J Oral Pathol Med (2007) 36: 136–41

www.blackwellmunksgaard.com/jopm

doi: 10.1111/j.1600-0714.2006.00505.x

# Oral lesions among persons with HIV disease with and without highly active antiretroviral therapy in southern India

**K. M. R. Umadevi[1], K. Ranganathan[1], S. Pavithra[1], R. Hemalatha[1], T. R. Saraswathi[1], N. Kumarasamy[2], Suniti Solomon[2], John S. Greenspan[3]**

[1]*Ragas Dental College and Hospital, Uthandi, Chennai;* [2]*YRG Centre for AIDS Research and Education, VHS, Chennai, India;* [3]*School of Dentistry, University of California, San Francisco, CA, USA*

**BACKGROUND: The advent of highly active antiretroviral therapy (HAART) has changed the scenario of human immunodeficiency virus (HIV) infection. HIV patients in India have now access to generic HAART and this is the first report describing oral lesions in patients on HAART from our country.**

**METHODS: Oral lesions were studied in HIV seropositive patients ($n = 50$ on HAART and $n = 50$ not on HAART) attending a tertiary HIV referral care centre in India and patients on HAART were followed up.**

**RESULTS: There was a difference in the occurrence of oral candidiasis (OC) between HAART and non-HAART participants (8%, 24%; $P < 0.05$). Pseudomembranous candidiasis was 4% and 18% in HAART and non-HAART groups respectively ($P < 0.05$). In patients with CD4 count ≤200, OC was 5.6% in the HAART group and 39.1% in the non-HAART group ($P < 0.05$). Among patients with CD4 count >200, pigmentation was 43.8% in the HAART group and 14.8% in the non-HAART group ($P < 0.05$).**

**CONCLUSION: The prevalence of OC in patients who had access to HAART was less when compared with those who did not have access to HAART.**

*J Oral Pathol Med* (2007) **36**: 136–41

**Keywords:** generic HAART; HIV; India; oral lesions

At the end of 2004, 95% of the 40 million people estimated to be infected with human immunodeficiency virus (HIV) infection in the world were in the developing countries (1). In India, the number of people living with HIV infection had reached 5.13 million by the end of 2004 (2).

The introduction of antiretroviral therapy (ART), especially combination therapy, highly active antiretroviral therapy (HAART), has led to a dramatic reduction in HIV morbidity and mortality in developed countries (3). People in the developing world are increasingly able to access antiretroviral drugs due to reduced cost and production by generic manufacturers. Indeed, generic HAART has reduced opportunistic infection morbidity and mortality (4).

Human immunodeficiency virus-related oral lesions are common and often an early finding in HIV infection (5, 6). Recognition of some oral manifestations of HIV disease notably oral candidiasis (OC) and oral hairy leukoplakia (OHL) is of significance because they are diagnostic and prognostic indicators of immunosuppression (7–9).

A significant relationship between HAART use and the reduced occurrence of OC has been reported (10–15). There are studies that have documented a decreased prevalence of OHL (11–13) and Kaposi's sarcoma (KS) associated with HIV infection after initiation of HAART. An increase in the prevalence of oral warts has also been reported among those patients on HAART compared with those who were not on HAART (12, 16). In our earlier studies, patients who were not on HAART had low prevalence of OHL and absence of oral KS as well as oral warts (6, 17). This is unlike other reports from the developed world. Given this difference and the fact that there are no existing data on the oral health in HIV-seropositive patients on HAART in India, we report oral lesions in HIV-seropositive patients initiated on HAART.

In developed countries, patients are treated by proprietary HAART, predominantly on a protease inhibitor (PI) unlike in developing countries, where patients are on generic HAART with non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimes (18).

Correspondence: Dr Krishna Mohan Rao Umadevi, Ragas Dental College and Hospital, 2/102 East Coast Road, Uthandi, Chennai-600119, Tamil Nadu, India. Tel: +91 44 24832859, Fax: +91 44 24844172, E-mail: umadevikrao@yahoo.co.in
Accepted for publication October 2, 2006

Thus the knowledge gained from this initial study performed in a resource-constrained setting will help in the long-term evaluation of oral lesions in patients who are on HAART.

## Methods

*Study population*

The participants enrolled in this study were adults (≥18 years) attending the YRG CARE (Center for AIDS Research and Education, Chennai, south India) during the period March 2003 to February 2004. Following World Health Organization (19) guidelines, the patients were started on ART when either CD4 lymphocyte counts were < 200 cells/μl or if they had an AIDS-defining illness. Fifty patients were initiated on HAART by the doctor in-charge at YRG CARE. The combination of two nucleoside reverse transcriptase inhibitors (NRTI) (lamivudine + stavudine or lamivudine + zidovudine) and an NNRTI (nevirapine or efavirenz) were prescribed to 49 (98%), while one patient (2%) was prescribed a two NRTI and PI combination. These patients were examined after the initiation of HAART (mean duration on HAART 4.6 months) and this examination is referred to as the first visit. The patients were subsequently followed at 3, 6 and 9 months. Fifty patients who did not have access to HAART were also enrolled in the study with age and CD4 count matched as closely as possible with those in the HAART group. They were seen for only one study visit. Thus the study had two components – the first consisted of patients not on HAART and these patients were compared with those who were on HAART (mean duration of HAART 4.6 months) at first visit. In the second component, we compared the oral lesions observed at the first visit in patients on HAART and during the subsequent follow-up visits. The institutional review board of YRG CARE approved the study and all the participants provided voluntary informed consent. All the potential risks and benefits were explained to the patients in their own language.

*Procedures*

Demographic data were collected using a standardized questionnaire. Present medical status, past medical history, family history and drug history were recorded. Clinical oral examination was performed. The medical findings were recorded by the doctor in-charge.

Extra-oral examination included the skin of the head and neck, parotid glands and lymph nodes. Intra-oral examination included the gingiva, periodontium, alveolar mucosa, buccal mucosa, lips, vestibule, dorsal, ventral and lateral surfaces of the tongue and floor of the mouth. The US Collaborative Group Criteria (20) and EC Clearinghouse Criteria (21) were used for diagnosing oral lesions. Examination data were recorded in a standard format that had been pre-tested. The examination and recording were made by a qualified dental surgeon, trained in diagnosing oral lesions associated with HIV infection.

*Statistical analysis*

Data entry, database management and all statistical calculations were performed with the Statistical Package for the Social Sciences (SPSS, version 10.0.5) software. Descriptive statistics were calculated for all variables. Chi-square test of association was used to find out the association in the occurrence of oral lesions between the HAART and non-HAART groups. In the HAART group, the chi-square test for trend was performed to determine any changes in the occurrence of oral lesions at the first visit, and then at 3, 6 and 9 months. The Student's *t*-test was performed to compare the mean differences in normally distributed data. The Mann–Whitney *U*-test was applied to assess the statistical differences between the groups of patients when the data were not normal. The Friedman test was used to determine CD4 count differences at the first visit, and then at 3, 6 and 9 months. The level of significance was set at 0.05 for all statistical tests.

## Results

The study population consisted of 100 HIV-seropositive subjects, 50 in the HAART group and 50 in the non-HAART group. There were 76 males (36 HAART and 40 non-HAART) and 24 females (14 HAART and 10 non-HAART). The mean age in the HAART group was 33.9 ± 6.3 and in the non-HAART group 35.2 ± 7.6 ($P = 0.35$). Ninety-six per cent of the patients acquired the infection through the heterosexual route (98% in the HAART group and 94% in the non-HAART group). CD4 counts were available for all 100 participants. There were no significant differences between the sample characteristics of the study groups (Table 1). The median CD4 counts in HAART and non-HAART groups were 241 and 219 respectively ($P = 0.019$). The median CD4 counts at 3, 6 and 9 months were 327, 368, and 416 respectively. The median CD4 counts were increased during the follow-up period ($P = 0.00$).

During the first visit, the most common HIV-related oral lesions present in the HAART and non-HAART groups were OC and pigmentation. There was only one

**Table 1** Demographics of the study population

| | *HAART* | | *Non-HAART* | | |
|---|---|---|---|---|---|
| *Variables* | *n = 50* | *%* | *n = 50* | *%* | *P-value* |
| Age groups | | | | | |
| ≤20 | 1 | 2.0 | 0 | 0 | 0.34 |
| 21–40 | 43 | 86.0 | 40 | 80.0 | |
| >40 | 6 | 12.0 | 10 | 20.0 | |
| Gender | | | | | |
| Male | 36 | 72.0 | 40 | 80.0 | 0.48 |
| Female | 14 | 28.0 | 10 | 20.0 | |
| Source of infection | | | | | |
| Heterosexual | 49 | 98.0 | 47 | 94.0 | 0.36 |
| Blood transfusion | 1 | 2.0 | 1 | 2.0 | |
| Unknown | – | – | 2 | 4.0 | |
| CD4 counts | | | | | |
| ≤200 | 18 | 36.0 | 23 | 46.0 | 0.42 |
| >200 | 32 | 64.0 | 27 | 54.0 | |

**Table 2** Oral lesions in HAART ($n = 50$) and non-HAART ($n = 50$) groups

| | *HAART*[a] | | *Non-HAART* | | *Total* | | |
|---|---|---|---|---|---|---|---|
| *Oral lesions* | *n = 50* | *(%)* | *n = 50* | *(%)* | *n = 100* | *(%)* | *P value* |
| Candidiasis | 4 | 8.0 | 12 | 24.0 | 16 | 16.0 | 0.05* |
| Pseudomembranous | 2 | 4.0 | 9 | 18.0 | 11 | 11.0 | 0.05* |
| Erythematous | 1 | 2.0 | 4 | 8.0 | 5 | 5.0 | 0.36 |
| Angular cheilitis | 1 | 2.0 | 2 | 4.0 | 3 | 3.0 | 1.0 |
| Pigmentation | 19 | 38.0 | 10 | 20.0 | 29 | 29.0 | 0.08 |
| Ulcers | – | – | 1 | 2.0 | 1 | 1.0 | 1.0 |
| Oral hairy leukoplakia | – | – | 1 | 2.0 | 1 | 1.0 | 1.0 |
| Any lesion | 26 | 52.0 | 25 | 50.0 | 51 | 50.0 | 0.79 |

[a]HAART at first visit (mean duration on HAART 4.6 months).
*$P \leq 0.05$.

case each of OHL and aphthous ulcer (AU) in the non-HAART group. OC was present in 8% of the HAART group and in 24% in the non-HAART group ($P = 0.05$). Pseudomembranous candidiasis (PC) was observed in 4% and 18%, respectively, in the HAART and non-HAART groups ($P = 0.05$). One case (2%) of erythematous candidiasis (EC) and one of angular cheilitis (AC) was observed in the HAART group, while 8% and 4% of non-HAART participants presented with EC and AC respectively. Pigmentation was present in 38% of the patients in the HAART group and in 20% in the non-HAART group (Table 2).

There was no statistically significant difference in the antifungal treatment in the HAART and non-HAART groups in patients with OC ($P = 1.0$).

In participants with CD4 ≤200, OC was observed in 5.6% in the HAART group and in 39.1% in the non-HAART group ($P = 0.025$). Of those with OC, 5.6% in the HAART group and 34.8% in the non-HAART group presented with PC ($P = 0.05$). EC was seen in 8.7% and AC in 4.3% in the non-HAART group. Pigmentation was observed in 27.8% and 26.1% in the HAART and non-HAART groups respectively. AU and OHL were observed in 4.3% of the patients in the non-HAART group.

In patients with a CD4 count >200, OC occurred in 9.4% and 11.1% in the HAART and non-HAART groups respectively. 3.1% in the HAART group and 3.7% in the non-HAART group had PC. EC was observed in 3.1% and 7.4% in the HAART and non-HAART groups respectively. AC was observed in 3.1% in the HAART group and in 3.7% in the non-HAART group. Pigmentation was observed in 43.8% and 14.8% in the HAART and non-HAART groups respectively ($P = 0.02$).

*Oral lesions in the HAART group at first visit, 3, 6 and 9 months*

Oral candidiasis was present in 8% and 4.5% of the patients during the first visit and at 3 months respectively. OC was not observed at 6 and 9 months. PC was observed in 4% and 2.2% during the first visit and at 3 months, respectively, while no cases were observed at 6 and 9 months. At the first visit, 2% and at 3 months 2.2% had EC, with no cases being observed at 6 and 9 months. AC was seen in 2% of the participants at the first visit and none at 3, 6 and 9 months. Except for OC ($P = 0.045$), there was no significant change in the occurrence of oral lesions during the follow-up period (Table 3).

## Discussion

The natural history of HIV infection has considerably changed in the developed world and the developing world has now begun to witness those changes (4). There have been studies in the developed world that have investigated the changing pattern in the occurrence of oral mucosal lesions among adults with HIV infection (11, 14, 15, 22–26). All those studies reported a decrease in the occurrence of OC.

Reduced occurrence of OC due to the direct inhibition of asparitic proteinase secreted by candida has been reported (10, 15, 27) Reduction in the occurrence of OC was not restricted to PI-included HAART therapy but was also seen in relation to the two NRTI and one

**Table 3** Oral lesions in the HAART group at first visit, and then at 3, 6 and 9 months

| | *First visit* | | *3* | | *6* | | *9* | | |
|---|---|---|---|---|---|---|---|---|---|
| *Oral lesions* | *n = 50* | *%* | *n = 44* | *%* | *n = 35* | *%* | *n = 20* | *%* | *P-value* |
| Candidiasis | 4 | 8 | 2 | 4.5 | 0 | 0 | 0 | 0 | 0.045* |
| Pseudomembranous | 2 | 4 | 1 | 2.2 | 0 | 0 | 0 | 0 | 0.161 |
| Erythematous | 1 | 2 | 1 | 2.2 | 0 | 0 | 0 | 0 | 0.36 |
| Angular cheilitis | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | – |
| Pigmentation | 19 | 38 | 14 | 31.8 | 13 | 37.1 | 7 | 35 | 0.88 |

*$P < 0.05$.

NNRTI combination therapies (25). This could be due to the fact that HAART suppresses viral replication, allowing for partial restoration of the immune system, and protection against opportunistic pathogens (28). There are other studies which have confirmed these findings and established that the reduction in opportunistic infections is due to a rise in the CD4 cell count and a reduction in the viral load (29, 30). In this study, the occurrence of OC was higher in the non-HAART group than in the HAART group at the first visit ($P = 0.05$). This finding is consistent with previous reports from other countries. Ceballos-Salobrena et al. (22), in their study of 154 patients who were on HAART therapy for a minimum of 6 months, reported a 30% reduction in the prevalence of OC. Greenspan et al. (12), in their prospective study on 1280 patients over a period of 12 years reported that, after adjusting for CD4 cell count and HIV viral load, the odds of having OC were lower in individuals on HAART (0.28 [0.12–0.63]) than in individuals who were not on HAART. Ramirez Amador et al. (13), in their 12-year prospective study in Mexico, observed a decrease in the prevalence of OC by half during the course of their defined study periods.

We observed all the variants of OC, except hyperplastic candidiasis, in both HAART and non-HAART groups. The percentage of patients with PC was higher than those with EC, both in the HAART and in the non-HAART groups. There was a significant decrease in the prevalence of PC in the HAART group than in the non-HAART group. In a UK study, a significantly higher prevalence of EC and PC was observed in patients who were not on ART ($n = 195$) than in those patients who were on ART ($n = 89$) (24). Our finding of a higher prevalence of PC compared with EC in this study was consistent with our earlier report of a cross-sectional study on 1000 Indian patients (17).

In patients with CD4 counts ≤200, there was a significant difference in the occurrence of OC between the non-HAART group and the HAART group at the first visit, and this association is well established (9). An interesting observation in this study was a significant difference in the prevalence of intra-oral melanin pigmentation between the HAART group and the non-HAART group in patients with CD4 counts >200. Some of the reasons that have been advanced to explain such intra-oral pigmentation include: increased release of α melanocyte-stimulating hormone caused by deregulation of cytokines in HIV disease; use of melanocyte-stimulating drugs; certain antiretrovirals, antifungals and Addison's disease. In this study, we excluded racial pigmentation based on the recent onset (as noticed by the patient/care provider) and the site of occurrence (e.g. buccal mucosa). We also had a well-documented history based on which we excluded the other possible causes of hyperpigmentation (31). Our group has previously reported hyperpigmentation of the oral mucosa in HIV-infected patients (6, 17) and in one of our earlier studies we established that there was a statistically significant increase in the prevalence of pigmentation in the HIV-seropositive group, both clinically and histologically when compared with the HIV-seronegative group, but the limitation in the study was the cause for pigmentation seen clinically could not be ascertained (31). Oral mucosal pigmentation in patients on HAART has been attributed to zidovudine (22). Of the 14 patients on HAART with CD4 counts >200 in this study, six were on combination therapy, which included zidovudine and none of the six patients had the habit of smoking. We plan to investigate this finding in future studies, including the estimation of plasma cortisol levels.

The median CD4 count during the first visit was 241, at 3 months 327, at 6 months 368 and at 9 months 416. We also observed a significant decrease in the occurrence of OC during the follow-up period in these patients. Schmidt-Westhausen et al. (11), in their prospective cohort of 103 patients, recorded 66% of OC prior to HAART, and in their first evaluation (at least 4 weeks after initiating HAART) observed OC in only 9.7% of the patients, and in their second evaluation (at least 7 months after the initiation of HAART) OC was not observed. Similar findings were also reported in a 12-year prospective study (13) in Mexico and in a retrospective study of 1280 HIV-seropositives over a period of 9 years in the United States (12).

There is a significant difference between reports from the western literature (11–13) and our study as regards the prevalence of oral lesions in patients initiated on HAART. The striking difference was the low prevalence of OHL and the absence of oral warts. We observed OHL in only one patient in the non-HAART group. Greenspan et al. (12) found a higher prevalence of warts among those on HAART than among those who were not on HAART, and this finding was statistically significant (6.80 [1.49–30.80], $P = 0.01$). They also speculated that a functionally incomplete reconstitution of the immune system, observed in patients initiated on HAART, could lead to the development of oral warts. In our study, we did not encounter oral warts in either the HAART or the non-HAART group. Our previous cross-sectional study also did not record oral warts (17). Acquisition of anogenital HPV infection and HPV type is associated with an increased number of lifetime sexual partners, high frequency of sexual activity and a history of sexual partners with genital warts (32). Oral mucosal abnormalities and more than one oral sex partner (33) and oral sex with men and HIV infection are known to be associated with HPV seroreactivity (34). It has also been documented that homosexual men have a prevalence of detectable HPV DNA ranging roughly from 80% to 93% (32). In our study, the participants were predominantly heterosexual in behaviour with the possibility of reduced frequency of orogenital contact, and this could possibly explain the absence of oral warts in this study.

In an Indian study of 288 patients, prevalence of 31% human papilloma virus 16 (HPV) in clinically normal mucosa, 34% in potentially premalignant lesions and 15% in oral cancers was reported (35). It has also been stated that HPV frequently establishes a subclinical or latent infection in the oral cavity, which could serve as a reservoir for HPV transmission and future disease. It

has also been established that most of the HPV types detected in the mouth were intermediate and high-risk oncogenic genital types (36). The absence of oral warts in this study would thus indicate the need for the study of oral carriage of HPV and alert us to handle oral warts if we encounter them in future, in view of their management which is challenging and their potential to cause oral malignancy. It could be true that we are in the early phase of post-HAART era and have therefore not seen this oral lesion. Alternative explanations relating to the relative prevalence of HPV oral colonization in our population are also possible.

This study of oral lesions in patients initiated on HAART, to our knowledge, is the first report from India. Information obtained from this study regarding the difference in the occurrence of oral lesions, viz. OC and pigmentation, should be further explored in the context of HAART. Despite the small sample size, the results of this study establish the changing scenario of oral lesions and stress the need for longitudinal studies to ascertain the role of oral lesions as markers of immune failure (37), in patients with HIV/AIDS undergoing HAART in a resource-constrained setting, such as in India.

## References

1. Fighting AIDS. Available at: http://www.theglobalfund.org/en/about/aids.
2. National AIDS Control Organization. 2004. Available at: http://www.nacoonline.org/facts_hivestimates04.htm
3. Murphy EL, Collier AC, Kalish LA, et al. Highly active antiretroviral therapy (HAART) decreases mortality and morbidity in patients with advanced HIV disease. *Ann Intern Med* 2001; **135**: 17–26.
4. Kumarasamy N, Solomon S, Sreekanth KC, et al. The changing natural history of HIV disease: before and after the introduction of generic antiretroviral therapy in Southern India. *Clin Infect Dis* 2005; **41**: 1525–8.
5. Greenspan JS. Sentinels and Signposts: The epidemiology and significance of the oral manifestations of HIV disease. *Oral Dis* 1997; **3** (Suppl. 1): 13–7.
6. Ranganathan K, Reddy BVR, Kumarasamy N, Solomon S, Viswanathan R, Johnson NW. Oral lesions and conditions associated with human immunodeficiency virus infection in 300 South Indian patients. *Oral Dis* 2000; **6**: 152–7.
7. Begg MD, Panageas KS, Mitchell-Lewis D, Bucklan RS, Phelan JA, Lamster IB. Oral lesions as markers of severe immunosuppression in HIV-infected homosexual men and injection drug users. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996; **82**: 276–83.
8. Greenspan D, Komaroff E, Redford M, et al. Oral mucosal lesions and HIV viral load in the Women's Interagency HIV Study (WIHS). *J Acquir Immune Defic Syndr* 2000; **25**: 44–50.
9. Kerdpon D, Pongsiriwet S, Pangsomboon K, et al. Oral manifestations of HIV infection in relation to clinical and CD4 immunological status in Northern and Southern Thai patients. *Oral Dis* 2004; **10**: 138–44.
10. Arribas JR, Hernandez-Albujar S, Gonzalez-Garcia JJ, et al. Impact of protease inhibitor therapy on HIV-related oropharyngeal candidiasis. *AIDS* 2000; **14**: 979–85.
11. Schmidt-Westhausen AM, Priepke F, Bergmann FJ, Reichart PA. Decline in the rate of oral opportunistic infections following introduction of highly active antiretroviral therapy. *J Oral Pathol Med* 1999; **29**: 336–41.
12. Greenspan D, Canchola AJ, MacPhail LA, Cheikh B, Greenspan JS. Effect of highly active antiretroviral therapy on frequency of oral warts. *Lancet* 2001; **357**: 1411–2.
13. Ramirez-Amador V, Esquivel-Pedraza L, Sierra-Madero J, Anaya-Saavedra G, Gonzalez-Ramirez I, Ponce de Leon S. The changing clinical spectrum of Human Immunodeficiency Virus (HIV)-related oral lesions in 1000 consecutive patients: A 12-year study in a referral center in Mexico. *Medicine* 2003; **82**: 39–50.
14. Greenspan D, Gange SJ, Phelan JA, et al. Incidence of oral lesions in HIV-1 infected women: reduction with HAART. *J Dent Res* 2004; **83**: 145–50.
15. Nicolatou-Galitis O, Velegraki A, Paikos S, et al. Effect of PI-HAART on the prevalence of oral lesions in HIV-1 infected patients. A Greek study. *Oral Dis* 2004; **10**: 145–50.
16. King MD, Reznik DA, O'Daniels CM, Larsen NM, Osterholt D, Blumberg HM. Human papilloma virus-associated oral warts among human immunodeficiency virus-seropositive patients in the era of highly active antiretroviral therapy: An emerging infection. *Clin Infect Dis* 2002; **34**: 641–8.
17. Ranganathan K, Umadevi M, Saraswathi TR, Kumarasamy N, Solomon S, Johnson N. Oral lesions and conditions associated with Human Immunodeficiency Virus infection in 1000 South Indian patients. *Ann Acad Med Singapore* 2004; **33** (Suppl. 4): 37–42.
18. Kumarasamy N, Vallabhaneni S, Cecelia AJ, et al. Reasons for modification of generic highly active antiretroviral therapeutic regimens among patients in southern India. *J Acquir Immune Defic Syndr* 2006; **41**: 53–8.
19. *World Health Organization scaling of antiretroviral therapy in resource-limited settings: Treatment guidelines for a public health approach*. 2003. Available at: http://www.who.int/3by5/publications/documents/arv_guidelines/en/.
20. Greenspan JS, Barr CE, Sciubba JJ, Winkler JR. For the USA Oral AIDS Collaborative Group. Oral manifestations of HIV infection. Definitions, diagnostic criteria and principles of therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1992; **73**: 142–4.
21. EC Clearinghouse on oral problems related to HIV infection and WHO collaborating centre on oral manifestations of the immunodeficiency virus. Classification and diagnostic criteria for oral lesions in HIV infection. *Oral Pathol Med* 1993; **22**: 289–91.
22. Ceballos-Salobreña A, Gaitan-Cepeda LA, Ceballos-Garcia L, Lezama Del Valle D. Oral lesions in HIV/AIDS patients undergoing highly active antiretroviral treatment including protease inhibitors: A new face of oral AIDS. *AIDS Patient Care STDs* 2000; **14**: 627–35.
23. Ceballos-Salobreña A, Gaitan-Cepeda L, Ceballos-Garcia L, Samaranayake LP. The effect of antiretroviral therapy on the prevalence of HIV-associated oral candidiasis in a Spanish cohort. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004; **97**: 345–50.
24. Tappuni AR and Fleming GJ. The effect of antiretroviral therapy on the prevalence of oral manifestations in HIV-infected patients: A UK study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; **92**: 623–8.
25. Eyeson D, Tenant-Flowers M, Cooper DJ, Johnson NW, Warnakulasuriya KA. Oral manifestations of an HIV positive cohort in the era of highly active anti-retroviral

therapy (HAART) in South London. *J Oral Pathol Med* 2002; **31**: 169–74.
26. Greenwood I, Zakrzewska JM and Robinson PG. Changes in the prevalence of HIV–associated mucosal disease at a dedicated clinic over 7 years. *Oral Dis* 2002; **8**: 90–4.
27. Cassone A, Tacconelli E, De Bernardis F, et al. Antiretroviral therapy with protease inhibitors has an early immune reconstitution-independent beneficial effect on candida virulence and oral candidiasis in human immunodeficiency virus-infected subjects. *J Infect Dis* 2002; **185**: 188–95.
28. Bower M, Fox P, Fife K, et al. Highly active antiretroviral therapy (HAART) prolongs time to treatment failure in Kaposi's sarcoma. *AIDS* 1999; **13**: 2105–11.
29. Ledergerber B, Egger M, Erard V, et al. AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: The Swiss cohort study. *JAMA* 1999; **282**: 2220–6.
30. Bart PA, Rizzardi GP, Tambussi G, et al. Immunological and virological responses in HIV–1 infected adults at early stage of established infection treated with HAART. *AIDS* 2000; **14**: 1887–97.
31. Blignaut E, Patton LL, Nittayanta W, Ramirez-Amador V, Ranganathan K, Chattopadhyay A. (A3) HIV phenotypes, oral lesions, and management of HIV-related disease. *Adv Dent Res* 2006; **19**: 122–9.
32. Panther LA, Schiecht HP, Dezube BJ. Spectrum of human papillomavirus-related dysplasia and carcinoma of the anus in HIV-infected patients. *AIDS Read* 2005; **15**: 79–82, 85–6, 88, 91 (Review).
33. Kreimer AR, Alberg AJ, Daniel R, et al. Oral human papillomavirus infection in adults is associated with sexual behavior and HIV serostatus. *J Infect Dis* 2004; **189**: 686–98.
34. Kreimer AR, Alberg AJ, Viscidi R, Gillison ML. Gender differences in sexual biomarkers and behaviors associated with human papillomavirus-16, -18, and -33 seroprevalence. *Sex Transm Dis* 2004; **4**: 247–56.
35. D'Costa J, Saranath D, Dedhia P, Sanghvi V, Mehta AR. Detection of HPV-16 genome in human oral cancers and potentially malignant lesions from India. *Oral Oncol* 1998; **34**: 413–20.
36. Coutlée F, Trottier A-M, Ghattas G, et al. *Risk factors for oral human papillomavirus in adults infected and not infected with human immunodeficiency virus: 1995*. Presented in part at the 14th International Papillomavirus Conference, Quebec City, Canada, 1995.
37. Gaitan-Cepeda LA, Martinez-Gonzaiez M, Ceballos-Salobrena A. Oral candidiasis as a clinical marker of immune failure in patients with HIV/AIDS on HAART. *AIDS Patient Care STDs* 2005; **19**: 70–7.

## Acknowledgements

We acknowledge Dr Arthur L. Reingold, AITRP Director, School of Public Health, University of Berkeley for the Fogarty grant (1 D43 TW00003), Dr Deborah Greenspan, Chair of the Department of Orofacial Sciences, University of California, San Francisco, for guidance (PO1 DE 07496), Dr Caroline Shiboski, Associate Professor, Department of Orofacial Sciences, University of California, San Francisco, for her valuable advice and guidance, and Dr R. Gunaseelan, Director, Chennai Dental Research Foundation.