

Correlation between oral lesions and opportunistic infections among human immunodeficiency virus – infected individuals in Indian population

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ABSTRACT

Background: Human immunodeficiency virus (HIV) infection is a major global health problem. Tuberculosis and cryptococcal meningitis are the leading cause of death among people living with HIV.

Aim: The purpose of this study was to determine whether any relationship exists between the occurrence of oral lesions and opportunistic infections among HIV-infected patients in Indian population.

Materials and methods: A cross-sectional analytical study was performed in 232 HIV-infected persons (148 males and 84 females, aged 20–60 years, mean 33.6 ± 2.3 years). χ^2 test and logistic regression were used for statistical analysis.

Results: Oral candidiasis was the most common oral lesion seen in 28.4% males and 22.6% females of HIV-infected persons, followed by hairy leukoplakia in 27% males and 20.2% females which was statistically significant. Tuberculosis (21.6%) followed by cryptococcosis (9.9%) and pneumocystis carinii pneumonia (4.7%) were the most commonly found opportunistic infections. Logistic regression analysis revealed a significant association, between the occurrence of tuberculosis and candidiasis (OR 2.3; 95% CI 1.4–2.9), cryptococcosis and candidiasis (OR 1.4; 95% CI 1.0–1.9), and pneumocystis carinii pneumonia with hairy leukoplakia (OR 1.6; 95% CI 1.0–2.9). Mean CD4 count was also less.

Conclusions: The results suggest a definite relationship in occurrence of oral lesions and opportunistic infections among HIV-infected patients.

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Key words: HIV-infected patients, cross sectional study, CD4 counts, opportunistic infections, tuberculosis

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is an infectious disease caused by the human immunodeficiency virus (HIV), and is characterised by profound immunosuppression that leads to opportunistic infections, secondary

neoplasm and neurologic manifestations along with oral manifestations [1]. The magnitude of this modern plague is truly staggering. Already, more than 30 million people around the world have died of AIDS-related diseases [2]. In 2010, 2.7 million people were newly infected with HIV,



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and 1.8 million men, women and children died of AIDS-related causes. Thirty four million people around the world are now living with HIV [3]. In 2009 it was estimated that 2.4 million people were living with HIV in India, which equates to a prevalence of 0.3% [4]. While this may seem low, because India's population is so large, it is third in the world after South Africa and Nigeria in terms of greatest number of people living with HIV [5]. With a population of around a billion, a mere 0.1% increase in HIV prevalence would increase the estimated number of people living with HIV by over half a million.

People with advanced HIV infection are vulnerable to infections and malignancies that are called 'opportunistic infections' (OI) because they take advantage of the opportunity offered by a weakened immune system. There are many types of OI. Tuberculosis (TB) and a serious related disease, *Mycobacterium avium* complex (MAC), are bacterial infections. Viral infections include cytomegalovirus (CMV) and hepatitis C, fungi causing thrush (candidiasis), cryptococcal meningitis, *Pneumocystis carinii* pneumonia and histoplasmosis, and parasites causing cryptosporidiosis and toxoplasmosis [6].

Tuberculosis is the leading cause of death among people living with HIV. Almost 1 in 4 deaths among people with HIV is due to TB. In 2010, 350,000 people died of HIV-associated TB. It is also the most common presenting illness among people living with HIV, including those who are taking antiretroviral treatment. There were an estimated 1.1 million HIV positive new TB cases globally in 2010. At least one-third of the 34 million people living with HIV worldwide are infected with TB. Persons co-infected with TB and HIV are 21–34 times more likely to develop active TB disease than persons without HIV [7].

Cryptococcal meningitis has been reported as the most common OI of the central nervous system of Indian patients with HIV infection [8]. Mortality from developed countries, secondary to HIV associated cryptococcal meningitis is in the range of 10–30% while in developing countries the mortality rate is substantial, around 13–40% because of late presentation, limited access to antifungal therapy, and inability to adequately monitor intracranial pressure among many other reasons [9]. The reported prevalence of *Pneumocystis jirovecii* pneumonia is much lower outside the United States among the approximately 38 million AIDS-infected individuals worldwide. In Africa, *Pneumocystis jirovecii* pneumonia occurs in only 9% of individuals with AIDS [10].

Oral manifestations can be the first clinical sign of the infections and also determine the progression of disease. Awareness of the variety of oral disorders which can develop throughout the course of HIV infection and coordination of health care services between a physician and a dentist may improve the overall health of the patient [11]. We performed

a task to check comprehensive literature but could not find any Indian study for association of oral manifestations with OI among HIV-infected individuals. Since the oral manifestations of HIV are common and can be considered as indicators of systemic diseases, the present study was carried out to investigate if there was a relationship between oral manifestations and OI among HIV-positive patients in Indian population.

MATERIALS AND METHODS

STUDY DESIGN AND STUDY POPULATION

This cross-sectional analytical study was conducted over 1-year period from January 2012 to December 2012. 232 HIV-infected persons (148 males and 84 females, aged 20–60 years, mean 33.6 ± 2.3 years) were selected from those attending the outpatient department according to criteria.

Inclusion criteria

Patients had to satisfy all of the following inclusion criteria: (1) HIV-infection as documented by positive HIV ELISA (Merind Diagnostics, Belgium) and Western Blot (Biotechnology kit, Singapore); (2) Ability and willingness of subject to understand study requirements and give written informed consent.

Exclusion criteria

Subject were considered ineligible for the study if any of the following criteria/s were satisfied: (1) Patients who had any systemic disease other than HIV; (2) Patient who were suffering from any psychological disorders; (3) Pregnant and lactating females; (4) Patients who were not willing for participation.

Ethical considerations

The research was conducted in full accordance with the World Medical Association Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Ethical Committee (A5368U10/22/12/2011). Written informed consent was obtained from all the study participants after explaining the nature and purpose of research.

Methodology

Sociodemographic data (age, gender, educational status, occupation and adverse oral habits) were obtained using a structured questionnaire. The source of infection was determined by asking the patients by indirectly questioning about their behaviour depending on condition and categorising them into different groups. The stage of HIV infection was categorised as: asymptomatic, symptomatic and AIDS according to the World Health Organisation (WHO)

clinical staging criteria. Immune status was determined by performing the absolute CD4 lymphocyte counts using flow cytometry (SRL, Ranbaxy laboratories, Mumbai) within 2 weeks of the oral examination. WHO proposed the immunological classification on the basis of CD4 count as none or not significant – Group 1 (> 500/mL), mild – Group 2 (350–499/mL), advanced – Group 3 (200–349/mL) and severe – Group 4 (< 200/mL) [11]. Medication taken by patients was assessed from patient's medical records.

A single trained dental surgeon with a physician performed clinical oral examination and systemic examination, respectively, and recorded the findings on presence of oral lesions and OI. Intra-oral examination was performed using disposable mouth mirrors, sterile gauze pads and incandescent head-mounted light. The oral lesions were diagnosed according to the criteria established by the European Commission Clearinghouse (presumptive approach) and WHO [12]. The following criteria were used to define common OI: pulmonary TB: clinical features suggestive of TB with radiological features compatible with TB on chest radiograph or computed tomographic (CT) scan and/or demonstration of acid-fast bacilli in sputum smears or growth of *Mycobacterium* TB in sputum culture. Cryptococcal meningitis was defined as a clinical feature of meningitis/meningoencephalitis along with positive cerebrospinal fluid (CSF) cryptococcal antigen test or positive CSF India ink preparation or isolation of *Cryptococcus neoformans* in the CSF culture. *Pneumocystis jiroveci* pneumonia: bilateral, diffuse interstitial infiltrates on chest radiograph or high-resolution CT, with hypoxemia ($\text{PaO}_2 < 12 \text{ kPa}$) and sputum smears/cultures negative for aerobic bacteria and acid-fast bacilli and/or demonstration of *pneumocystis jiroveci* in induced sputum. Tissue biopsy procedure was performed for diagnosing oral hairy leukoplakia.

STATISTICAL ANALYSIS

The data obtained were analysed using SPSS (Statistical Package for Social Sciences) version 15.0 (SPSS Inc., Chicago, Illinois, USA). A χ^2 test of association was used to find out the association between variables. Logistic regression with odds ratio (OR) and 95% confidence interval (CI) were calculated for all infections. A p-value of < 0.05 was considered statistically significant.

RESULTS

Table 1 shows the sociodemographics of 232 enrolled HIV seropositive patients. 148 (63.8%) were males and 84 (36.2%) were females with a male to female ratio of 1.8:1. The maximum number of cases in males was in the 30 to 40 years age group, while for females it was the 20 to 30 years age group (48.6% and 54.8%, respectively). The difference observed was statistically significant. A greater percentage

(40.5%) of the population in both age groups had education up to primary school only which was statistically not significant. A statistically significant association was found with the presence of HIV among truck drivers (32.4%) in males and housewives (71.4%) in females. Around 70% were smokers, 50% tobacco chewers, 58.1% alcohol drinkers and 60.8% with combination of habits in males when compared to less than 10% prevalence of all these habits in females.

The main source of infection for both males and females (93.2% and 89.3%, respectively) was through the heterosexual route (Table 2), followed by infection via blood transfusion (2.7% in males and 3.6% in females). Table 3 shows the prevalence of HIV-related oral lesions by gender. Of the 232 patients, 19.39% (25 males, 20 females) had no oral lesions. More males (83.1%) than females (76.2%) had oral lesions and this was statistically significant. Oral candidiasis was the most common oral lesion seen in 28.4% males and 22.6% females of HIV infected persons, followed by hairy leukoplakia in 27% males and 20.2% females which was statistically significant. Other lesions found among the study subjects which were statistically significant include pseudomembranous and erythematous candidiasis, necrotizing ulcerative gingivitis, necrotizing ulcerative periodontitis and linear gingival erythema. The odds were almost two times higher in males than females for candidiasis and multiple oral manifestations. It was 4.2% more in males for hairy leukoplakia. This difference was statistically significant. The CD4 count was also assessed for 232 HIV-positive patients. The mean CD4 count of these patients was found to be 201 cells/mm³ (males = 82 cells/mm³ and females = 119 cells/mm³) (SD = 100 cells/mm³).

Table 4 shows the prevalence of HIV-related OI by gender. Of 232 (63,79%) patients (91 males, 57 females) were not affected with OI. More males (38.5%) than females (32.1%) had OI and this was statistically significant. Tuberculosis was the most common OI seen in 28.4% males and 19% females. This higher prevalence in males was statistically significant. Other OI include cryptococcosis (10.1% males and 9.5% females) and *pneumocystis carinii* pneumonia (5.4% males and 3.6% females). This difference observed between the genders with higher prevalence in males was statistically significant. The odds were 2.2, 1.5 and 1.1 times higher in males than females for TB, cryptococcosis and *pneumocystis carinii* pneumonia, respectively.

Logistic regression analysis of the association, between the occurrence of oral lesions and OI is shown in Table 5. The occurrence of TB was found to be significantly associated with the presence of oral candidiasis (OR 2.8; 95% CI 1.2–3.5); whereas the occurrence of *pneumocystis carinii* pneumonia was significantly associated with the presence of oral hairy leukoplakia (OR 1.6; 95% CI 1.0–2.9). There also seemed to be an association between the occurrence of TB

Table 1. Sociodemographic characteristics of the study population

Variable	Male	Female	Total	P
Age group:				
20–30	51 (34.5%)	46 (54.8%)	97 (41.8%)	0.005*
30–40	72 (48.6%)	31 (36.9%)	103 (44.4%)	
40–50	23 (15.5%)	06 (7.1%)	29 (12.5%)	
50–60	2 (1.4%)	1 (1.2%)	3 (1.3%)	
Educational status:				
No formal education	16 (10.8%)	22 (26.2%)	38 (16.4%)	0.231
Primary school	60 (40.5%)	34 (40.5%)	94 (40.5%)	
Secondary school	47 (31.8%)	18 (21.4%)	65 (28%)	
College	25 (16.9%)	10 (11.9%)	35 (15.1%)	
Occupation:				
Business	28 (18.9%)	1 (1.2%)	29 (12.5%)	0.001*
Commercial sex worker	2 (1.4%)	10 (11.9%)	12 (5.2%)	
Truck driver	48 (32.4%)	–	48 (20.7%)	
Healthcare worker	2 (1.4%)	1 (1.2%)	03 (1.3%)	
Housewife	–	60 (71.4%)	60 (25.9%)	
Labourer	31 (20.9%)	7 (8.3%)	38 (16.4%)	
Farmer	30 (20.2%)	1 (1.2%)	31 (13.4%)	
Unemployed	3 (2.0%)	2 (2.4%)	5 (2.2%)	
Student	2 (1.4%)	2 (2.4%)	4 (1.7%)	
Others	2 (1.4%)	–	2 (0.9%)	
Adverse oral habits:				
Smokers	102 (68.9%)	2 (2.4%)	104 (44.8%)	0.07
Tobacco chewers	74 (50%)	8 (9.5%)	82 (35.3%)	
Alcohol consumption	86 (58.1%)	1 (1.2%)	87 (37.5%)	
Combined habits	90 (60.8%)	6 (7.1%)	96 (41.4%)	
Total (n = 232)	148 (63.8%)	84 (36.2%)	232 (100%)	

Test applied: Chi-square/Fischer's exact test; *p ≤ 0.05 (statistically significant)

Table 2. Distribution of HIV-positive patients according to source of infection

Source of infection	Male (n = 148)	Female (n = 84)	Total (n = 232)
Heterosexual	138 (93.2%)	75 (89.3%)	213 (91.8%)
Homosexual	1 (0.7%)	–	1 (0.4%)
Intravenous drug use	2 (1.4%)	–	2 (0.9%)
Blood transfusion	4 (2.7%)	3 (3.6%)	3 (1.3%)
Vertical transmission	–	3 (3.6%)	3 (1.3%)
Needle prick injuries	1 (0.7%)	1 (1.2%)	4 (1.7%)
Unknown	2 (1.4%)	2 (2.4%)	6 (2.6%)

and angular cheilitis (OR 1.8; 95% CI 1.1–2.9; p < 0.003). Cryptococcosis infection was also found to be significantly associated with the presence of oral candidiasis (OR 1.4; 95% CI 1.0–1.9).

DISCUSSION

People living with HIV in India come from incredibly diverse backgrounds and cultures. In the present study the maximum number of cases belonged to the second and

Table 3. Prevalence of HIV-related oral lesions according to gender

Oral lesions	Male (n = 148)	Female (n = 84)	Total (n = 232)	Odds ratio	95% CI
Group I: Lesions most commonly associated with HIV infection					
Any oral manifestation†	123 (83.1%)	64 (76.2%)	187 (80.6%)	2.1*	1.38–4.65
Oral candidiasis	42 (28.4%)	19 (22.6%)	61 (26.3%)	2.0*	1.42–2.93
Pseudomembranous	31 (20.9%)	11 (13.1%)	42 (18.1%)	1.6*	1.23–4.32
Erythematous	6 (4.1%)	2 (2.4%)	8 (3.4%)	1.7*	0.94–3.98
Hyperplastic	3 (2%)	1 (1.2%)	4 (1.7%)	0.9	0.40–2.05
Angular cheilitis	12 (8.1%)	3 (3.6%)	15 (6.5%)	1.8	0.97–2.06
Oral hairy leukoplakia	40 (27%)	17 (20.2%)	57 (24.6%)	4.2*	1.60–8.30
Necrotizing ulcerative gingivitis	6 (4.1%)	3 (3.6%)	9 (3.9%)	1.2*	0.72–2.04
Necrotizing ulcerative periodontitis	7 (4.7%)	1 (1.2%)	8 (3.4%)	1.6*	1.26–6.82
Linear gingival erythema	33 (22.3%)	16 (19%)	49 (21.1%)	1.6*	1.09–2.32
Group II: Lesions less commonly associated with HIV infection					
Melanotic hyperpigmentation	37 (25%)	15 (17.9%)	52 (22.4%)	1.4	0.86–2.12
Xerostomia	2 (1.4%)	1 (1.2%)	3 (1.3%)	0.7	0.44–1.65
Herpes zoster	1 (0.7%)	–	1 (0.4%)	0.7	0.24–2.26
Group III: Lesions associated with HIV infection					
Recurrent aphthous ulcers	7 (4.7%)	5 (6%)	12 (5.2%)	0.8	0.35–1.63

†Many patients had more than one oral manifestation; *indicates statistical significance at $p < 0.05$; CI – confidence interval

Table 4. Prevalence of opportunistic infections according to gender

Opportunistic infections	Male (n = 148)	Female (n = 84)	Total (n = 232)	Odds ratio	95% CI
Tuberculosis	34 (28.4%)	16 (19%)	50 (21.6%)	2.2*	1.60–3.29
Cryptococcosis	15 (10.1%)	8 (9.5%)	23 (9.9%)	1.5*	1.12–2.32
<i>Pneumocystis carinii</i> pneumonia	8 (5.4%)	3 (3.6%)	11 (4.7%)	1.1*	0.72–2.04

*Indicates statistical significance at $p < 0.05$; CI – confidence interval

third decades. HIV and AIDS affect all segments of India's population, from children to adults, businessmen to homeless people, female sex workers to housewives, and gay men to heterosexuals. There is no single 'group' affected by HIV. However, HIV prevalence among certain groups (sex workers, injecting drug users, truck drivers, migrant workers, men who have sex with men) remains high and is currently around 6 to 8 times that of the general population [13]. Oral manifestations were seen more in smokers (68.9%) which may be attributed to particulate matter, noxious chemicals, and heat that can modify more local factors. Similarly oral manifestations were more prevalent in tobacco chewers and alcohol drinkers (50% and 58.1%, respectively). No statistical significance was also observed for individual oral manifestations with gender, smoking, tobacco chewers and alcohol ($p > 0.05$).

In the study, the source of infection was mainly heterosexual (92%). The vast majority of infections occur through heterosexual sex (80%), and is concentrated among high

risk groups including sex workers, and injecting drug users as well as truck drivers and migrant workers. According to Joint United Nations Programme on HIV/AIDS (UNAIDS), there has been improvement over time. Between 1996 and 2010 the rate of new HIV infections fell by 56% [14]. This trend is mainly due to a drop in infections in southern states; in other areas there has been no significant decline.

The occurrence of oral manifestations is favoured by immune deterioration. The overall prevalence of HIV-related oral lesions in the study was 80.6%. These finding was similar to studies conducted in Thailand (77%) [15] and Nigeria (84%) [16]. In another Indian study the prevalence of oral manifestations were seen in 72.3% patients [17]. A statistically significant higher prevalence of oral lesions was observed in males (83.1%) than females (76.2%). This finding is similar to other studies where males had more oral manifestations [17–19]. In the present study, the most common oral manifestation of HIV-infected patients was candidiasis (26.3%).

Table 5. Logistic regression analysis between oral lesions and opportunistic infections among HIV-infected subjects

Opportunistic infections	Odds ratio	95% CI
Tuberculosis		
Any oral lesions	2.8*	1.2–3.5
Candidiasis	2.3*	1.4–2.9
Angular cheilitis	1.8*	1.1–2.9
Hairy leukoplakia	1.2	1.7–3.3
Linear gingival erythema	0.9	0.6–1.8
Cryptococcosis		
Any oral lesions	1.1	0.7–2.5
Candidiasis	1.4*	1.0–1.9
Angular cheilitis	0.7	0.2–0.9
Hairy leukoplakia	0.5	0.2–1.1
Linear gingival erythema	0.5	0.2–0.9
<i>Pneumocystis carinii</i> pneumonia		
Any oral lesions	1.3	0.6–2.1
Candidiasis	1.5	0.7–2.3
Angular cheilitis	0.8	0.2–1.2
Hairy leukoplakia	1.6*	1.0–2.9
Linear gingival erythema	0.7	0.4–1.6

*Indicates statistical significance at $p < 0.05$; CI – confidence interval

In accordance with oral hairy leukoplakia, there are no as such symptoms associated with the lesion itself, although varied signs and symptoms may be associated with the underlying cause of immunosuppression. The lesion is a white patch, which almost exclusively occurs on the lateral surfaces of the tongue, although rarely it may occur on the buccal mucosa, soft palate, pharynx or oesophagus. The lesion may grow to involve the dorsal surface of the tongue. The texture is vertically corrugated (“hairy”) or thickly furrowed and shaggy in appearance. Oral hairy leukoplakia was observed in 24.6% patients. This figure is higher to studies conducted by Laurengo and Figueiredo (11.8%) and Pedreira et al. (9%) [20–22]. Previous studies, however, reported pseudomembranous candidiasis as the most common oral manifestation [23]. Even the recent studies have indicated a definite relationship between pseudomembranous candidiasis (mostly erythematous) and progressing HIV infection [23, 24]. The prevalence of pseudomembranous candidiasis is only 18.1% in the present study. This difference can be due to differences in the prescribed medications, the stages of the disease or the way of transmission of the infection. Also pseudomembranous and erythematous candidiasis are supposed to be better markers of immune suppression than any other oral lesions as indicated by Bodhade et al. [25].

Opportunistic infections were once the leading cause of HIV/AIDS-related morbidity and mortality, but widespread use of highly active anti-retroviral therapy and OI prophylaxis has been highly effective in reducing the incidence of such infections [26]. Tuberculosis (21.6%) was the most common OI in the study population. This was significantly less than the 32% reported in a study on south Indian population [17]. Patients who had oral candidiasis were 2.3 times at higher risk of having TB which was statistically significant. This is similar to the report from De Cock et al. (1992) [27] and Nittayananta et al. (2002) [18] where a significant association between the occurrence of oral candidiasis and TB was observed. In Asia, a region with 60% of the world’s population and 72% of the global TB burden, HIV has been advancing rapidly in recent years, threatening a resurgence of TB [28]. HIV-infected individuals with hairy leukoplakia had 1.6 times higher risk of having *pneumocystis carinii* pneumonia. The significant association between oral candidiasis and hairy leukoplakia with the occurrence of TB and *pneumocystis carinii* pneumonia suggests that these two oral lesions may be used as clinical indicators for prophylaxis against the diseases.

The fact that oral candidiasis and hairy leukoplakia can be readily detected by trained clinicians in a standardised, objective fashion without complicated or expensive diagnostic techniques, further increases their utility [29]. An early and timely diagnosis will help in improved treatment planning and prognosis of patients.

CONCLUSIONS

The results indicated that among the patients being infected HIV, there exists a relationship between the occurrence of oral lesions and OI. So, diagnosis of oral lesions is of utmost importance to help identify the underlying or predisposing diseases, if any. Frequent follow up of such patients may be required.

Physicians and other clinicians providing care for HIV-infected individuals should be trained in the diagnosis of oral lesions so that counselling and medical management can be improvised. Dentists with regular intraoral examinations at frequent intervals can play a small but significant role of ensuring an effective integrated delivery of health services for HIV-infected patients. This can occur only if there is joint action/strategy between health care providers and various HIV-related government as well as non-government organisations.

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