumarasamy *et al*. 1995 and Kaur *et al*. 1992 studies in India, sexual mode of transmission was the most common in 32 (53.3%) patients (heterosexuality accounting for 94% of these), followed by intravenous drug abuse (8.3%) and blood transfusion (5%).[15-19]

Early diagnosis of HIV infection, access to medical care and HAART plays an important role in HIV-related oral disease prevention. A study conducted by Tappuni and Fleming 2001 in 284 HIV-infected patients in the United Kingdom found that HIV patients on dual or triple HAART were significantly less likely to have HIV-related oral manifestations, reductions in viral load and increase in CD4 counts.[20,21] This helps in improving the patient's quality of life by reconstituting the immune system.[22] On analyzing occupation, daily wage laborers were mostly infected with HIV, followed by housewives, farmers, students and teachers. Similar observations were made by Annapurna *et al*. 2012, Kerdpon *et al*. 2004, in their study on Tamil Nadu, South and North Thai patients.[22,23] Despite their smaller proportion, students had shown remarkable improvement after HAART. The authors hypothesized lifestyle, nutrition, general health and body response to HAART might be the imparting factors for such progression among students.

In the current study, both initial and final CD4 counts were recorded along with the period of HAART administration. Observations exposed a significant reduction in clinical as well as oral manifestations along with an improvement in CD4 count. Our study was in accordance with Samaranakayake, Tsang 1999, Ranganathan *et al*. 2000, Kerdpon D 2004, Nantez *et al*. 2014 who found oral candidiasis as the only lesion which had a significant association with CD4 count. Individuals with oral candidiasis are thrice as likely to be immunosuppressed as those without candidiasis. These circumstantiate oral examination as a crucial and beneficial signpost in the management of the HIV patients.[14,23-26]

Goulart *et al*. 2018 and Fidel 2011 in their studies observed oropharyngeal candidiasis as the first clinical sign of HIV.[27,28] Persistent colonization of oral cavity by candida species has gained high incidence in HIV patients. Considering it, as a chief factor, it can be used as an important marker in the disease initiation and progression. Colonization of candida varies with factors such as smoking, alcohol consumption, gender, geographical, climatic, ethnic differences, immune status, CD4 count, HIV viral load and use of HAART. Although the predominant species among candida was albicans, there was an increased percentage of NAC species which had effect on the health of HIV patients.[5,29] Hyphae, biofilm formation, acid proteinase and phospholipase production are considered the most important virulence factors facilitating the candida to become pathogenic in HIV seropositive patients. NACs being deficient in total or partial virulence factors the candida species actually possess are less virulent when compared to the albican species.[30-32]

Out of 200 subjects in the study, *C. albicans* species was observed in 94 (47%) patients, while NACs (106, 53%) was the species predominantly recovered in our study.

Challocombe *et al.* 1995 and Enwuru *et al.* 2008 reported 54% and 59.5% of NACs, respectively, in their studies.[33,34] In contrast, studies of Lattiff *et al.* 2004, Menezes *et al.* 2015, Clark *et al.* 2017 and Khedri *et al.* 2018 reported 86%, 67.6%, 71.8% and 52.9% of *C. albicans,* respectively.[5,29,35,36] Among NACs, *C. glabrata* (72, 36%) and *C. krusei* (34, 17%) were the two variants that are persistently identified. Studies carried out by Sao Paulo disclosed *C. glabrata* as the most frequently isolated NACs which is in accordance with the present study.[37] Conversely, contradictory observations were disclosed in western country studies which revealed *C. tropicalis* and *C. parapsilosis* as the frequently isolated species.[38] All such elucidations emphasize that distribution of NACs has geographical precision[39] and also emerging drug-resistant NACs profile in HIV patients confront the challenge to select an empiric treatment.

Although NACs were identified in considerable percentage of our study subjects, a number of *C. albicans* colonies prevailed over them. Inspite of intrinsic low susceptibility, NACs have high resistance to azole antifungal agents.[40] Usage of these drugs in past by HIV patients would have lead for greater proportion of NACs. Protease and transcriptase inhibitor classes of HAART inhibit proteolytic enzymes secreted by Candida species that are crucial for the growth of Candidal hyphae leading to colonization. HIV-positive patients under such HAART eventually resist colonization of Candida and their adherence to the oral mucosa, result of which the number of colonies among NACs was insignificant.[5]

Colonization by more than one candida species has been reported in the literature. In our study, 104 (52%) of the patients were colonized by atleast 2 species and association was predominantly between *C. albicans* and *C. glabrata* 67 (64%). A study conducted by lakshmansamaranayake *et al.* 1987 exposed the most common yeast combinations isolated from oral samples as *C. albicans* with *C. krusei, C. tropicalis* or *C. glabrata*.[41] In accordance with the present study, Erkose *et al.* 2007, Junqueira *et al.* 2012 and Li *et al.* 2013 have shown predominant association between *C. albicans* and glabrata.[37,42,43] In disparity, the study of Menezes *et al.* 2015 has shown a predominant association between *C. albicans* and parapsilosis.[5] Authors predicted the associations could be due to the presence of a specialized set of proteins called adhesins in candida, which mediate the connotation to more than one Candida species and to host cells.[44]

From the observations of the present study, an increase in CD4 count among HIV patients had shown a strong association with a rise in Candidal colonization. This encloses a fact that enhancement in CD4 count is required but not sufficient to protect HIV-infected patients from colonization by Candida.[45] A similar assessment was observed by Erkose *et al.* 2007 and Sanchez-Vargas *et al.* 2005, while De Brito Costa *et al.* 2003 study contradicted our findings.[42,46,47] Host characteristics such as salivary flow rate, salivary anticandidal proteins and oral hygiene and/or strain features such as virulence are the factors that has to be ruled out for a better confirmation of candida colonization and its association with CD4 count.

Although there were no oral manifestations, substantial candidal growth was observed in our study population which heralded the importance of identifying asymptomatic patients. All asymptomatic patients demonstrated colonization of candidal species which included both albicans and NAC species. The use of antibiotics, a predisposing factor, used in the initial stages of disease would have favored the growth of candida species.[38] Conversely, regional differences and selective pressure of antifungal drugs might have also changed the trend of infection.[5] Thus, dentists and clinical microbiologists are at an urge to identify Candida at the species level, to en route appropriate therapeutics and optimize treatment.[39,48]

CONCLUSION

The colonization of Candidal species is an index to predict immunosuppression in HIV seropositive patients. Identifying candida at its species level will promote in bringing an early first step in the management of HIV patients. However, to incorporate it as an index certain host characteristics, regional parameters, antifungal resistance and the use of HAART should be considered. This outcome can be brought about through a detailed case history given by the patients, lack of which seizes the advancement. Stigma, discrimination and widespread inequalities are the barriers for such a breakthrough. Further investigation notably larger longitudinal studies are warranted to clarify the role of CD4 count, viral load, regional parameters and the influence of ART on manifestations of oral candidiasis.

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Conflicts of interest
There are no conflicts of interest.

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