



CORRELATION OF CANDIDAL SPECIES DIVERSITY BETWEEN NORMAL INDIVIDUALS AND HIV POSITIVE PATIENTS

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Introduction:

Oral Candidiasis is considered one of the most prone opportunistic infection in patients of HIV (Human Immuno-deficiency Virus) infection in India. Candida being one of most important etiological agents for morbidity and mortality among patients with AIDS (Acquired Immuno-Deficiency Syndrome). Antifungal agents can effectively treat mucosal candidiasis, but however prolonged management can lead to colonization with minimal amount of species present along with other normal susceptible strains. ⁽¹⁾

Less commonly found candidal non-albicans species such as *C. glabrata*, *C. parapsilosis*, *C. krusei* and several other species may cause the disease. *C. dubliniensis*, a species almost similar to *C. albicans* might involve 15% of infections previously occurred due to *C. albicans*.

By the presence of variable candidal species as pathogenic organisms and a change in the development of susceptibility pattern of *C. albicans*, providing the need for isolation and identification of the particular causing organisms.

Oral colonizing species with drug resistant organisms is more common in advanced HIV infection warranting the discussion on different species of candida and their potential to harbor resistance against anti-fungal drugs. ⁽²⁾

Analyzing all these characteristics, study was done to know the candidal species variations/diversity in HIV positive individuals with and without highly active anti-retroviral therapy (HAART), attending the Regional Voluntary Counselling & Confidential Testing Center (VCCTC), Mumbai.

Aims and Objectives:

To analyze and assess the candidal strain diversity in HIV positive individuals who had undergone anti-retroviral therapy and in patients who are not on anti-retroviral therapy.

Materials and Methods:**Materials:**

The study was conducted in the department of Microbiology, at the institute hospital. The study population included 30 patients each of group I and group II attending the facility.

1. Group I: Included 30 patients who were people living with HIV/AIDS naive to HAART.
2. Group II: Included 30 patients who were people living with HIV/AIDS who were registered for Highly Active Antiretroviral Therapy (HAART) and started on drug regimen. The patients from group I and Group II were direct walk-in patients in the Voluntary Counselling and Confidential Testing Centre (VCCTC), who were positive for HIV by three tests (COOMBS AIDS; TRI DOT; TRILINE), according to the guidelines of National AIDS Control Organization.
3. Group III: Included 30 HIV seronegative healthy subjects as controls.

Inclusion Criteria:

1. 30 HIV positive patients who were being treated with HAART regimen, atleast for a duration of 1 month and with a known CD4 + T-lymphocyte count.
2. 30 HIV positive patients who were not yet initiated with the treatment of HAART and with a known CD4 + T-lymphocyte count.

Exclusion Criteria:

1. Patients with history of tuberculosis, diabetes mellitus, cardiovascular diseases, rheumatoid arthritis and any systemic ailments were excluded. Pregnant females and denture wearers were also excluded from the study.
2. HIV+ve patients with HAART duration less than a month were also excluded.



Figure 1: ARMAMENTARIUM USED FOR CLINICAL EXAMINATION OF PATIENT

Methods:

1. All the patients included in this study were asked to rinse with 10 ml of normal saline for 60 seconds before expectorating into the sterile container. (Colour Plate 1: Fig 2)
 2. The oral rinse sample was immediately taken to the Microbiology department for inoculation of the sample on a Sabouraud's Dextrose Agar, specific for candidal growth.
 3. 0.1 ml of undiluted oral rinse sample was inoculated on two plates of Sabouraud's Dextrose Agar (SDA) containing chloramphenicol.
 4. 0.1 ml of diluted (10^{-1}) oral rinse sample of HIV +ve patients was also inoculated on two plates of Sabouraud's Dextrose Agar plates containing chloramphenicol.
- Note: 10^{-1} dilution of the oral rinse sample is prepared by mixing 0.1 ml of oral rinse sample of HIV +ve patients with 0.9 ml of sterile normal saline.
5. The above plates were, then incubated aerobically at 37°C for 48-72 hrs.
 6. The growth appeared in 2 to 3 days as creamy white, smooth, pasty colonies. In a few, the growth was observed within 24 hours i.e overnight incubation.

7. The complete growth of any candidal colonies on the culture plates was recorded as a positive growth and the subject as positive candidal carrier. (i.e POSITIVE CANDIDAL CARRIAGE RATE)

8. The number of colonies on each plate was counted manually, and an average count of both the diluted (10^{-1}) plates was taken.

9. Various different colony forming units (CFU's) per ml was calculated to indicate the CANDIDAL DIVERSITY.

The calculation was as follows.

N : no of colonies in 0.1 ml of 10^{-1} dilution. (since 0.1ml of 10^{-1} was spread on the agar plate).

10N : no of colonies in 1 ml of 10^{-1} dilution of the normal saline.

100N : no. of colonies in 1 ml of sterile saline which gives the CFU's/ml.

7. The representative colonies of candida species on SDA plate were then purified on blood agar with a streak method. Further identification of species was done by VITEK TEST using the purified colonies grown on blood agar.

8. Some of the samples were tested retrospectively with the help of germ tube test, chlamyospore formation test and with CHROM agar.

9. Germ Tube Test:

The principle of this test is the ability of *Candida albicans* and its variants to produce germ tubes when incubated with various substances like, human or sheep serum, rabbit plasma, egg albumin, saliva, tissue culture medium, thioglycolate trypticase soya broth and various peptone mediums. This is a rapid screening procedure for differentiating *C. albicans* from other *Candida* species.

10. Chlamyospore Formation Test:

Cultivation on cornmeal agar facilitates and appreciates Chlamyospore formation. This property is peculiar to *C. albicans* and to very rare isolates of *C. tropicalis* and *C. stellatoidea*. The Chlamyospore has been defined as a thick walled non-deciduous intercalary or asexual spore formed by rounding off of a cell or cells.

11. CHROM agar Test:

CHORM agar is a novel differential culture medium for isolation and presumptive to identification of different species of *Candida* and has revealed mixtures of *Candida* species in many types of clinical samples more often than would have been expected. The species of *Candida* can be identified by different coloured colonies. The different coloured colonies produced on the CHROM agar is as follows:

1. *Candida albicans*: Light Green
2. *Candida glabrata*: Purple
3. *Candida tropicalis*: Blue with Pink hallow
4. *Candida parapsilosis*: Cream
5. *Candida krusei*: Pink (Rough, Fuzzy spreading)
6. *Candida dubliniensis*: Dark Green.



Figure 2: STERILE BOTTLE CONTAINING 10ml OF STERILE NORMAL SALINE FOR PATIENTS ORAL RINSE SAMPLE



Figure 3: ARMAMENTARIUM USED FOR INOCULATION OF ORAL RINSE SAMPLE



Figure 4: WORKING PLACE FOR THE ASEPTIC INOCULATION OF ORAL RINSE SAMPLE

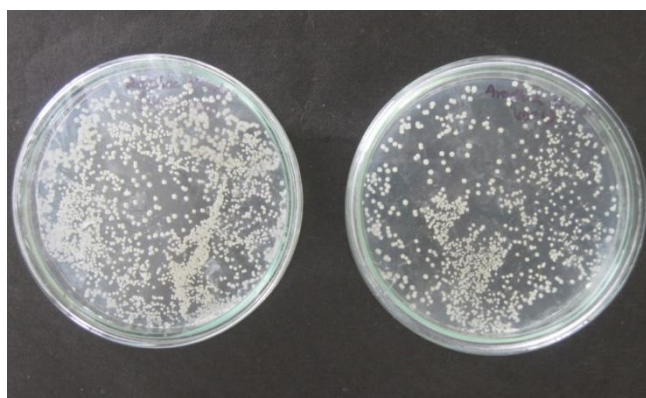


Figure 5: POSITIVE GROWTH OF CANDIDA SPECIES IN UNDILUTED AND DILUTED (10⁻¹) PLATES

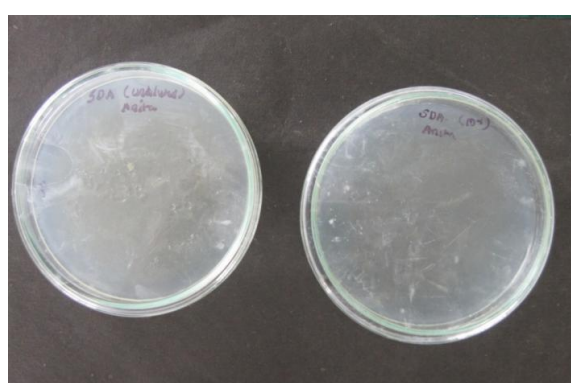


Figure 6: NEGATIVE GROWTH OF CANDIDA SPECIES IN UNDILUTED AND DILUTED (10⁻¹) PLATES



Figure 7: VITEK MACHINE FOR RAPID IDENTIFICATION OF DIFFERENT STRAINS OF CANDIDA SPECIES.



Figure 8: YEAST IDENTIFICATION CARD AFTER PERFORMING THE TEST IN VITEK MACHINE

STATISTICAL ANALYSIS:

1. To test the association between the species diversity among the HIV positive individuals with and without HAART, chi-square test was applied.
2. To test the association between the candidal species diversity with the CD4 count ≤ 200 and >200 cells/mm³, again the chi square test was applied.

RESULTS

It is well known that Candida species and HIV infection have a long association with each other. Mucosal candidiasis remains a significant infection in HIV disease and is considered as an important marker for disease and its progression. Today the HAART is considered as the main stay treatment for human immunodeficiency virus infection. Investigators have reported an increase in the latency, a decrease in the incidence of opportunistic diseases or changes in their clinical aspects, including the oral lesions related to HIV infection with advent of HAART.

Hence the present study was undertaken to analyse the candidal diversity (i.e species diversity) in HIV +ve infected subjects undergoing HAART and not on HAART .

In the present study, the asymptomatic candidal carriage rate has been shown to be much more common in HIV- seropositive individuals than in healthy groups. It is well known that candida species are more likely to be isolated in HIV infected patients than healthy individuals. Amongst the HIV seropositive individuals the candidal carriage rate was higher in subjects with HAART therapy than in subjects naive to HAART.

In normal individuals, candida species is also present as a member of the normal oral flora. Therefore, mere presence and isolation of candida species from both normal and HIV seropositive patients with and without HAART does not indicate the presence of the clinical candidiasis.

The ability of the yeasts, to overcome host clearance mechanisms and to colonize mucosal surfaces, can be considered a precondition to oral candidiasis. Persistence of this candidal colonization is hence considered to have a better predictive value in the induction and development of clinical candidiasis in immune-compromised hosts. These findings suggest that though HAART is marginally effective in completely eliminating candida species from the oral cavity, it definitely has resulted in significant decrease in CFU's/ml resulting in a reduction in the incidence of clinical candidiasis. The most likely scenario would be that most patients receiving HAART will continue to be colonized by candida, but will not develop oral candidiasis, suggesting its role in changing pattern in the occurrence of oral lesions.

The isolated cultures of candida species from HIV seropositive patients were subjected to Biomereux VITEK 2 system for identification of different candida strains. Among the positive isolates, *Candida albicans* accounted for being the predominant species. The non albicans species were also isolated in a considerable number of cases, which also included the one which had shown mixed species. Among the non albicans species, *Candida glabrata* and *Candida famata* was the most frequent isolate. Isolation of *Candida famata* is interesting to note, as to our knowledge this is the first isolated case of a rare non albicans candida species from the oral cavity of HIV positive individuals. Patients receiving HAART showed more non-candida albicans species diversity than patients not on HAART therapy. This could be due to the direct inhibitory action of HAART on the *Candida albicans* thereby allowing other species of candida to occupy a place in the oral flora.

In our study we also found no statistical significant association between the candidal species diversity with CD4⁺ lymphocyte count ≤ 200 and >200 cells/mm³. Traditionally CD4 count has been cited as the greatest risk factor for development of mucocutaneous candidiasis. Our study supports the results of previous studies in experimental models, which showed no enhancement of OPC even in absence of CD4 count. The change in the phenotype switch of the CD4⁺ T cell from Th 1 to Th 2 in the presence of HIV infection has been implicated as a reason for this finding. Further studies are needed to explore the possible relationship of OPC with levels of blood HIV viral load in patients with HAART and non-HAART.

The present study was aimed at identification of **different species** of candida in the oral cavity of HIV positive individuals with and without HAART therapy. The study included patients visiting the O.P.D of the institute hospital, as well as outpatients visiting private HIV clinics (direct walk-in clients of VCCTC, ART Centre).

The results of the present study was tabulated as follows :

TABLE 1 – Correlation of Candidal Species Diversity Between Normal Individuals And HIV +ve Patients: (Graph 1)

| Individuals | Albicans | Non albicans | Total |
|-------------|-------------|--------------|-------|
| HIV | 80.55% (29) | 19.44% (07) | 36 |
| NORMAL | 100% (11) | 0% (0) | 11 |
| TOTAL | 40 | 07 | 47 |

To test if there was any association between the Normal and HIV +ve subjects and the candidal diversity, the contingencies are prepared as shown in the Table 1.

In order to assess whether there was a significant relationship between the species diversity between the normal individuals and HIV seropositive patients, the chi – square test at 95% of confidence level was applied to the data which showed that the calculated value of chi – square was 6.39 with p – value of 0.041. This showed that the correlation of the species diversity between the normal individuals and HIV +ve patients was significant.

GRAPH 1– CORRELATION OF CANDIDAL SPECIES DIVERSITY BETWEEN NORMAL INDIVIDUALS AND HIV +ve PATIENTS

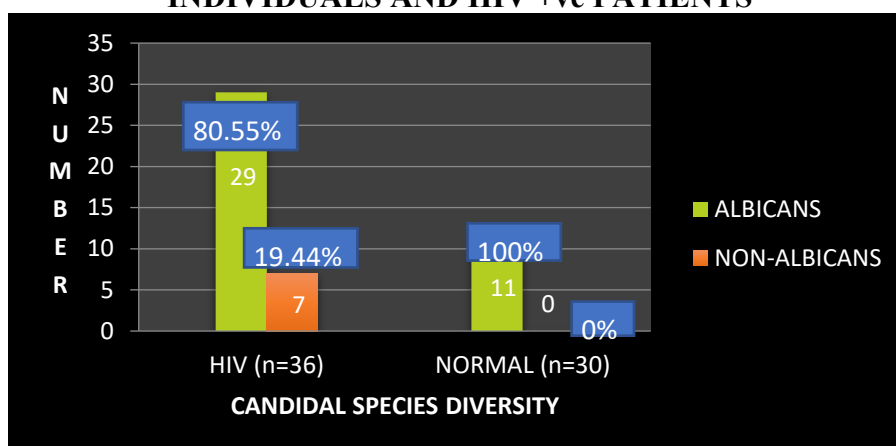


Table 2:

TABLE 2 – Correlation of Candidal Species Diversity Between HIV +ve Patients With And Without HAART: (Graph 2)

| HIV individuals | Albicans | Non- albicans | Total |
|-----------------|-------------|---------------|-------|
| With HAART | 78.26% (18) | 21.73% (05) | 23 |
| Without HAART | 92.30% (12) | 7.69% (01) | 13 |
| TOTAL | 30 | 06 | 36 |

Table 2 showed, the total Candida species isolated in the present study which included the HIV +ve individuals with and without HAART. The chi – square test at 95% confidence level was applied to the data. The calculated value of chi-square was 8.033 with p – value of 0.18, which indicated there was a significant relationship between the species diversity in HAART and non-HAART HIV seropositive individuals.

GRAPH 2– CORRELATION OF CANDIDAL SPECIES DIVERSITY BETWEEN HIV +ve PATIENTS WITH AND WITHOUT HAART

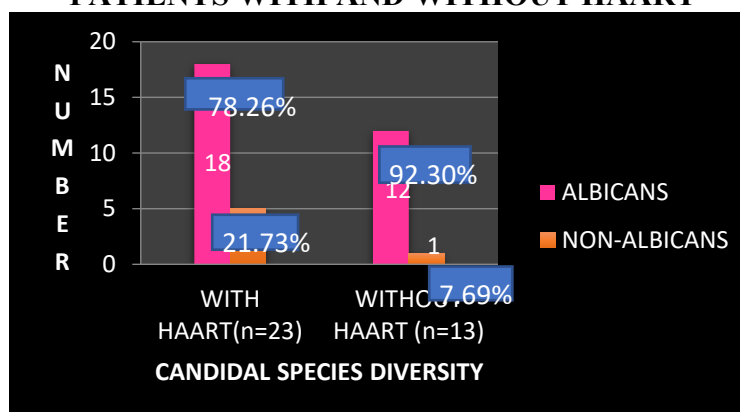


Table 3 :

TABLE 3 – Correlation Between CD4 Count (≤ 200 , >200 cells/mm³) in HIV +ve Patients And Candidal Carriage Rate: (Graph 3)

| CD4 COUNT (cells/mm ³) | Candida species (Present) | Candida species (Absent) | Total |
|------------------------------------|---------------------------|--------------------------|-------|
| ≤ 200 | 65.51% (19) | 34.48% (10) | 29 |
| >200 | 54.83% (17) | 45.16% (14) | 31 |
| TOTAL | 36 | 24 | 60 |

To know the association between the prevalence of candida and the CD4 count chi – square test was applied at 95% confidence level. The standard classification of CD4 count ≤ 200 and >200 cells/mm³ was used for HIV +ve subjects under study. The calculated value of chi – square was 0.712 with p – value of 0.399 which showed no significant relation between the prevalence of candida carriage rate and CD4 count of HIV +ve individuals.

GRAPH 3 – CORRELATION BETWEEN CD4 COUNT ($\leq 200, >200$ cells/mm³) IN HIV +ve PATIENTS AND CANDIDAL CARRIAGE RATE

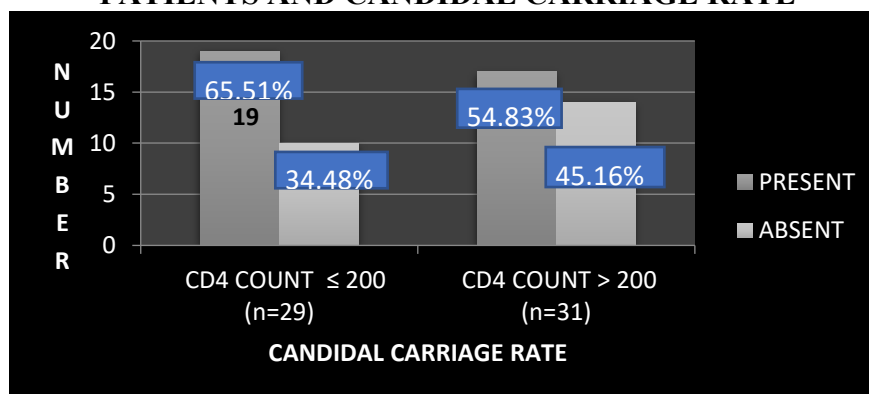


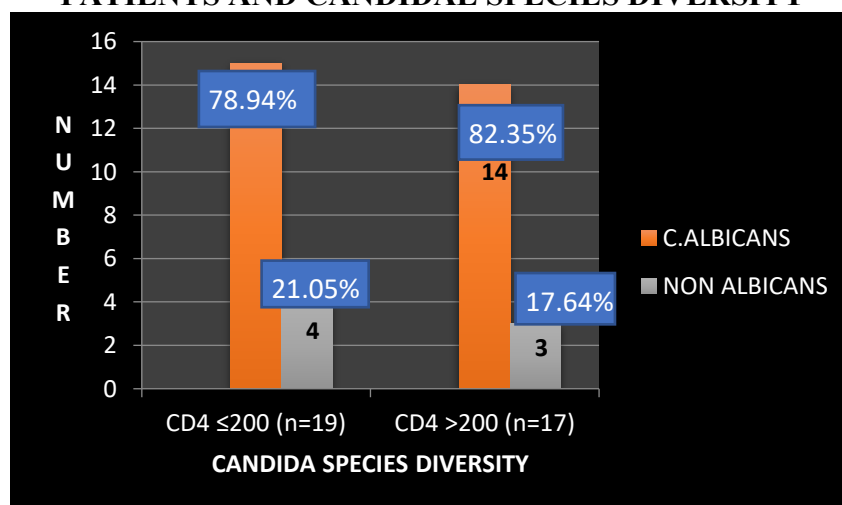
Table 4 :

TABLE 4 – Correlation Between CD4 Count ($\leq 200, >200$ cells/mm³) In HIV +ve Patients And Candidal Species Diversity: (Graph 4)

| CD4 COUNT(cells/mm ³) | Candidal species diversity | | Total |
|-----------------------------------|----------------------------|---------------|-------|
| | Albicans | Non- albicans | |
| ≤ 200 | 78.94% (15) | 21.05% (04) | 19 |
| >200 | 82.35% (14) | 17.64% (03) | 17 |
| TOTAL | 29 | 07 | 36 |

To know the relationship between CD4 count and candidal diversity chi – square test was applied at 95% of confidence level. The calculated value of chi - square was 0.066 with p – value of 0.799. The results indicated that there was no significant relationship between CD4 count and candidal diversity.

GRAPH 4 C – CORRELATION BETWEEN CD4 COUNT ($\leq 200, >200$ cells/mm³) IN HIV +ve PATIENTS AND CANDIDAL SPECIES DIVERSITY



DISCUSSION:

Since 1980s, AIDS has caused more than 30 million deaths and orphaned more than 14 million children worldwide. The origin of AIDS has puzzled scientists ever since illness was brought into lime-light in early 1980s. No disease has struck with such serious consequences as AIDS. In India, the detection of HIV case traced back to 1986 where first case detected in southern states of India. After which there has been a steady increase in number of AIDS seeking treatment in various hospitals across the country. Later on, investigations made it clear that AIDS was a newly recognized human disease caused by an infectious agent and spread primarily by sexual contact.

Gottlieb MS et al.⁽³⁾ in 1981, observed a new outbreak as “GRID” (Gay Related Immune Deficiency), stigmatizing gay community as carriers of this deadly disease. About a year later, Centre for Disease Control(CDC) linked the illness to blood and coined the term AIDS(Acquired Immune Deficiency Syndrome).

In 1983, Dr.Luc Montagnier isolated a retro-virus from a West-African patient with persistent generalized lymphadenopathy and called it “lymphadenopathy associated virus”(LAV).

In December 1983, Gallo submitted a paper for publication proposing the theory that an HTLV type retrovirus was the cause of AIDS.

Coffin JM et al.⁽⁴⁾ 1986, recommended the new term Human Immunodeficiency Virus to reduce the confusion created by different names for the same virus.

Oral candidiasis and other oral manifestation in the era of antiretroviral therapy

Since 1996, the importance of anti-HIV drug combination regimens has become widely accepted. What has been common practice for the treatment of tuberculosis (i.e. a combination of three tuberculostearic has also been introduced for the treatment of AIDS: it was even given its own acronym, HAART, for highly active antiretroviral therapy. Combination of three (or more) anti-HIV compounds is aimed at the same goals as for the treatment of tuberculosis:

- (i) to obtain synergism between different compounds acting at different molecular targets.
- (ii) to lower the individual drug dosages to reduce their toxic side effects; and
- (iii) to diminish the likelihood of development of drug resistance

Ranganathan et al.⁽⁵⁾(2000), reported there was marked decrease in overall incidence of oral lesions in people living with HIV/AIDS on HAART. A reduction in oral candidiasis seems to be the main contributor to the overall reduction of oral lesions. Patton LL et al. (2000), concluded that the introduction of HAART has contributed to a global reduction in oral lesions in adults and children. A decreased prevalence of HIV-related oral lesions of 10–50% following the advent of HAART has been reported.

Greenspan et al.⁽⁶⁾(2001), stated in contrast there was an increased prevalence of oral warts in subjects on HAART has been reported mainly from western countries. An increase in benign human papilloma virus associated neoplastic lesions including papillomas, condylomas, and focal epithelial hyperplasia in patients on HAART has been observed. Mocroft A and Lundgren JD⁽⁷⁾ (2004), emphasized that HAART therapy has dramatically improved the prognosis of the patients with HIV, although the best time to start the treatment so as to reduce the risk of clinical progression is unclear. Ceballos-Salobrena A, Gaitain – Cepeda L, Samarnayake LP et al.⁽⁸⁾ (2004), concluded that although oral candidiasis in HIV infected Spanish individuals has not decreased significantly after the introduction of HAART, there appears to be significant reduction in hyperplastic and pseudomembranous variants of disease with compensatory increase in erythematous candidiasis.

Hung CC et al.⁽⁸⁾ (2004), performed a study in HIV infected Taiwan patients. They found an increased risk of oropharyngeal colonization(OC) and candidiasis in HIV infected patients with progressive immunodeficiency.

Gaitán-Cepeda LA et al.⁽⁹⁾ (2005), concluded oral candidiasis should be considered as the clinical marker of immune failure in patients with HIV/AIDS undergoing HAART. In their study the presence of oral candidiasis was closely related to immune failure in patients with HIV/AIDS undergoing HAART. The probability of immune failure in the presence of OC was 91% for men who have sex with men, 95.5% for heterosexuals, and 96% for intravenous drug users.

Costa et al.⁽¹⁰⁾ (2006), carried out a study to evaluate *Candida* species diversity in the oral cavity of HIV-infected patients undergoing highly active antiretroviral therapy and to determine whether there was association of CD4 + cell count and viral load with asymptomatic oral *Candida* carriage. Out of 99 HIV-positive patients studied, 62 (62.6%) had positive culture for *Candida* (oral carriage) and 37 patients (37.4%) had *Candida* negative culture (no oral carriage). The etiologic agents most common were *C. albicans* and *C. tropicalis*. The range of CD4+ was 6-2305 cells/mm³ in colonized patients and 3-839 cells/mm³ for non-colonized patients, while the viral load was 60- 90016 copies/ml for colonized patients and 75-110488 copies/ml for noncolonized patients. The viral load was undetectable in 15 colonized patients and in 12 noncolonized patients. Their results showed that there was no significant difference of the variables CD4+ cell count and viral load between oral *Candida* carriage and no oral *Candida* carriage patients.

Yang YL et al.⁽¹¹⁾ (2006) concluded in HAART is highly effective in decreasing oral candidiasis in association with a rise in CD4 +lymphocyte count, but there is continual colonisation and only marginally effective in eliminating *Candida* from the oropharynx.

Umadevi KMR et al.⁽¹²⁾ (2007) reported that the prevalence of oral candidiasis who had access to HAART was less than compared with those who did not have access to HAART. There was a difference in the occurrence of oral candidiasis between HAART(8%) and non-HAART (24%) participants.

Pomarico L et al.⁽¹³⁾ (2009) suggested that the use of antiretroviral therapy in HIV +ve children was associated with immune reconstitution, decrease in the prevalence of oral candidiasis and a lower candidal species carriage. Also their data suggested children who used Protease Inhibitor(PI) as a part of antiretroviral therapy showed additional reduction in the oral candidiasis(OC) prevalence and candidal carriage. It is possible to speculate that the protease inhibitors might have an anti-candidiasis effect, resulting not only immune reconstitution, but also from a direct anti yeast mechanisms.

Ortega KL et al.⁽¹⁴⁾ (2009), studied oral lesions related to HIV infection in 850 patients, including OC, Hodgkin's Lymphoma(HL), Angular Cheilitis, Aphthous Ulceration, Herpes Simplex (HS), Necrotizing Ulcerative Gingivitis, Necrotizing Ulcerative Periodontitis, Linear Gingival Erythema, Kaposi's sarcoma, Lymphoma and Condyloma Acuminatum.

Oral candidiasis, Kaposi's sarcoma and HL were the oral manifestations that were strongly associated with HIV infection that presented with a greater incidence than that of the other lesions. Later he concluded following the introduction of HAART , there was a reduction in the incidence of all lesions of oral candidiasis and HL.

Thompson GR III et al.⁽¹⁵⁾ (2009), concluded in his study that oropharyngeal candidiasis remains a significant problem in those with HIV and have illustrated the potential for resistant species to emerge despite therapy and have mandated clinicians possess a working knowledge of alternative antifungal agents.

Nittayananta W et al.⁽¹⁶⁾ (2010), observed a dramatic decrease in the prevalence of HIV related oral lesions. Before the introduction of HAART, oral lesions were found in 82% of Thai people with AIDS. OC and OHL were shown to be the two most common oral lesions found in 54% and 13% of Thai people with AIDS, respectively. However, in this study, OC and OHL were diagnosed in only 2% and 1% of HIV-infected subjects who received HAART, respectively. HIV-infected subjects who were not on HAART had a higher prevalence of OC compared with those on HAART. These findings are consistent with a UK cross-sectional study, which showed a higher prevalence of OC in adults not on any antiretroviral medication , compared with those on HAART.

Nittayannanta W et al.⁽¹⁶⁾ (2010), also demonstrated that oral health of HIV- infected subjects was improved with short term use of HAART. However long term use of HAART seemed to have adverse effects on oral health status of subjects. The author also concluded HIV- infected subjects without HAART and those who were on long term use of HAART seemed to have a greater risk of developing cervical caries than those with the short term use of HAART.

Ananthalakshmi R et al.⁽¹⁷⁾ (2011), concluded in their study that asymptomatic oral candidal carriage rate in HIV positive group was higher than the healthy group. Also asymptomatic oral

candidal colonisation is not related to CD4 lymphocyte count of blood in individuals in HIV infection. The frequency of oral candidiasis increase with the decrease in CD4 count. Pseudomembranous candidiasis is the common clinical form of oral candidiasis which could predict the immune suppression status of the host. Protease inhibitor therapy has been demonstrated to decrease both frequency and recurrence of OC in HIV-infected individuals. A decreased prevalence of OC with the advent of HAART was found to be associated with the use of Protease Inhibitor.

Murno CA et al ⁽¹⁸⁾ (2002), proposed the ability of PI to inhibit candida infection may be related to similarities between candida secreted aspartic proteinases (SAP's), which are the key virulent factors for candida albicans, and HIV proteinase, and inhibition of both by PI. Ortega KL et al ⁽¹⁹⁾ (2009), in contrast to the above study concluded that the superiority of NNRTI regimens in decreasing OC incidence is consistent with the current therapeutic guidelines which recommend NNRTI-based (Non-Nucleoside Reverse Transcriptase Inhibitor) therapy as the treatment of choice for the initial ARVT. (Anti-Retro Viral Therapy)

CONCLUSION:

HIV positive individuals undergoing HAART therapy showed higher candidal carriage rate and lower candidal density than the non-HAART group.

Further studies should be conducted to gain insight about the effect of HAART on the albicans and non albicans species, and the resistance to it at the molecular level. Also no significant association was found between OPC (OroPharyngeal Candidiasis) and CD4 count in our study and hence HIV viral load should be taken in consideration as a parameter.

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