

Oral Manifestations of Human Immunodeficiency Virus (HIV)-infected Patients in Singapore

A A T Lim,*^{BDS, MDS, FRACDS}, Y S Leo,**^{FAMS, M Med (Int Med), MRCP (UK)}, C C Lee,***^{FAMS, M Med (Int Med), MRCP (UK)},
A N Robinson,****^{BDS, MSc (Lond), FRACDS}

Abstract

Introduction: Oral lesions have been recognised as prominent features of acquired immune deficiency syndrome (AIDS) and human immunodeficiency virus (HIV) infection since the beginning of the epidemic. **Objective:** This descriptive study was conducted to study the types of oral lesions among HIV-infected patients in Singapore. **Materials and Methods:** Oral examination was done on 81 randomly selected HIV-infected patients attending the specialist outpatient clinic at the Communicable Disease Centre. **Results:** A total of 9 different lesions were observed in 45 (56%) patients. The lesions observed were oral candidosis (35%), periodontal disease (16%), aphthous-like ulcers (5%), oral hairy leukoplakia (5%) and lymphoma (1%). **Conclusion:** The oral manifestations of HIV-infected patients in Singapore appear to be less frequent in comparison with those patients from Africa and Europe. Similarities in oral findings among the HIV-infected patients in Asia are evident with a notable lack of oral Kaposi's sarcoma (KS) and a low prevalence of non-Hodgkin's lymphoma and oral hairy leukoplakia.

Ann Acad Med Singapore 2001; 30:600-6

Key words: AIDS, Hairy leukoplakia, Oral candidosis, Oral lymphoma

Introduction

The spread of human immunodeficiency virus (HIV) disease has pursued a relentless course since it was first recognised in the early 1980s and if current trend continues, it is most likely to carry on well into the 21st century. Asia and South Asia are expected to shoulder the greatest burden of this pandemic.^{1,2} Currently, an estimated 6 to 7 million adults and children live with HIV/acquired immune deficiency syndrome (AIDS) in South and Southeast Asia. High transmission rates of new infections have been reported from many developing countries including India, Thailand and Myanmar. The more developed countries in this region such as Japan, Hong Kong, Korea and Singapore have also shown a steady increase in the number of HIV cases.³

Since the description of AIDS, there have been numerous research and clinical studies worldwide on HIV-associated oral lesions. HIV-related oral lesions have been documented since the start of the AIDS epidemic in 1981.⁴ Many studies on the oral manifestations in patients with HIV/AIDS have

been published from the United States, Europe, the United Kingdom and Africa. There is also an increase in data from Asian countries⁵⁻⁸ but there is none from Singapore as yet. Hence, the aim of this descriptive study was to assess the prevalence of oral lesions among HIV-infected patients in Singapore.

Singapore is a multi-racial country with a population of about 3.8 million. Chinese make up the largest racial group (77%), followed by the Malays (14%), Indians (7.6%) and other races (1.4%).⁹ The first case of HIV infection was reported in 1985 and figures for HIV infection in Singapore have been increasing at a rate of about 20% per annum since 1990. By the end of September 1999, the total cumulated HIV/AIDS cases of patients with HIV/AIDS stood at 1080. The majority of the patients infected were males (male to female ratio was 8:1). The main mode of transmission was sexual (heterosexual 72%, homosexual 14%, bisexual 11%), 21 cases (1.9%) were attributed to injecting drug use (IDU), 3 cases were from blood

* Senior Registrar
Department of Oral and Maxillofacial Surgery
National Dental Centre

** Clinical Director

*** Consultant
Department of Infectious Diseases

Communicable Disease Centre, Tan Tock Seng Hospital

**** Private Practice

Address for Reprints: Dr Asher Ah-Tong Lim, Department of Oral and Maxillofacial Surgery, National Dental Centre, 5, Second Hospital Avenue, Singapore 168938.

transfusion, 5 cases resulted from renal transplants (performed overseas) and 9 paediatric cases were reported from perinatal transmission.¹⁰

Materials and Methods

The study group consisted of 81 HIV-infected patients randomly selected from the pool of patients attending the specialist outpatient clinic at the Communicable Disease Centre (CDC), Tan Tock Seng Hospital, Singapore. This study was conducted at the CDC, which is the national referral centre for all infectious diseases and manages more than 90% of all patients with HIV infection in Singapore. This study was conducted over a period of 9 months.

Oral screening was conducted when these patients attended the outpatient clinic at CDC for review and blood tests by the infectious disease physicians. Oral examination was done by a dental surgeon trained in oral medicine. Patients' consent was obtained before oral screening. The investigator was blinded from the patient clinical stage of HIV disease at the time of screening. The diagnosis and classification of the oral lesions followed the criteria set forth by EC-Clearinghouse.¹¹

Oral lesions were mostly diagnosed by clinical examination, smears/swabs and biopsy were performed when necessary. Tissue biopsies were done at the Department of Oral and Maxillofacial Surgery, National Dental Centre. All other necessary information including demographic data, medical history, social history, CD4+ counts and medications were obtained from the patients' medical records. SPSS version 8 was used to find out the significance of anti-retroviral therapy (ART) on oral lesions.

Results

The demographic and clinical characteristics of the study group are shown in Table I. The sample consisted of 81 patients, 75 (93%) were males. The median age was 39 years (range 20 to 81 years). The majority of the patients in our study were ethnic Chinese (88%). Out of the 81 patients, 73% of the patients examined had CD4 counts less than 200 cells/uL. Using the revised CDC classification of 1993, 72% were in category C, 17% in category B and 11% in category A. About half of the patients were on ART (42 patients; 52%). Twenty-three patients were taking only nucleoside analogues, 18 patients were taking nucleoside analogue together with a protease inhibitor and 1 patient was taking a non-nucleoside analogue with a protease inhibitor. Among the 42 patients, 19 were taking at least one protease inhibitor. The most common opportunistic infections among these patients were *Pneumocystis carinii* pneumonia (27 patients; 33%), followed by tuberculosis (19 patients; 24%). None of these patients were actively infected at the time of oral examination. Table II shows the

TABLE I: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF STUDY GROUP (n = 81)

Age (years)	
Mean	42.7
Median	39
Range	20 to 81
Gender	
Male	75 (93%)
Female	6 (7%)
Ethnic group	
Chinese	71 (88%)
Malay	6 (7%)
Indian	3 (4%)
Others	1 (1%)
Risk group	
Heterosexual	63 (78%)
Homosexual	12 (15%)
Bisexual	3 (4%)
Intravenous drug users	3 (4%)
CDC classification	
A	9 (11%)
B	14 (17%)
C	58 (72%)
CD4+ count	
less than 200	59 (73%)
200 to 499	21 (26%)
more than 500	1 (1%)
Anti-retroviral therapy	
With	42 (52%)
Without	39 (48%)

prevalence of oral lesions observed in this cohort. A total of 9 different types of lesions/conditions were observed in 45 (56%) of the 81 patients. Thirty-eight (84%) of these 45 patients had CD4 counts below 200 cells/uL. Eighteen (40%) of these 45 patients were on ART; with 8 taking at least one protease inhibitor. Out of the 36 patients without oral lesions, 24 (67%) were on ART; with 11 taking at least 1 protease inhibitor. Twenty-seven (60%) out of the 45 patients with oral lesions were not on ART.

Oral candidosis (Figs. 1 to 5) was the commonest oral mucosal lesion (35%), followed by periodontitis (Fig. 6) (16%), aphthous-like ulcers (Fig. 7) (5%), oral hairy leukoplakia (Fig. 8) (OHL) (5%), oral pigmentation (4%) and xerostomia (3%). Pseudo-membranous candidosis was the commonest form of oral candidosis. All 18 patients with oral candidosis had CD4+ counts below 200 cells/uL. Only 1 individual out of the 81 cases screened had bilateral swelling of the parotid glands (Fig. 9) with xerostomia.

A total of 3 tissue biopsies were performed. Patient A presented with a large ulcerative mass on the right buccal mucosa and oral pseudomembranous candidosis. Patient B had a white adherent lesion with striations on the left buccal mucosa. Patient C presented with a purplish-red macular

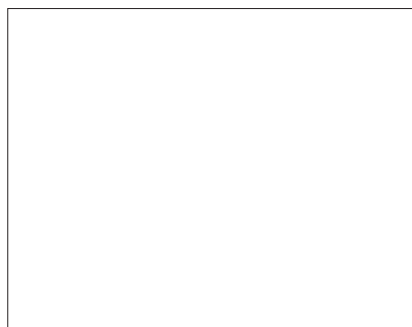


Fig. 1. Oral candidosis—Pseudomembranous candidosis over the hard and soft palate.

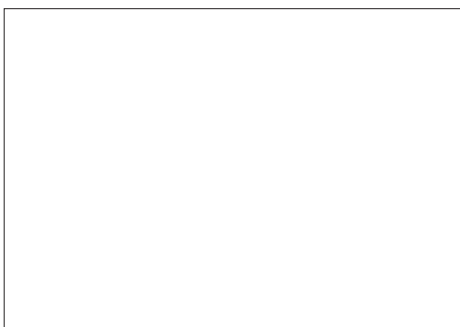


Fig. 2. Oral candidosis—Pseudomembranous candidosis over the lower mucosa and tongue.

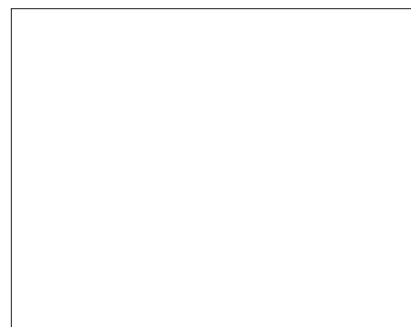


Fig. 3. Oral candidosis—Erythematous candidosis over the palate.



Fig. 4. Oral candidosis—Angular cheilitis.



Fig. 5. Oral candidosis—Angular cheilitis.

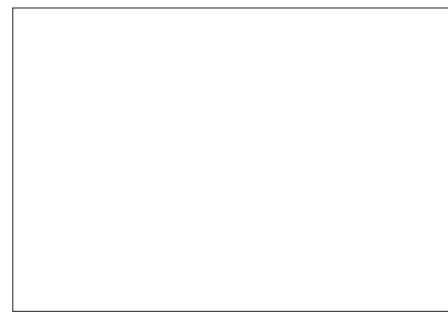


Fig. 6. Necrotising ulcerative periodontitis.



Fig. 7. Aphthous-like ulceration over the tongue.



Fig. 8. Oral hairy leukoplakia over the lateral border of the tongue.



Fig. 9. Parotid gland enlargement of a HIV-infected patient.



Fig. 10. Oral non-Hodgkin's lymphoma of patient A—ulceration over the right buccal mucosa.

lesion at the palatal mucosa adjacent to the upper left second and third molar. Interestingly, patient C also had previous cutaneous Kaposi's sarcoma on his shoulder and hip. Histopathological examination of the three biopsies from patients A, B and C revealed non-Hodgkin's lymphoma (Fig. 10), leukoplakia and a pigmented lesion caused by haemosiderin deposits, respectively.

Table III shows the results of the statistical analysis using SPSS version 8. There was no statistical significance in the age, gender and CD4 count when the sample is categorised according to their ART status. The analysis showed that those not on ART were 3 times (95% CI, 1.2 to 7.5; $P = 0.017$) more likely to have oral lesion when compared to those on ART. Performing a logistic regression forward fit on oral lesion using age, sex, CD4 count and ART, only CD4 count ($P = 0.009$; OR = 0.993; 95% CI, 0.992 to 0.999) and ART ($P = 0.031$; OR = 2.9; 95% CI, 1.1 to 7.6) were significant variables. The higher the CD4 count, the less likely the patient will have oral lesions. Adjusting for CD4 ($P = 0.14$), the ART option was still significant ($P = 0.0395$; OR = 2.75; 95% CI, 1.05 to 7.18). The results showed no statistical significance in the prevalence of oral lesion when comparing those on ART with and without protease inhibitor.

TABLE II: THE PREVALENCE OF ORAL LESIONS IN THE HIV STUDY GROUP

	Number (%) (n = 81)	On ART	Not on ART	CD4+ count 200 to 499	CD4+count <200
Angular cheilitis	5 (6)	2	3	2	3
Pseudomembranous candidiasis	18 (22)	4	14		18
Erythematous candidiasis	5 (6)	3	2	1	4
Oral hairy leukoplakia (OHL)	4 (5)	2	2	1	3
Aphthous-like ulcer	4 (5)	1	3		4
Oral hyperpigmentation	3 (4)	3	0	1	2
Non-Hodgkin's lymphoma	1 (1)	0	1		1
Periodontitis	13 (16)	6	7	1	12
Xerostomia	2 (3)	1	1		2
Other lesions—salivary gland swelling	1 (1)	1	0	1	0

ART: anti-retroviral therapy

TABLE III: CD4 READINGS AND ORAL LESIONS BY TREATMENT GROUPS

Anti-retroviral therapy (ART)	No ART (n = 39)	ART without protease inhibitor (n = 23)	ART with protease inhibitor (n = 19)	
Max	81	66	63	
CD4 count				
Mean $\pm$ SD	109.49 $\pm$ 164.72	138.30 $\pm$ 129.96	122.47 $\pm$ 122.89	
Min	4	5	3	ns**
Max	777	342	343	
CD4				
Below 200	33	15	13	
200 to 499	5	8	6	ns*
500 or more	1	0	0	
Oral lesion				
No	12	13	11	
Yes	27	10	8	P = 0.058*
		Combining the Yes and Yes with protease inhibitor		
No	12		24	
Yes	27		18	P = 0.017*

*Chi-square test; ** Anova; ns: not significant

Discussion

The sample consisted of 78% heterosexuals. With such high proportion of the sample being heterosexual, one would expect a more even distribution in terms of gender. However, the male to female ratio in this sample was 12.5:1. In Singapore, many of the heterosexual males are single (never-married or divorced) and have contracted HIV-infection through commercial sex either locally or overseas. This may explain why there is a discordant figure relative to the high percentage of heterosexual and a low number of HIV-infected females both in Singapore and in this sample. It was difficult to recruit a large sample size as many of the HIV-infected have low priority for oral care.

The range of oral lesions noted in our study group is similar to those reported from other countries.^{5-8,12-15} Nevertheless, the prevalence of oral lesions differs

especially when compared to the West (Table IV and V).

Oral candidosis was the most common oral lesion (35%) in our study group, in accordance with other studies worldwide.^{5,6,12-15} Nevertheless, the prevalence of this lesion was one of the lowest among some recent Asian studies (Table V), although rather similar figures were reported in a Malaysian study.⁸ Pseudomembranous candidosis was the predominant form of candidosis presenting in 18 of our patients, all of whom had CD4 counts less than 200 cells/uL. Indeed, it is generally accepted that the pseudomembranous form of candidosis (thrush) is associated with severe/advanced HIV disease.^{13,16}

Recent reports appear to suggest a decrease in prevalence of oral lesions for those on ART.¹⁷⁻²¹ A recent study by Patten²¹ showed the prevalence of certain HIV-associated oral lesions had decreased significantly as the use of

TABLE IV: THE PREVALENCE OF ORAL LESIONS AS REPORTED BY VARIOUS STUDY GROUPS

Oral lesion	Study group			
	United States ¹² n = 238	United Kingdom ¹³ n = 120	Greek ¹⁴ n = 160	South Africa ¹⁵ n = 600
Oral candidiasis	20%	47%	61%	37.8%
Oral hairy leukoplakia	26.5%	27%	24%	19.7%
Non-Hodgkin's lymphoma	0.8%	0	0	0.5%
Kaposi's sarcoma	1.7%	15%	12%	1.5%
Aphthous ulcer	4.2%	7%	4%	2.9%
Xerostomia	7%	nr	26%	0
Periodontal disease	8.8%	6%	19%	8.5%

TABLE V: THE PREVALENCE OF ORAL LESIONS IN HIV-INFECTED PATIENTS IN ASIA

Oral lesion	Study group				
	Malaysia ⁸	India ⁵ (n = 96)	Thailand ⁶ (n = 124)	Hong Kong ⁷ (n = 32)	Singapore (n = 81)
Oral candidiasis	35.9%	55.7%	66%	12.4%	34.6%
Oral hairy leukoplakia	2.8%	2%	13%	11%	4.9%
Non-Hodgkin's lymphoma	0	0	4%	0	1.2%
Kaposi's sarcoma	0	0	0	0	0
Aphthous-like ulcer	nr	3%	11%	27.4%	4.9%
Xerostomia	nr	nr	nr	17.8%	2.5%

nr: not recorded

protease inhibitor became more widespread. Two groups of HIV-infected patients were examined; the first, when protease inhibitor had just been introduced and the other group during the later period when protease inhibitors were used more extensively. Statistically significant reductions in the prevalence of OHL and HIV-associated periodontal disease were noted. Smaller reductions in the prevalence of oral candidiasis, aphthous ulcers and Kaposi's sarcoma were also observed. Nevertheless, there was a significant increase in HIV salivary gland disease. In this study, among those without oral lesions and on ART, 11 (46%) out of 24 were taking protease inhibitor. Among those with oral lesions and on ART, 10 (56%) out of 18 were not taking protease inhibitor. This observation does not support the impression that protease inhibitor decreases the frequency of oral lesion. Statistical analysis showed that protease inhibitor did not significantly decrease the prevalence of oral lesion. However, with a small sample number, these observations are not conclusive. It is necessary to conduct more clinical studies with a larger sample size before a conclusion can be made.

OHL was seen in only 4 (5%) of our study patients, a relatively low figure when compared to other recent Asian studies.⁵⁻⁸ Three of these patients had CD4 count less than 200 cells/uL; 2 were on ART and 1 had a CD4 count more than 200 cells/uL. OHL was first described by Greenspan et al in 1981.²² The appearance of OHL in HIV-infected patients is associated with a more rapid progression of the

disease to AIDS.^{13,16} Since its identification, it has been ascertained that hairy leukoplakia is caused by infection of the lesional epithelium in the Epstein-Barr virus (EBV).²² However, the exact pathogenicity of EBV in hairy leukoplakia is still not established. It is interesting to note that despite of the fact that this is a region where EBV prevalence and chronic EBV-related disease is high, the number of OHL seen in this study is lower than expected. Generally, Western literature have reported a higher prevalence of OHL, ranging from 24% to 27%¹²⁻¹⁵ as compared to a range of 2% to 13%⁵⁻⁸ reported in Asian studies. It is unclear why the prevalence of this lesion in our study patients is so low even though 73% of this sample has CD4 counts less than 200 cell/uL. It could be that OHL may be "subclinical", and not detected as few biopsies were done.

Oral Kaposi's sarcoma is one of the lesions strongly associated with HIV infection.¹¹ However, in our study, none of our patients had oral KS, a similar observation among the other Asian studies (Table IV). Oral KS has traditionally been more common among the HIV-infected homosexual/bisexuals in United States, Europe and Africa.²³⁻²⁵ In this study, the patients consisted mainly of heterosexual males (78%), which may explain why no oral KS was observed. In a 1998 annual report on infectious diseases in Singapore,¹⁰ among the HIV-infected patients presenting with AIDS, only 3.5% (17 out of 486 patients) had KS (non-oral KS). The low incidence of oral KS and

KS in the Asian population may be related to the low prevalence of human herpes virus-8 (HHV-8) in the South-east Asian population. Indeed, a recent report²⁶ has shown a low prevalence of HHV-8 in both the healthy and HIV-infected population in Malaysia, Sri Lanka and Thailand when compared with similar population groups in the United States, Africa and the Caribbean.

Patient A, as mentioned previously, presented with an oral non-Hodgkin's lymphoma as the first manifestation of HIV infection and also the first AIDS-defining condition. This 60-year-old Chinese male was referred to the National Dental Centre by a private general dental practitioner for the management of a large ulcerative mass at the right aspect of his cheek mucosa. Biopsy revealed a large B-cell malignant lymphoma. Underlying HIV infection was suspected because of his HIV-associated risk factors. He was referred to the CDC, where he was tested positive for HIV. His CD4 count at that time was 40 cells/uL. Further staging revealed dissemination of the lymphoma to the central nervous system (pons). Both lesions responded extremely well to chemotherapy. This patient was still alive 17 months after the diagnosis of his oral non-Hodgkin's lymphoma in August 1998. He is currently on ART and his latest CD4 count has risen to more than 200 cells/uL. The prevalence of oral lymphoma in Asian HIV-infected patients is generally low. No oral lymphomas was reported in 2 recent studies on HIV-infected patients among ethnic Chinese in Hong Kong⁷ and Malaysia.⁸ In a Thai study,⁶ 5 out of the 124 patients with AIDS (4%) presented with oral lymphomas (all were small cell Burkitt's lymphoma). All the patients were adult males who presented with gingival masses and tooth mobility.

Advanced periodontal disease was relatively common in our study group (16%). The majority of our patients had poor oral hygiene, a notable exception being the homosexual group. Severe periodontal disease, especially of the "necrotising ulcerative periodontitis" type, is associated with severe immunosuppression.²⁷ According to EC-Clearing house,¹¹ periodontal disease [linear gingival erythema (LGE), necrotising/ulcerative gingivitis, necrotising/ulcerative periodontitis] is strongly associated with HIV infection. None of the patients in this study had LGE. This study concurs with studies conducted in India⁵ and Thailand⁶ which showed periodontal disease as the second most common oral lesion in the HIV-infected patients. The prevalence of periodontal disease varies greatly from country to country; 7% in Thailand, 16% in Singapore and 55.7% (LGE and periodontitis) in India. Studies from the United States²³ and the United Kingdom¹³ reported periodontal disease to be a less common lesion with a prevalence of 8.8% and 6%, respectively. The wide variations in prevalence could be attributed to the different

diagnostic criteria employed. Moreover, clinically similar lesions can occur in the non-HIV infected patients.

In conclusion, the oral manifestations of HIV-infected patients in Singapore are reported, noting a lack of oral KS and a low prevalence of non-Hodgkin's lymphoma and OHL. These findings are in accordance with other Asian studies.⁵⁻⁸ However, in the Western studies¹²⁻¹⁴ there was a higher prevalence of KS and OHL. This variation warrants further investigation. Recent reports appeared to suggest a significant reduction in HIV-related oral lesions, with the use of ART (in particular with the use of protease inhibitors); although this cannot be concluded from this current study. It is important to note that HIV infection may manifest in the oral cavity as the various types of oral lesions. It is well documented in the literature that oral cavity may show some of the first signs of HIV infection.^{23,28} Thus, clinicians, especially the dental surgeons, may be able to aid in the early diagnosis of HIV infection in an unknown case, including children.²⁹

Acknowledgements

The authors would like to express their thanks to Dr Chan Yiong Huak, Senior Medical Statistician of the Clinical Trials and Epidemiology Research Unit, Ministry of Health, Singapore for his advice on the statistical analysis of the results. We would also like to thank the National Dental Centre for funding part of this study.

REFERENCES

1. Quinn T C. Global burden of the HIV pandemic. *Lancet* 1996; 348: 99-106.
2. Fauci A S. The AIDS epidemic. *N Engl J Med* 1999; 341:1046-50.
3. World Health Organisation 1999. Global AIDS Surveillance. *Wkly Epidemiol Rec* 1999; 4:402-4.
4. Gottlieb M S, Schroff R, Schantz H M. *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. *N Engl J Med* 1981; 305:1425-31.
5. Ranganathan K, Reddy B V R, Kumarasamy N, Solomon S, Viswanathan R, Johnson N W. Oral lesions and conditions associated with human immunodeficiency virus infection in 300 south Indian patients. *Oral Dis* 2000; 6:152-7.
6. Nittayananta W, Chungpanich S. Oral lesions in a group of Thai people with AIDS. *Oral Dis* 1997; 3(suppl 1):S41-5.
7. Samaramayake L P, Tsang P C S. Oral manifestations of HIV infection in a group of predominantly ethnic Chinese. *J Oral Pathol Med* 1999; 28:122-7.
8. Jing W, Ismail R. Mucocutaneous manifestations of HIV infection: a retrospective analysis of 145 cases in a Chinese population in Malaysia. *Int J Dermatol* 1999; 38:457-63.

9. The People. Singapore: Ministry of Information and Arts, 1999:42-8.
10. Communicable Disease Centre. Tan Tock Seng Hospital Annual Report. Singapore: TTSH, 1998.
11. EC-Clearinghouse on oral problems related to HIV infection and WHO Collaborating Centre on oral manifestations of human immunodeficiency virus. Classification and diagnosis criteria for oral lesions in HIV infection. *J Oral Pathol Med* 1993; 22:289-91.
12. Patton L L, McKaig R G, Strauss R P, Eron Jr J J. Oral manifestations of HIV in a southeast USA population. *Oral Dis* 1998; 4:158-65.
13. Palmer G D, Robinson P G, Challacombe S J, Birnbaum W, Croser D, Erridge P L. Aetiological factors for the oral manifestations of HIV infection. *Oral Dis* 1996; 2:193-7.
14. Lasuaris G, Hadjiuassilio U M, Stratigo S. Oral signs and symptoms in 160 Greek HIV-infected patients. *J Oral Pathol Med* 1992; 21:120-3.
15. Arendorf T M, Bredekamp B, Cloete C A C, Sauer G. Oral manifestations of HIV infection in 600 South African patients. *J Oral Pathol Med* 1998; 27:176-9.
16. Greenspan J S. Sentinels and signposts: the epidemiology and significance of the oral manifestations of HIV disease. *Oral Dis* 1997; 3 (suppl 1):S13-7.
17. Margiotta V, Campisi G, Mancuso S, Accurso V, Abbadessa V. HIV infection: Oral lesions, CD4+ cell count and viral load in an Italian study population. *J Oral Pathol Med* 1999; 28:173-7.
18. Aguirre J M, Echebarria M A, Ocina E. Reduction of HIV-associated oral lesions after highly active anti-retroviral therapy. *Oral Surg Oral Med Oral Pathol* 1999; 88:114-5.
19. Dizdios P, Ocampo A, Miralles C, Otero I, Iglesias I, Rayo N. Frequency of oropharyngeal candidiasis in HIV-infected patients on protease inhibitor therapy. *Oral Surg Oral Med Oral Pathol* 1999; 87:437-41.
20. Mood S, Bonnington A, Evans J, Denning D. Reduction in oropharyngeal candidiasis following introduction of protease inhibitors. *AIDS* 1998; 12:447-8.
21. Patten L L, McKaig R, Strauss R, Rogers D, Eron J J. Changing prevalence of oral manifestations of human immunodeficiency virus in the era of protease inhibitor therapy. *Oral Surg Oral Med Oral Pathol* 2000; 89:299-304.
22. Greenspan D, Greenspan J S, Conant M, Petersen L, Silverman S, De Souza Y. Oral "hairy" leukoplakia in male homosexuals: evidence of association with both papillomavirus and a herpes-group virus. *Lancet* 1984; 2:831-4.
23. Friedman R B, Gunsolley J, Gentry A I. Periodontal status of HIV-seropositive and AIDS patients. *J Periodontol* 1991; 62:623-7.
24. Ficarra G, Eversole L E. HIV-related tumors of the oral cavity. *Crit Rev Oral Biol Med* 1994; 5:159-85.
25. Porter S R, Di Alberti L, Kumar N. Human herpes virus 8 (Kaposi's sarcoma herpes virus). *Oral Oncol* 1998; 34:5-14.
26. Ablashi D, Chatlynne L, Cooper H, Thomas D, Yadav M, Norhanom A W. Seroprevalence of human herpesvirus-8 (HHV-8) in countries of Southeast Asia compared to the USA, the Caribbean and Africa. *Br J Cancer* 1991; 81:893-7.
27. Lamster I B, Grbic J T, Bucklan R S, Mitchell-Lewis D, Reynolds H S, Zambon J J. Epidemiology and diagnosis of HIV-associated periodontal diseases. *Oral Dis* 1997; 3(suppl 1):S141-8.
28. Greenspan J J, Barr C E, Sciubba T J. Oral manifestations of HIV infection: Definitions, diagnostic criteria and principles of therapy. *Oral Surg Oral Med Oral Pathol* 1992; 73:142-4.
29. Ramos-Gomez F J. Oral aspects of HIV in children. *Oral Dis* 1997; 3(Suppl 1):S31-5.