ORIGINAL RESEARCH PAPER

Dental Science

Volume - 7 | Issue - 4 | April-2017 | ISSN - 2249-555X | IF : 4.894 | IC Value : 79.96

RELATION OF ORAL LESIONS WITH CD4 COUNT AND DURATION OF HAART IN HIV INFECTED PATIENTS IN RURAL PART OF SOUTH INDIA

KEYWORDS

Antiretroviral therapy, CD4 lymphocytes, human immunodeficiency virus, oral manifestations.

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ABSTRACT

Oral lesions in HIV infection are important indicators of disease progression and occur in approximately 30 to 80 percent of the affected population and in late stages in AIDS contributes to more than 90%[1, 2, 3] . Factors which predispose expression of oral lesions include CD4 counts less than 200 cells/mm^3, viral load greater than 3000 copies/mL, xerostomia, poor oral hygiene and smoking[4,5]. This study aimed to determine the therapeutic effects of highly active anti-retroviral therapy (HAART) on the clinical presentations of HIV related oral lesions based on the duration of therapy and its relation with CD4 count. We considered 50 HIV positive patients and screened for oral leaions and CD4 count was evaluated simultaneously with duration of patients on HAART. Then we analysed using the measures of central tendency. The prevalence of oral lesions has changed since the advent of HAART. Long-term HAART therapy causes pigmentation, xerostomia and angular cheilitis. So we conclude that recognition, significance and treatment of the oral lesions in patients with HIV infection can be treated with basic primary health care.

INTRODUCTION:

The pandemic disease HIV/AIDS has become a human and social disaster, particularly in resource limited settings. Recently reported by the Government of India, our country has the third largest of people living with HIV/AIDS. It is estimated that a total of 23.9 lakh people is affected with this virus. The populations mostly affected were adults, and an estimated 0.8% of adults worldwide are suffering with this deadly virus. Age group that was most commonly affected was found to be 15-49 years. There has also been a regional disparity in the prevalence of this fatal disease with the Southern states being among the top with a high number of reported cases[6].

Highly active antiretroviral therapy (HAART) is now a standard treatment for HIV infection. A marked reduction in viral load and increase in the CD4+ cell count after initiation HAART leading to a declination in morbidity and mortality of HIV-infected patients. The development of HAART after 1995, has significantly modified the course of HIV disease, at least in the industrialized world, into a manageable chronic disease with longer survival and improved quality of life in HIV-infected subjects. HAART generally consists of a dual nucleoside analogue reverse transcriptase inhibitor (NRTI) backbone" and a third or "cornerstone" drug, such as a nonnucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor, usually a "boosted" one. The use of an NNRTI as a third drug is less potent and, therefore, in most settings not a preferred option and it is recommended that baseline resistance testing should guide the specific regimen design[7].

The fundamental factor to be considered to reduce the mortality and morbidity rates for patients with HIV is early diagnosis and determining the features with prognostic significance. In this regard oral lesions of AIDS have played a very significant role and many authors have studied the same and have concluded that some of the oral lesions have both diagnostic and prognostic values. The more common of the oral lesions that occur along with HIV are the candidiasis, hyperpigmentation, angular cheilitis, gingivitis, peridontitis, aphthous ulcers, herpes simplex infections and oral hairy leukoplakia. Among these oral candidiasis is of significance as far as prognostic indicators of immune-suppression are concerned[8,9,10,11].

HAART has played an important role in reducing the occurrence of the oral lesions in patients has been described by various authors. One study by Patton et al. noted a reduction of oral lesions from 47.6% prepotent ART to 37.5% during the potent ART era[3]. Nicolatou-Galitis *et al.*, in a study observed that patients under HAART had a significantly reduced occurrence of oral lesions especially oral candiadiasis[12]. Similarly, studies conducted by Tamí-Maury *et al.*, Eweka *et al.*, and Hodgson *et al.*, have shown that the occurrence of, angular cheilitis and periodontitis are reduced with patients on HAART[13,14,15]. All these studies have been conducted in the population of the western world and there have been very limited studies conducted in the rural southern Indian population. Hence, we conducted a study to analyze the effects of HAART on the oral lesions of patients with HIV in rural part of South India.

MATERIALS AND METHODS:

This study was done in District Hospital, KOPPAL, Karnataka. Fifty patients were randomly chosen who were diagnosed as HIV positive and were on HAART therapy, who are visiting outpatient department / ART centre of District Hospital KOPPAL for regular follow-up. All the patients were examined for their oral lesions, current CD4 counts and duration of the HAART therapy.

The patients who were in the window period and not on HAART therapy were excluded from this study. We also excluded the patients with co-infection of tuberculosis, having chronic liver disease, active hepatitis, pregnant women and pediatric patients.

All the findings were tabulated and the results were analyzed using measures of central tendency. The subjects were grouped according to the status of CD4 count and duration of HAART received as follows:

The CD4 counts which were recorded were divided into under three ranges:
1. CD4 count <350
2. CD4 count between 350 and 500
3. CD4 count >500.

The duration of the HAART therapy was also divided into two ranges:
1. HAART therapy >2 years
2. HAART therapy between 6 months to 2 years.

RESULTS:

Out of 50 adult study subjects, 32(64%) were male and 18(36%) were female. The mean age of the subjects is 38.6 years. The incidence of oral lesions observed are, melanin pigmentation (30%), oral candidiasis(08%), gingivitis(08%), xerostomia(06%) and combination of the same [Table 01].

The relation of oral lesion with the CD4 count is tabulated in Table 02. In the subgroup of subjects with CD4 count <350 (52% of the study subjects), melanin pigmentation was present in 15.38%, oral candidiasis in 11.53%, xerostomia in 7.69% and gingivitis in 7.69%.

Volume - 7 | Issue - 4 | April-2017 | ISSN - 2249-555X | IF : 4.894 | IC Value : 79.96

The combination of lesions melanin pigmentation and gingivitis is seen in 23.07 % and melanin pigmentation and xerostomia is seen in 19.23% of the study group.

In the subgroup of subjects with CD4 count between 350 and 500 (40% of the study subjects), melanin pigmentation was seen in 45%, oral candidiasis in 5%, xerostomia in 5%, gingivitis in 10%, and while 15% of these subjects had no oral lesions.

In the subgroup of subjects with CD4 count more than 500 (08% of the study group), 50% showed melanin pigmentation and the rest had combination of the lesions along with melanin pigmentation.

Table 03 shows the relation between HAART duration and the prevalence of the oral lesions in HIV infected patients of our study. In patients with HAART between 6 months and 2 years, oral melanin pigmentation was the commonest

DISCUSSION:

Human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) is a spectrum of conditions caused by infection with the human immunodeficiency virus (HIV). HIV is a retrovirus that primarily infects components of the human immune system such as $CD4^+$ T cells, macrophages and dendritic cells. It directly and indirectly destroys $CD4^+$ T cells. The mechanism of $CD4^+$ T cell depletion differs in the acute and chronic phases. During the acute phase, HIV-induced cell lysis and killing of infected cells by cytotoxic T cells accounts for $CD4^+$ T cell depletion, although apoptosis may also be a factor. During the chronic phase, the consequences of generalized immune activation coupled with the gradual loss of the ability of the immune system to generate new T cells appear to account for the slow decline in $CD4^+$ T cell numbers. HIV-positive patients with CD4+ lymphocyte counts less than 200 cells/ml are severely immune compromised and the HIV-positive patient with viral load greater than 10,000 copies/ml show active viremia and are more prone for many opportunistic infections.

According to UNAIDS/WHO (2016 update) report there are about 36.7 million people are living with HIV infection. As per the recently released annual report from NACO, India HIV Estimation 2015 report, National adult (15–49 years) HIV prevalence in India is estimated at 0.26% (0.22%– 0.32%) in 2015. In 2015, adult HIV prevalence is estimated at 0.30% among males and at 0.22% among Females. Among the States/UTs, in 2015, Manipur has shown the highest estimated adult HIV prevalence of 1.15%, followed by Mizoram (0.80%), Nagaland (0.78%), Andhra Pradesh & Telangana (0.66%), Karnataka (0.45%), Gujarat (0.42%) and Goa (0.40%). Besides these States, Maharashtra, Chandigarh, Tripura and Tamil Nadu have shown estimated adult HIV prevalence greater than the national prevalence (0.26%), while Odisha, Bihar, Sikkim, Delhi, Rajasthan and West Bengal have shown an estimated adult HIV prevalence in the range of 0.21– 0.25%. All other States/UTs have levels of adult HIV prevalence below 0.20%.

Oral lesions have been reported to be early clinical features of HIV infection (Greenspan et al., 1992)[16]. They are multiple and varied, and are occasionally the first sign that patients harbor the virus. Studies have estimated that more than 90% of persons with HIV infection will have at least one oral manifestation during the course of their disease (Weinert et al., 1996)[17]. These lesions may be present in up to 50% of people with HIV infection and in up to 80% of those with a diagnosis of AIDS (Palmer et al., 1996)[18]. In cases where a person's HIV status is unknown the lesions provide a strong indication of the presence of HIV infection (Maeve et al., 2005)[19]. Some of these lesions may have a predictive value, warning of a progression from HIV seropositivity to clinically manifest as AIDS. They are often indicators of immune suppression and can be used for early testing, diagnosis and management of patients with HIV/AIDS (Scully et al., 1991; Arendorf et al., 1998; Agbelusi and Wright, 2005)[20,21,22]. Oral lesions in HIV may serve as markers for immune deterioration and disease progression and may also indicate poor prognosis (Adurogbangba et al., 2004)[23].

Among many oral lesions, the cardinal lesions strongly associated with AIDS are: oral candidiasis, kaposi's sarcoma, hairy leukoplakia, linear gingivial erythema, necrotizing ulcerative gingivitis, necrotizing ulcerative periodontitis and non-Hodgkin's lymphoma[18].

The patients who are on HAART will also show some common secondary manifestation like oral melanotic pigmentation, which is one of the physiologic manifestations. The possible reason for the occurrence of this pigmentation may be the increased release of melanocyte stimulating hormone due to deregulated release of cytokines in HIV and use of melanocyte stimulating drugs like certain antiviral or antifungal agents and Addison's disease.

Oral cadidiasis is strongly associated with a low CD4 count, OC occurred in as many as 90% of patients before introduction of HAART. The prevalence of OC among patients who receive antiretroviral treatment is 50% lower compared to the prevalence before HAART era.

The next finding seen was xerostomia. The protein inhibitors drugs in HAART therapy can reduce salivary flow rates and also have a role to play in salivary gland enlargement in HIV-positive patients. The ART drugs could cause cumulative damage that affects the amount of salivary flow. Xerostomia may be a side effect of drugs or may be due to the proliferation of CD8+ cells in salivary glands. This may be a factor responsible for dental decay in HIV patients on longstanding HAART. Gingivitis is seen due to reduced CD4 counts leading to susceptibility to opportunistic infections.

In our study melanin hyper pigmentation [Image 1] is most common (30%) oral lesion which may present as isolated lesion or it may coexist with other oral lesions like, xerostomia, candidiasis and with many other. In the study conducted by Patil[24] et al and Satyakiran GV[25] et al also shown that the melanin hyper pigmentation is the commonest in their study. While Hamza[26] et al and Ranganathan[27] et al reported this lesion as 2nd and 3rd most common in their study. This study also reveals that the prevalence of melanin hyper pigmentation increases with increase in duration of HAART.

The next common findings in our study are oral candidiasis [Image 2], gingivitis [Image 3] and xerostomia (6%). Even though the prevalence of these lesions are similar in this study, the important point to be notice is that their incidence decreases as the duration of HAART increases and with the increase in CD4 count.

One more interesting factor observed in our study is that the many oral lesions can coexist together.

With the advent of highly active antiretroviral therapy (HAART) for HIV patients the CD4 count is increasing and the viral load is decreasing and thus the decrease in opportunistic infection. The same is true for the prevalence of oral lesions[4]. Life expectancy is also gradually increasing in HIV infected patient[28]. The study of Umadevi[29] et al, also shows decrease in prevalence of oral lesions with the initiation of HAART.

CONCLUSION:

The prevalence of oral lesions associated with HIV infection tends to decrease with increase in CD4 count. Except melanin hyper-pigmentation, other oral lesions decrease with increase in duration of HAART.

Overall prevalence of oral lesion in rural population is more compared to urban population because of poor oral hygiene, less awareness of disease and the treatment options.

Since our study is from very minute fraction of the total HIV patients, we do advice for further larger population based study.

Table 01: Prevalence of oral lesions:

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Oral lesions	Number of patients
With no lesions	05 (10%)
Melanin pigmentation	15 (30%)
Xerostomia	03 (06%)
Gingivitis	04 (08%)
Oral candidiasis	04 (08%)
Melanin pigmentation + Gingivitis	08 (16%)
Melanin pigmentation + Xerostomia	07 (14%)
Melanin pigmentation + Xerostomia + Gingivitis	01 (02%)
Melanin pigmentation + Xerostomia + Gingivitis + Oral candidiasis	01 (02%)
Gingivitis + Oral candidiasis	02 (04%)

Table 02: relation between CD4 count and oral lesions:

Oral lesions	CD4 <350 (26= 52% of the study subjects)	Cd4 350- 500 (20= 40% of the study subjects)	CD4 >500 (04= 08% of the study subjects)
With no lesions	02 (7.69%)	03 (15%)	00
Melanin pigmentation	04 (15.38%)	09 (45%)	02 (50%)
Xerostomia	02 (7.69%)	01 (05%)	00
Gingivitis	02 (7.69%)	02 (10%)	00
Oral candidiasis	03 (11.53%)	01 (05%)	00
Melanin pigmentation + Gingivitis	06 (23.07%)	02 (10%)	00
Melanin pigmentation + Xerostomia	05 (19.23%)	02 (10%)	00
Melanin pigmentation + Xerostomia + Gingivitis	00	00	01 (25%)
Melanin pigmentation + Xerostomia + Gingivitis + Oral candidiasis	01 (3.84%)	00	00
Gingivitis + Oral candidiasis	01 (3.84%)	00	01 (25%)

Table 03: Percentage distribution of oral lesions in study patients with different duration of highly active antiretroviral therapy (n=50).

Oral lesions	HAART between 6 months and 02 years (21= 42% of the study group)	HAART more than 02 years (29=58% of the study group)
With no lesions	02 (09.52%)	03 (10.34%)
Melanin pigmentation	06 (28.57%)	09 (31.03%)
Xerostomia	02 (09.52%)	01 (03.45%)
Gingivitis	01 (04.76%)	03 (10.34%)
Oral candidiasis	02 (09.52%)	02 (06.89%)
Melanin pigmentation + Gingivitis	03 (14.28%)	05 (17.24%)
Melanin pigmentation + Xerostomia	02 (09.52%)	05 (17.24%)
Melanin pigmentation + Xerostomia + Gingivitis	01 (04.76%)	00
Melanin pigmentation + Xerostomia + Gingivitis + Oral candidiasis	01 (04.76%)	00
Gingivitis + Oral candidiasis	01 (04.76%)	01 (03.45%)

Image 1: Oral melanin hyper-pigmentation:

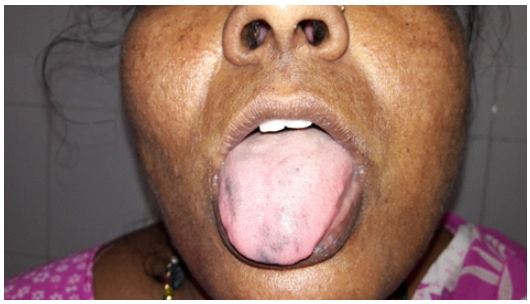


Image 2: Oral Candidiasis:

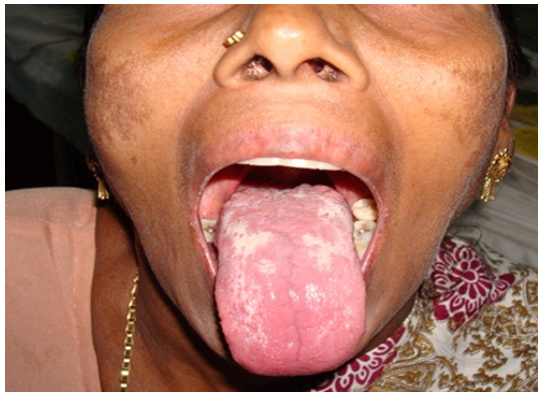
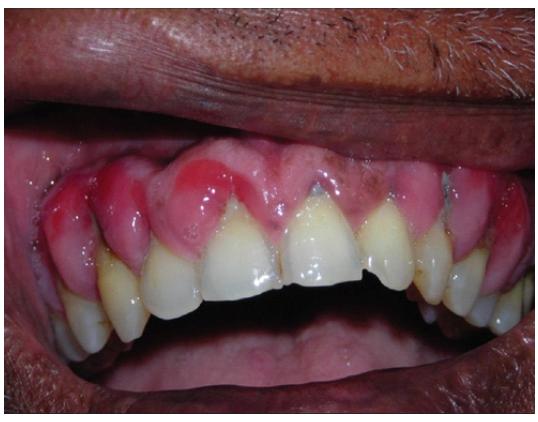


Image 3: Gingivitis



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