Prevalence of oral and peri-oral lesions among a group of Saudi HIV-infected patients

Safia A. Al-Attas, MSc, FAAOM.

ABSTRACT

الأهداف : التحقيق في معدل انتشار آفات الفم وما حول الفم بين مجموعة من المرضى السعودين المصابين بفيروس نقص المناعة البشرية

الطريقة: أجريت دراسة مقطعية مراقبة خلال الفترة من نوفمبر 2012م حتى يونيو 2013م، وشملت 50 سعودياً مريضاً بفيروس نقص المناعة البشرية من مستشفى الملك فهد للقوات المسلحة و 100 أفراد اصحاء من جامعة الملك عبدالعزيز ، كلية طب الأسنان، خضع الجميع لكشف الفم التقليدي لتحديد الآفات المخاطية وفقا لتصنيف -EC ومنظمة الصحة العالمية.

النتائج: كشفت النتائج أن %68 من مجموعة فيروس نقص المناعة البشرية اصيبت بالآفات المتصلة بفيروس نقص المناعة مقارنة مع %4 في مجموعة المراقبة. لوحظ أن مظاهر فيروس نقص المناعة البشرية الفموية وما حول الفم الأكثر شيوعاً، والتي كانت تختلف إحصائياً بين المجموعتين، حسب الترتيب التنازلي كالتالي: زيادة التصبغات المخاطية 28 (%56)، الفطريات 7 (14%)، الشفاه الجافة / مخاطية جافة 6 (%11) وتورم الغدد اللعابية الكبرى من جانب واحد أو الثنائية 5 (%10) . الآفات الأخرى والغير متعلقة بفيروس نقص المناعة البشرية والأكثر في مجموعة فيروس نقص المناعة البشرية والأكثر في المتعلقة بفيروس نقص المناعة البشرية والأكثر في المتعلقة بفيروس نقص المناعة البشرية والأكثر في المتعلقة بفيروس نقص المناعة البشرية والأكثر في الطبيلة لمرضى فيروس نقص المناعة البشرية ولكن أظهرت النتائج أنه لم يلاحظ أي علاقات ذات دلالة إحصائية انه لم يلاحظ أي علاقات ذات الحرام.

الخاعمة : الآفات الفموية المخاطية واسعة الانتشار لدى المرضى المصابين بفيروس نقص المناعة البشرية، والتي تشير إلى أن المرضى الذين يعانون من فيروس نقص المناعة البشرية يجب أن يخصعوا إلى كشف فموي سريري دوري، والمرضى الذين يعانون من آفات الفم المتصلة بفيروس نقص المناعة البشرية.

Objectives: To investigate the prevalence of oral and peri-oral lesions among a group of Saudi human immunodeficiency virus (HIV)-infected patients.

Methods: A cross-sectional controlled study was conducted on 50 HIV-infected Saudi patients from

King Fahad Armed Forces Hospital, and 100 healthy individuals recruited from Faculty of Dentistry, King Abdulaziz University, Jeddah, Saudi Arabia between November 2012 to June 2013. All subjects underwent conventional oral examinations to identify mucosal lesions according to the EC-Clearinghouse/World Health Organization classifications.

Results: The findings revealed that 68% of the HIV group exhibited HIV-related lesions compared with 4% in the control group. The most commonly observed oral or peri-oral HIV manifestations, which were statistically different between the groups were in descending order, mucosal hyperpigmentation: 28 (56%), candidiasis: 7 (14%), dry lips/dry mucosa: 6 (12%), and unilateral or bilateral swelling of major salivary glands: 5 (10%). Other non HIV-related oral lesions that were reported more in the HIV group than the control group was coated tongue and leukoedema (p<0.05). The relationship of the reported HIV oral manifestations to demographic data, some relevant local and systemic risk factors, and medical characteristics of the HIV population were analyzed, however, the results showed no statistical significant relations were observed (*p*>0.05).

Conclusion: Oral mucosal conditions were highly prevalent in HIV-infected patients, which suggested that patients with HIV should undergo periodic oral examinations, and patients with HIV-related lesions should undergo screening tests for HIV infection.

Saudi Med J 2014; Vol. 35 (9): 1113-1119

From the Oral Medicine Division, Department of Oral Diagnostic Sciences, Faculty of Dentistry, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia.

Received 4th May 2014. Accepted 10th June 2014.

Address correspondence and reprint request to: Dr. Safia A. Al-Attas, Oral Medicine Division, Department of Oral Diagnostic Sciences, Faculty of Dentistry, King Abdulaziz University, PO Box 80209, Jeddah 2158, Kingdom of Saudi Arabia. Tel. +966 (12) 6401000 Ext. 23213. Fax. +966 (12) 6952847. E-mail: salattass@kau.edu.sa



since the onset of the human lobally, Jimmunodeficiency virus infection (HIV), millions of people have been infected with HIV and millions of patients have died of acquired immune deficiency syndrome (AIDS).1 According to the Joint United Nations Programme on HIV and AIDS (UNAIDS) and the World Health Organization (WHO), approximately 35.3 million people lived with the disease in 2012. The number has increased compared with the previous years, as more people were treated with the anti-retroviral drugs.^{1,2} Oral manifestations of HIV infection are found to be good markers of disease progression and immunosuppression.³ They could represent the initial signs of the infection. With early recognition and subsequent treatment, reduction in the disease morbidity and mortality is anticipated. Moreover, HIV-oral associated lesions correlated well with the CD4 cell count and viral load, and the latter are highly predictive markers of immune status and disease progression.⁴ The frequently encountered oral lesion in HIV infective patients were Candidal infections and oral hairy leukoplakia (OHL), especially among those not taking the highly active anti-retroviral drugs (HAART), and with low CD4 cell counts. However, in the literature, the prevalence of oral manifestations among HIV infective population showed a wide variation (9.5-99.5%). This was explained by the differences in study design, diagnostic criteria used, as well as variations in patient's age, gender, race, socioeconomic status, medication, risk behaviors, duration of HIV infection, and degree of immunosuppression.5-7 During the last few years, many researchers reported a change in the oral manifestations in the HIV populations. They recorded a reduction in AIDS-strongly-associated lesions, and the emergence of new types of lesions that are considered to be a side effect of HAART, or a type of immune reconstitution syndrome.³ The latter is a paradoxical transient deterioration of immune function during initial response to HIV medication.8 According to the Ministry of Health in Saudi Arabia, the reported number of HIV cases between 2000 and 2010 was mainly of non-Saudi than Saudi citizens.9 While in the last 10 years, there was a decrease in new HIV cases among non-Saudis, and an increase in new cases of Saudi HIV

Disclosure. Author has no conflict of interests, and the work was not supported or funded by any drug company.

with an incidence of 1.5/100,000/year among Saudis, and 1.2/100,000/year among non-Saudis.⁹ Also, over the last decade the male to female ratio was 4:1 among Saudi nationals, and almost 78.4% of HIV cases were infected through sexual intercourse.⁹ However, there is no published report in the oral manifestations of HIV among Saudi infected people. The objectives of this study were to investigate the prevalence of oral and peri-oral lesions among a group of Saudi HIV-infected patients, and to assess the relationship between the HIV associated lesions and demographic data, some local and systemic risk factors, medical history, and disease staging.

Methods. A cross-sectional controlled study was conducted between November 2012 to June 2013 on 50 Saudi HIV-positive patients and 100 healthy control subjects.

Sample size calculation. Assuming an expected prevalence of oral and peri-oral lesions among HIV cases of 50% with an allowable error of 11%, and 95% confidence level, the minimum required sample size was 78 cases. A total of 50 patients responded to examination (constituting 75% of the required sample size). For each case, 2 controls were selected. Post-hoc calculations of sample size for a case-control study with anticipated odds ratio of 3.5 and 15% prevalence among controls, 5% alpha error, and 80% power revealed that a sample of 50 cases and 100 controls is sufficient. The sample size calculation was performed using Epi-Info version 3.2.2 (CDC, Atlanta, USA).

Patients were recruited from the adult HIV clinic in King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia, and were seen during their routine follow up appointments. Their HIV status was already confirmed by ELISA and western blot tests. Consecutive eligible patients in the list present on the sampling day were invited to participate, and 75% of those invited agreed for an examination. Cases with active tuberculosis were excluded. Patients' hospital records and a structured questionnaire were used to obtain information regarding demographic data, presence of associated risk factors, such as tobacco and alcohol use, fillings and denture wearing, as well as, medical history including CD4 and CD8 cells counts and viral load, which were available within 2 weeks of oral examination. The control group comprised of 100 healthy Saudi subjects group matched for age group and gender collected from Faculty of Dentistry, King Abdulaziz University, Jeddah, Saudi Arabia including students and patients. All subjects voluntarily underwent conventional oral examination to identify possible mucosal lesions and dry mouth. An oral medicine consultant assisted by a specialist performed the examinations under incandescent headmounted light, using disposable mirrors in accordance with biohazard safety procedures. Oral manifestations were diagnosed according to EC-Clearinghouse/ WHO classifications,¹⁰ and OHARA case definitions.¹¹ Diagnosis was based on clinical presentation, as well as patient's history supplemented by biopsy when needed. The OHL was diagnosed clinically without biopsy.¹² The diagnosis of oral dryness was based on symptoms of oral dryness according to Bardow et al,¹³ and clinical observation of lip and oral mucosa dryness.¹⁴ All subjects in both groups gave informed signed consent prior to participation in the study. The ethics committee of the KAU Faculty of Dentistry approved the study protocol that was conducted according to the Principles of the Helsinki Declaration.

Data were analyzed using the Statistical Package for Social Sciences version 16 (SPSS Inc., Chicago, IL, USA). Descriptive statistics such as frequency and percentages were used. Independent t-tests were utilized to compare the means, and chi-square and Fisher's exact tests were used to analyze the qualitative variables. Oral lesions relationships to demographic data, local risk factors, tobacco and alcohol use habits, as well as medical history were evaluated. Pearson's correlation analysis was used to calculate any correlation between the oral lesions prevalence and disease characteristics (duration, viral load, CD4 count, CD8 count, and CD4/CD8 ratio). In all analyses, p<0.05 was considered statistically significant.

Results. The HIV group comprised 35 males (70%) and 15 females (30%), with a combined mean age of 39.7 years (range: 19-68 years). While the control group was composed of 68 males (68%), and 32 females (32%), and their mean age was 33.6 years (range: 19-70 years). As the data were collected only from the adult clinics, the absence of children cases is justified. Some relevant local and systemic oral mucosal health risk factors of the participants are summarized in Table 1. While there were no differences between the groups in brushing frequency (p=0.075), presence of fillings (p=0.192), or dentures (p=1.000), as well as, tobacco use habits (p=0.286), there was statistically significant difference between the groups regarding alcohol use with 8% of HIV cases consuming alcohol more than the controls (p=0.015). Medical characteristics of the HIV

 Table 1 - Participants' characteristics and behavior in a study conducted among HIV-positive patients and healthy control subjects.

Variables	HIV patients	Healthy subjects	P-value
	'n		
Tobacco use habits			
Yes	21 (42.0)	30 (33.0)	0.286
No	29 (58.0)	61 (67.0)	
Tobacco forms*			
Shisha	2 (4.0)	10 (11.0)	0.155
Moasel	1 (2.0)	8 (8.9)	0.111
Cigarettes	16 (32.0)	19 (20.9)	0.144
Chewing tobacco	2 (4.0)	1 (1.1)	0.287^{\dagger}
Khat	0 (0.0)	2 (2.2)	0.359
Do you brush your teeth?			
2-3 times daily	10 (20.8)	15 (39.5)	0.075
Once daily	15 (31.2)	13 (34.2)	
Rare/never	23 (47.9)	10 (26.3)	
Alcoholic drinks			
Yes	4 (8.0)	0 (0.0)	0.015^{+}
Presence of dentures			
Yes	2 (4.0)	2 (4.4)	1.000^{+}
Presence of fillings			
Yes	16 (32.0)	20 (22.0)	0.192
*percentage r	not equal to 100 d †Fisher's exa	ue to multiple respon ct test	ses.

 Table 2 - Medical characteristics of HIV patients according to a study conducted in Jeddah, Saudi Arabia.

Variables	Mean (SD)	Range			
Disease duration (years)	5.08	3 months - 22			
	(5.3492)	years			
Viral load (copies/mL)	3.61 x10 ⁴	0 - 590324			
	(120123.606)				
CD4 count (cells/mm ³)	405.14 (253.889)	7-1314			
CD8 count (cells/mm ³)	1.1203 x 10 ³	43-2344			
	(541.41548)				
CD4/CD8 ratio	0.4645 (0.53125)	0.06-3.34			
Medical status, n (%)					
Diabetes mellitus	10 (20.0)				
Hypertension	5 (10.0)				
Hypothyroidism	3 (6.0)				
Heart disease	2 (4.0)				
Medications, n (%)					
Nothing	4 (8.0)				
Combivir+Effavirenz	18 (36.0)				
Combivir+Kaletra	15 (30.0)				
Truvada+Effavirenz	3 (6.0)				
Combivir+Darunavir+Ritonavir	3 (6.0)				
Truvada+Darunavir+Ritonavir	2 (4.0)				
Truvada+ Kaletra	2 (4.0)				
Combivir+Atazanavir	1 (2.0)				
Tenofovir+Darunavir+Ritonavir	1 (2.0)				
Combivir	1 (2.0)				
HIV - human immunodeficiency virus					

group are summarized in Table 2. The mean duration of HIV infection was 5.08 years (range: 3 months-22 years), and the average viral load detected was 3.61 x 10⁴ copies/mL (range: 0-590324). Sixteen percent of the HIV-positive group has a viral load greater than 10,000 copies/mL. The CD4 cell counts ranged from 7-1314 cells/mm³ (mean: 405.14 cells/mm³). Twenty-two per cent had CD4 cell counts less than 200 cells/mm³. Most (24 [48%]) had CD4 cell counts between 200-500 cells/mm³. The test group had a mean CD4/CD8 ratio of 0.5. In comparison by gender, there was no statistically significant difference in the HIV group between the 2 genders regarding cell counts of CD4 (p=0.965) and CD8 (p=0.323), or viral load (p=0.125). Diabetes mellitus was the most frequent systemic disease present in 20% of the HIV patients, followed by hypertension, which occurred in 10% of the patients. Out of 50 HIV-infected patients, 46 (92%) received antiviral therapy, and 4 (8%) did not. Most (18

Table 3 - Prevalence of oral and peri-oral lesions among the HIV and controls groups according to a study conducted in Jeddah, Saudi Arabia.

Oral lesions	HIV patients	Healthy subjects	P-value Fisher's Exact test		
Pseudomembranous candidiasis	2 (4.0)	0 (0.0)	0.110		
Angular cheilitis	2 (4.0)	0 (0.0)	0.110		
Median rhomboid glossitis	2 (4.0)	0 (0.0)	0.110		
Atrophic candidiasis	1 (2.0)	0 (0.0)	0.333		
Any type candidiasis	7 (14.0)	0 (0.0)	0.000		
Hairy leukoplakia	1 (2.0)	0 (0.0)	0.333		
Linear gingival erythema	1 (2.0)	0 (0.0)	0.333		
Chronic periodontitis	4 (8.0)	9 (9.0)	0.837*		
Mucosal hyperpigmentations	28 (56.0)	0 (0.0)	0.000*		
Purpura/petechiae	2 (4.0)	1 (1.0)	0.258		
Unilateral or bilateral swelling of the major salivary glands	5 (10.0)	0 (0.0)	0.004		
Dry lips/dry mucosa	6 (12.0)	0 (0.0)	0.001		
Herpes labialis	1 (2.0)	1 (1.0)	1.000		
Recurrent aphthous stomatitis	0 (0.0)	2 (2.0)	0.553		
Lichenoid reactions/lichen planus	2 (4.0)	0 (0.0)	0.110		
Taste disturbances	1 (2.0)	0 (0.0)	0.333		
Oral submucous fibrosis	1 (2.0)	0 (0.0)	0.333		
Nicotine stomatitis	9 (18.0)	8 (8.0)	0.069*		
Smoker's melanosis	6 (12.0)	8 (8.0)	0.427		
Coated tongue	18 (36.0)	15 (15.0)	0.003*		
Leukoedema	8 (16.0)	2 (2.0)	0.001*		
Frictional keratosis	7 (14.0)	7 (7.0)	0.165*		
*Pearson's Chi-square test					

[36%]) were on the Combivir+Effavirenz combination, or were on a combination of Combivir+Kaletra (15 [30%]) (Table 2). Intra-oral examination revealed that a total of 102 soft tissue lesions were encountered among the HIV-infected group in contrast to 53 oral lesions found among the control group. While a total of 54 HIV-related lesions were diagnosed in 34 HIV patients (68%), only 4 subjects (4%) among the control group exhibited 3 HIV-related lesions. According to the results, 32% of the HIV patients did not show any HIV-associated manifestations, while 44% had at least one oral, or peri-oral manifestation, 12% had 2 conditions combined, and 12% had a combination of 3 or 4 different conditions. Comparison of the prevalence of oral or peri-oral lesions between the HIV patients and the control groups showed statistically significant differences between the groups, as indicated in Table 3. The most commonly observed oral or peri-oral HIV manifestations that were statistically different between the groups were, in descending order: mucosal bluish hyperpigmentations (28 [56%]); candidiasis (7 [14%]); dry lips/dry mucosa (6 [12%]), and unilateral or bilateral swelling of the major salivary glands (5 [10%]). Other non HIV-related oral lesions as reported statistically significant more in the HIV studied group than the control were coated tongue (p=0.003) and leukoedema (p=0.001). Most patients with oral or peri-oral HIV manifestations (52.9%) presented with 200-500 CD4 cells/mm³ count, whereas 20.6% of HIV patients who had less than 200 CD4 cells/mm³ count presented oral AIDS manifestations. Almost 94% of patients taking therapy presented with oral or peri-oral HIV manifestations as compared with 6% of patients not taking therapy. Among the therapy cases, the highest prevalence of manifestations was encountered in patients on Combivir+Effavirenz (41.2%), as well as Combivir+Kaletra (29.4%). While among the non therapy group, the highest prevalence of HIV-related lesions was in a newly diagnosed male patient who presented also with the lowest CD4 cell counts, and the highest viral load. The case was diagnosed with 4 different HIV-related lesions at the same time included mucosal hyperpigmentations, pseudomembranous candidiasis, dry mouth, and OHL.

The relationships of the reported HIV oral manifestations to demographic data, some relevant local and systemic oral health risk factors, and medical characteristics of the HIV population were analyzed. The results showed that patient's age, gender, presence of fillings or dentures, brushing frequency, tobacco, and alcohol use habits had no significant effects on lesions prevalence among the group (p>0.05). Likewise, no statistically significant relations were observed for individual oral manifestations with commonly used drugs (Zidovudine, Lamivudine, Ritonavir), disease characteristics, and medical history of diabetes, or hypertension. Moreover, there were no statistically significant correlations between the lesions' prevalence and HIV duration (p=0.48), CD4 counts (p=0.14), CD8 count (p=0.62), CD4/CD8 ratio (p=0.22), or viral load (p=0.15).

Discussion. The HIV associated oral lesions are well-known early markers of HIV infection and progression.^{15,16} According to WHO policy, prevention of HIV-associated oral disease is based on primary healthcare workers and oral health professionals involvement in the early detection and screening, as well as on oral disease prevention and oral health promotion integration into community and national HIV/AIDS programs.¹⁶ Many authors indicated that studying the prevalence of HIV oral manifestations in different regions of the world is important for better assessment of the problem, and to provide a scientific basis for proper actions.^{5,17} The current study investigated the prevalence of oral and peri-oral lesions among a group of Saudi HIV-infected patients in Jeddah city.

In the present study, the most common age of occurrence of HIV infection based on the group's mean age and disease duration was in the third decade of life with a male predilection. This agreed with several reports from many parts of the world, except an African report where females constituted a larger percentage.¹⁸ Ninety-two percent of the HIV studied group were on HAART. It is well-known that HAART helps in viral replication reduction, and CD4 cell count rise.¹⁶ The CD4 cell count and viral load are usually used to evaluate the immune status and disease staging.¹⁶ Interestingly in the studied sample, the lowest CD4 counts and highest viral load presented in a patient that had not started the treatment yet. In addition, only 22% of the HIV group had CD4 cell counts less than 200 cells/mm³, and 16% showed a viral load greater than 10,000 copies per milliliter that is suggestive of an advanced immunodeficiency, and an active viremia.¹⁹

Our results revealed that 68% of the HIV patients compared with 4% in the control group exhibited HIV/ AIDS-related oral- and peri-oral lesions. Comparable prevalence rates have been reported from several studies.^{20,21} However, the literature showed a wide range of prevalence in most reports all over the world $(9.5-99.5\%)^6$ The main reasons for this difference are variable sample size, stage of the disease, and degree of immunosuppression among other factors.¹⁷ Therefore, the present results agree with Davoodi et al¹⁷ in that comparing the reported prevalence of existing studies may not be very informative. More important is that, the studied HIV group showed the significantly highest prevalence of oral lesions, although the patients and the control groups were almost homogeneous based on their demographic data, local oral mucosal health risk factors, and smoking habits. Moreover, the results of a published study on oral mucosal lesions conducted on a Saudi population,²² showed that 15% of Saudi adult dental patients had oral mucosal lesions, which is still far less than the prevalence reported in the current study on the HIV group.²² Fortunately, with the introduction of HAART in HIV treatment, many authors reported a decrease in the prevalence of HIV/ AIDS oral manifestations,²³ but a recent review by Patton et al⁷ summarized that "the information derived from developing countries suggests that HIV-oral lesions continue to be significant".

According to our results, bluish hyperpigmentations, candidiasis, dry lips/dry mucosa, and unilateral or bilateral swelling of major salivary glands were reported in descending order with highest frequencies among the HIV group compared with the control group. Although the literature showed discrepancies in the sequence of most occurring lesions in the different populations, mucosal hyperpigmentation was the first,²⁴ or second prevalent oral lesion reported among the HIV patients receiving anti-retroviral therapy (ART)/HAART.^{23,25,26} Interestingly, one study indicated that a decrease in the prevalence of individual oral manifestations was observed among patients on ART therapy compared with the non-ART group except melanotic hyperpigmentation.⁶ The HIV hyperpigmentation has been reported among Indian, African, and Mexican studies.²⁷ The pathogenesis of the hyperpigmentation in HAART patients was linked with the increase of melanin production in the epithelium due to the release of a'-melanocytestimulating hormone (a'-MSH).²⁴ Zidovudine therapy is the most claimed drug found to be associated with mucosal hyperpigmentation.²⁵ Seventy-six percent of the current patients were on a HAART combination containing Zidovudine. However, in our sample, as well as others,²⁸ oral pigmentation has been recorded in individuals who were not on HAART medications. Thus, the etiology remains undetermined.

Oral candidiasis is the most reported oral lesion in HIV populations worldwide. The type of candidiasis reported more commonly among HIV adults patients is the pseudomembranous type, followed by erythematous candidiasis.5 However, erythematous candidiasis was recorded more frequently than the pseudomembranous type in our sample, similar to Gaurav et al's²⁶ report among HIV-infected population in southern India. Unilateral or bilateral parotid enlargement (10%) and dryness (12%) were found among our studied HIV sample. Salivary glands enlargement occurs frequently in HIV patients specially in children, and it could be the first clinical manifestation. The etiologies included reactive/inflammatory conditions, infections, and neoplasms.²⁹ Previous studies revealed that 10-15% of patients with HIV infection complained of xerostomia, and the reported causes usually were HIV gland disease, or medications side effects.6

Although some studies showed that low CD4 counts, or high HIV load, or low CD4/CD8 ratio and tobacco use are confirmed risk factors for oral manifestations in HIV infection,^{8,26} others reported statistically significant relationships of oral lesion prevalence with the presence of HIV-related systemic diseases,^{23,25} with an increase in duration of HIV infection,³⁰ with gender differences,^{3,4} and type of therapy.²³ However, on the other hand, some studies including our results failed to confirm such a relation.^{26,31}

Comparison of the prevalence of oral non-HIVrelated lesions between the groups revealed that coated tongue and leukoedema were found more among the HIV studied group than the controls. Although group comparisons did not yield a significant difference related to smoking, or brushing habits factors mostly associated with these common lesions in the normal population.^{32,33} We can say that the possible explanation for those lesions among the studied HIV group is multifactorial including, poor oral hygiene and tobacco use, dryness of the mouth, alcohol consumptions, and drugs.

The small study size and cross-sectional nature of the study are among the limitations of the research. Thus, the resulted data which are preliminary at best and need cautious interpretation, have to be confirmed in larger longitudinal population studies. Overall, oral and peri -oral lesions are common in the HIV-infected Saudi studied population, and the pattern of occurrence is not markedly different from those reported elsewhere. The occurrence of these common symptoms signifies a good reason for the Saudi government to incorporate oral health care into the national HIV/AIDS program. Therefore, dentists and the oral health profession have an active role in the early diagnosis, and management of these patients.

In conclusion, oral and peri-oral mucosal lesions were highly prevalent in patients with HIV infections. Thus, patients with HIV infection should undergo periodic oral examinations, and patients with HIV-related lesions should undergo screening tests for HIV infection.

Acknowledgments. The author gratefully acknowledges the administrators and staff in King Fahad Armed Forces Hospital, Jeddah for their help and assistance, with special thanks to Dr. Adnan Mushtag, Dr. Khawla Alshijary, and Dr. Abdallah AlJifry at the HIV clinic, and Dr. Ziad Rahbini in the Oral Surgery Department. Sincere thanks also to the Intern doctors: Maha Ismail, Dina Hammouda, Zainab Saati, and Doaa Al Ahdel for helping in participants' recruitment and recording.

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