



## Effects of long-term use of HAART on oral health status of HIV-infected subjects

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**BACKGROUND:** The aim of this study was to determine the effects of long-term use of highly active antiretroviral therapy (HAART) on oral health status of HIV-infected subjects.

**METHODS:** Oral examination and measurement of saliva flow rate of both unstimulated and wax-stimulated whole saliva were performed in HIV-infected subjects with and without HAART, and in non-HIV individuals. The following data were recorded; duration and risk of HIV infection, type and duration of HAART, CD4 cell count, viral load, presence of orofacial pain, oral dryness, oral burning sensation, oral lesions, cervical caries, and periodontal pocket. Multiple logistic regression analysis was performed to determine the effects of long-term use of HAART on oral health status of HIV-infected subjects. **RESULTS:** One hundred and fifty-seven HIV-infected subjects – 99 on HAART (age range 23–57 years, mean 39 years) and 58 not on HAART (age range 20–59 years, mean 34 years) – and 50 non-HIV controls (age range 19–59 years, mean 36 years) were enrolled. The most common HAART regimen was 2 NRTI + 2 NNRTI. HIV-infected subjects without HAART showed greater risks of having orofacial pain, oral dryness, oral lesions, and periodontal pockets than those with short-term HAART ( $P < 0.01$ ). The subjects with long-term HAART were found to have a greater risk of having oral lesions than those with short-term HAART ( $P < 0.05$ ). The unstimulated and stimulated salivary flow rates of the subjects with HAART were significantly lower than in those without HAART ( $P < 0.05$ ).

**CONCLUSION:** We conclude that long-term HAART has adverse effects on oral health status of HIV-infected subjects.

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**Keywords:** HAART; HIV; oral health; oral lesion; risk factor; salivary flow rate

### Introduction

Highly active antiretroviral therapy (HAART) has become a standard treatment for HIV infection. It induces a marked reduction in viral load and increase in the CD4<sup>+</sup> cell count (1) leading to a declination in morbidity and mortality of HIV-infected subjects (2). At present, HAART includes more than 30 different drugs of six separate classes: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors, entry inhibitors, and HIV integrase inhibitors (3).

In HAART therapy, a range of different combinations of drugs are used, and each drug combination has advantages and disadvantages. In general, there are three commonly used combinations: 1 NNRTI + 2 NRTI; 1 or 2 PIs + 2 NRTIs; and 3 NRTIs (3). They are administered simultaneously to bring about a sustained block in viral replication and restore immune function, as well as to minimize viral resistance to the drugs (4).

Before the HAART era, some oral lesions including oral candidiasis (OC) and oral hairy leukoplakia (OHL) were commonly observed among HIV-infected individuals both in developed and developing countries (5–10). The introduction of HAART has contributed to a global reduction in oral lesions in adults and children (11–13). A decreased prevalence of HIV-related oral lesions of 10–50% following the advent of HAART has been reported (11, 14–16). However, the impact of long-term use of HAART on oral health status of HIV-infected subjects is poorly documented.

Salivary glands are affected by HIV infection. HIV-infected subjects show decreased salivary flow rates and often complain of dry mouth or xerostomia (17–19).

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Previous studies reported salivary gland hypofunction and xerostomia in 2–10% of HIV-infected individuals (8, 17, 20). The presence of oral symptoms has a significant impact on health-related quality of life (21, 22). However, it is not well established if long-term use of HAART results in any adverse effects on oral health that may affect the patients' quality of life. In addition, it is not clear about the nature and significance of HIV salivary gland disease, and whether HIV-infected individual on HAART is at risk of increased dental caries.

Thailand began a national HAART program in 2000 (23). So far, no report is available on changes in the pattern of HIV-related oral lesions among Thai people with HIV infection in the HAART era. In addition, the effects of long-term use of HAART on their oral health remain unknown. The objectives of this study were to determine: (i) the oral health status of HIV-infected subjects in the HAART era compared with non-HIV controls and (ii) the effects of long-term use of HAART on oral health status of HIV-infected individuals.

## Materials and methods

A cross-sectional study was performed in HIV-infected subjects who came to receive HAART at the Internal Medicine Clinic at Songklanagarind Hospital and Hat Yai Regional Hospital in southern Thailand. The inclusion criteria of subjects enrolled were: (i) seropositive for antibody to HIV when tested by a particle agglutination test for antibodies to HIV (SERODIA<sup>®</sup>-HIV, Fujirebio Inc., Shinjuku-ku, Tokyo, Japan) and enzyme-linked immunosorbent assay (ELISA) (Enzygnost<sup>®</sup> Anti-HIV 1/2 Plus, Behring, Behringwerke AG, Marburg, Germany), (ii) currently taking HAART, and (iii) willing to participate in the study. The exclusion criteria were: (i) HIV-infected subject with history of local radiation therapy on head and neck region and (ii) severely ill HIV-infected subject who could not cooperate with the study procedures of saliva collection. HIV-infected individuals who came to those hospitals, but had not yet started HAART, and non-HIV-infected volunteers were asked to participate as controls.

### Ethics

The study protocol was approved by the research committee at the Prince of Songkla University, and at the Ministry of Public Health. All information about the patients and their identity was anonymous. Subjects were given both verbal and written information about the nature of the study, and written consent was obtained. Subjects were allowed to leave the study at any time during the procedures.

### Clinical examination

History taking and oral examination were performed in HIV subjects with and without HAART and in non-HIV individuals. Clinical diagnosis of HIV-related oral lesions was made according to the criteria proposed by the EC-Clearinghouse (24). Unstimulated salivary flow rate using the draining method and paraffin-stimulated salivary flow rate were measured.

The following data were recorded: duration of HIV infection, risk group of HIV infection, use of HAART, CD4<sup>+</sup> cell count, presence of orofacial pain, presence of oral lesions, presence of cervical caries, periodontal health status, bleeding on probing, feeling of oral dryness, and oral burning sensation.

### Measurement of saliva flow rate

A measurement of saliva flow rate was conducted only in the morning between 9:00 AM and 12:00 AM. All subjects were asked to rinse their mouths with 0.9% normal saline and spit out, and thereafter swallow before starting the collection procedure. The measurement comprised unstimulated and wax-stimulated whole saliva flow rates by the draining technique as described in detail by Navazesh and Christensen (25). In brief: unstimulated whole saliva was collected over 15 min. The subjects were instructed to lean their body forward and drain their saliva passively into a plastic cup, pre-weighed using a digital scale (OHAUSE, USA), for 5 min. They were asked to repeat the procedure two more times in two other pre-weighed plastic cups, and saliva was collected for 5 min. One gram of saliva is assumed to be equal to 1 ml of saliva. The unstimulated salivary flow rate (ml/min) was calculated by dividing the mean weight of the three collected saliva samples by time (5 min).

Stimulated saliva was collected over 6 min. The subjects were instructed to chew a cube of 1 g paraffin without taste with a frequency of 25 times per minute for 2 min. They were instructed not to swallow saliva during the course of saliva collection. Persons with denture were asked to chew the cube of paraffin without removal of their denture. The patients passively drained their saliva into a pre-weighed plastic cup four times at 30 s interval. They were asked to repeat the procedure two more times in two other pre-weighed plastic cups, and saliva was collected for 2 min. The stimulated saliva flow rate (ml/min) was calculated by dividing the mean weight of the three collected saliva samples and by time (2 min).

### Statistical analysis

Descriptive statistics were used to analyze the data, breaking down of subjects by status of HIV test and duration of HAART received. Chi-square test was employed to explore the possible association between oral health status, oral lesions and HIV/HAART status. Finally, as the risk for oral health problem may be influenced by the duration of HIV infection, levels of CD4 count, and smoking and drinking behaviors, linear and logistic regression, respectively, were used to analyze the relationship between salivary flow rate and oral health problems with duration of HAART use. Statistical significance was set at  $P=0.05$ .

## Results

### Subjects and use of HAART

Ninety-nine HIV-infected subjects receiving HAART (age range 23–57 years, mean age 39 years), 58 not

receiving HAART (age range 20–59 years, mean age 34 years), and 50 non-HIV individuals (age range 19–59 years, mean age 36 years) were enrolled. Most HIV-infected subjects who were on HAART did not receive PI-based regimen ( $n = 84$ , 85%). Different combinations of HAART used among HIV-infected subjects were 2 NRTIs + 1 NNRTI ( $n = 82$ , 83%), 2 NRTIs + 2 PIs ( $n = 7$ , 7%), 2 NRTIs + 1 PI ( $n = 3$ , 3%), and others ( $n = 7$ , 7%). Those who had been taking ART <3 years were classified as a group with short-term use of HAART and those who had been taking HAART for  $\geq 3$  years were classified as a group with long-term use of HAART. Various characteristics of the subjects and controls are shown in Table 1.

#### *Prevalence of oral lesions*

Prevalence of oral lesions among HIV-infected subjects with and without HAART and non-HIV individuals is shown in Table 2. Hyperpigmentation was the most common oral lesion seen in all groups. Only two and one HIV-infected subjects who received HAART showed OC and OHL, respectively. Of interest, no oral warts were observed among the subjects.

#### *Oral health status of HIV-infected subjects and non-HIV controls*

Oral health status including the presence of orofacial pain, oral dryness, oral burning sensation, presence of oral lesions, cervical caries, periodontal pocket depth, gingival bleeding on probing, and salivary flow rates of both unstimulated and stimulated saliva was analyzed according to HIV status and HAART status. With respect to HIV status, prevalence of oral lesions was found to be statistically significantly higher in HIV-infected subjects than in non-HIV controls (Chi-square test,  $P < 0.001$ ). Salivary flow rates of both unstimulated and stimulated saliva in HIV-infected subjects were statistically significantly lower than in non-HIV controls (Chi-square test,  $P < 0.001$ ). Oral health status of HIV-infected subjects was also found to be statistically significant difference due to HAART status (Table 3).

#### *Effects of long-term use of HAART on oral health status of HIV-infected subjects*

Effects of long-term use of HAART on oral health status of HIV-infected subjects were analyzed by multiple logistic regression analysis. After controlling for duration of HIV infection, CD4<sup>+</sup> cell counts, smoking habits, and alcohol consumption, HIV-infected subjects with long-term use of HAART were found to have a greater risk of developing oral lesions than those with short-term use of HAART ( $P < 0.05$ ) (Table 4). HIV-infected subjects without HAART showed greater risks of having orofacial pain, oral dryness, oral lesions, and periodontal pockets than those with short-term use of HAART ( $P < 0.01$ ). In addition, HIV-infected subjects with long-term use of HAART showed a greater risk of gingival bleeding on probing than those with short-term use of HAART ( $P < 0.05$ ).

Using linear regression analysis, both unstimulated and stimulated salivary flow rates of HIV-infected subjects without HAART were found to be significantly higher than in those with short-term use of HAART ( $P < 0.05$ ). In contrast, no statistically significant difference of salivary flow rates was observed between HIV-infected subjects with long-term use of HAART and those with short-term use of the medication. Of other four variables put in the model, none was statistically significant (Table 5).

## Discussion

Our study demonstrated that oral health of HIV-infected subjects was improved with short-term use of HAART. However, long-term use of HAART seemed to have adverse effects on oral health status of the subjects. A dramatic decrease in the prevalence of HIV-related oral lesions was observed in this study. Before the introduction of HAART, oral lesions were found in 82% of Thai people with AIDS (10). OC and OHL were shown to be the two most common oral lesions found in 54% and 13% of Thai people with AIDS, respectively (10). However, in this study, OC and OHL were diagnosed in only 2% and 1% of HIV-infected subjects who received HAART, respectively. HIV-infected subjects who were not on HAART had a higher prevalence of OC compared with those on HAART. These findings are consistent with a UK cross-sectional study, which showed a higher prevalence of OC in adults not on any antiretroviral medication, compared with those on HAART (15).

It is well documented that frequency and severity of opportunistic diseases in HIV-infected subjects are decreased following the introduction of HAART (26). The frequency and characteristic of HIV-related oral manifestations have changed as a result of HAART (11, 15, 16). Protease inhibitor therapy has been demonstrated to decrease both frequency and recurrence of OC in HIV-infected individuals (27). A decreased prevalence of OC with the advent of HAART was found to be associated with the use of PI. A study by Cauda et al. (28) ( $n = 93$ ) reported that 7% of patients on PI had OC, compared with 36% of non-PI-treated patients (28). Another study by Cassone et al. (29) reported that in two groups of HAART-naïve patients started either a PI-based HAART or an NNRTI-based HAART regimen, a significant decrease in episodes of OC and *Candida* carriage was observed in the PI group, but not in the NNRTI group. It has been proposed that the ability of PI to inhibit *Candida* infection may be related to similarities between candidal secreted aspartic proteinases (SAPs), which are the key virulence factors for *Candida albicans*, and HIV proteinase, and the inhibition of both by PI (30). However, a study by Patton et al. (11) found no significant difference in the prevalence of OC with the use of PI. In our study, most HIV-infected subjects received 2 NRTI + 1 NNRTI, while only a few of them received PI. We did not find any association between the PI-based therapy and the presence of OC. This may be attributable to the low

**Table 1** Demographic data and characteristics of HIV-infected subjects with and without HAART and non-HIV individuals

Variables	HIV-infected subjects			Non-HIV subjects (n = 50)
	No HAART (n = 58)	With HAART (n = 99)		
		Short-term HAART (<3 years) (n = 45)	Long-term HAART (≥3 years) (n = 54)	
Age (years)				
Mean	34	37	40	36
Range	20–59	23–57	27–53	19–59
Gender				
Male	20 (34.5%)	18 (40%)	33 (61.1%)	25 (50%)
Female	38 (65.5%)	27 (60%)	21 (38.9%)	25 (50%)
Marital status				
Single	13 (23.6%)	5 (15.2%)	13 (31.7%)	21 (42%)
Married	33 (60.0%)	17 (51.5%)	16 (39.0%)	27 (54%)
Divorced	4 (7.3%)	7 (21.2%)	7 (17.1%)	0 (0%)
Widowed	5 (9.1%)	4 (12.1%)	5 (12.2%)	2 (4%)
Religion				
Buddhism	56 (96.6%)	42 (93.3%)	51 (94.4%)	24 (48%)
Islam	2 (3.4%)	3 (6.7%)	3 (5.6%)	26 (52%)
Highest education				
Primary school level	33 (56.9%)	15 (33.3%)	12 (22.2%)	24 (48%)
Secondary school level	18 (31.0%)	16 (35.6%)	21 (38.9%)	10 (20%)
Polytechnic level	2 (3.4%)	4 (8.9%)	10 (18.5%)	3 (6%)
University level	4 (6.9%)	9 (20.0%)	9 (16.7%)	11 (22%)
Other	1 (1.7%)	1 (2.2%)	2 (3.7%)	2 (4%)
Occupation				
Employee	31 (53.4%)	23 (51.1%)	21 (38.9%)	21 (42%)
Trading	6 (10.3%)	5 (11.1%)	2 (3.7%)	4 (8%)
Agriculture	3 (5.2%)	2 (4.4%)	1 (1.9%)	8 (16%)
Government servant	0 (0.0%)	2 (4.4%)	9 (16.7%)	2 (4%)
Student	1 (1.7%)	0 (0.0%)	0 (0.0%)	8 (16%)
Others	14 (24.1%)	12 (26.7%)	17 (31.5%)	7 (14%)
Unemployed	3 (5.2%)	1 (2.2%)	4 (7.4%)	0 (0%)
Income (Baht)/month				
< 5000	25 (43.1%)	18 (40.0%)	13 (24.5%)	23 (46%)
5000–10 000	26 (44.8%)	17 (37.8%)	19 (35.8%)	22 (44%)
10 001–20 000	7 (12.1%)	6 (13.3%)	11 (20.8%)	5 (10%)
20 001–30 000	0 (0.0%)	2 (4.4%)	6 (11.3%)	0 (0%)
> 30 000	0 (0.0%)	2 (4.4%)	4 (7.5%)	0 (0%)
Risk group				
Sex with person with HIV	43 (74.1%)	30 (66.7%)	41 (75.9%)	–
Commercial sex worker	4 (6.9%)	2 (4.4%)	3 (5.6%)	–
Men who have sex with men	3 (5.2%)	2 (4.4%)	3 (5.6%)	–
Intravenous drug user	2 (3.4%)	7 (15.6%)	3 (5.6%)	–
Blood transfusion	1 (1.7%)	0 (0.0%)	1 (1.9%)	–
Other	5 (8.6%)	4 (8.9%)	3 (5.6%)	–
Duration of HIV infection (years)				
Mean	3.8	4.8	8.8	–
Range	0.1–16	0.4–15	3–24	–
Smoking habit				
Smoker	39 (67.2%)	16 (35.6%)	18 (33.3%)	34 (68%)
Non-smoker	19 (32.8%)	29 (64.4%)	36 (66.7%)	16 (32%)
Alcohol consumption				
Drinker	37 (63.8%)	12 (26.7%)	13 (24.1%)	34 (68%)
Non-drinker	21 (36.2%)	33 (73.3%)	41 (75.9%)	16 (32%)
Presence of HIV-related systemic diseases				
Yes	15 (25.9%)	14 (34.1%)	9 (18.8%)	–
No	43 (74.1%)	27 (65.9%)	39 (81.2%)	–
Oral hygiene				
Good	1 (1.7%)	3 (6.7%)	0 (0.0%)	1 (2%)
Fair	35 (60.3%)	23 (51.1%)	31 (57.4%)	27 (54%)
Poor	22 (37.9%)	19 (42.2%)	23 (42.6%)	22 (44%)
Total lymphocyte cell counts (cell/mm <sup>3</sup> )				
< 1000	9 (16.7%)	12 (26.7%)	6 (11.1%)	–
1000–2000	22 (40.7%)	14 (31.1%)	14 (25.9%)	–
> 2000	23 (42.6%)	19 (42.2%)	34 (63.0%)	–
CD4 cell counts (cell/mm <sup>3</sup> )				
Mean	245.5	250.1	530.7	–
Range	5–669	9–630	74–1600	–
Viral load (copies)				
Mean	782.6	21 560	5627	–
Range	0–30 100	50–750 000	50–139 000	–

**Table 2** Prevalence of oral lesions in HIV-infected subjects with and without HAART and in non-HIV-infected individuals

Oral lesions	HIV-infected subjects			Non-HIV individuals (n = 50)
	No HAART (n = 58)	With HAART (n = 99)		
		Short-term HAART ( $<3$ years) (n = 45)	Long-term HAART ( $\geq 3$ years) (n = 54)	
Absence of oral lesions	28 (48%)	20 (44%)	23 (43%)	33 (66%)
Presence of oral lesions <sup>a</sup>	30 (52%)	25 (56%)	31 (57%)	17 (34%)
Hyperpigmentation	16 (28%)	19 (35%)	25 (46%)	15 (30%)
Denture stomatitis	5 (9%)	4 (9%)	4 (7%)	1 (2%)
Erythematous candidiasis	4 (7%)	0 (0%)	0 (0%)	0 (0%)
Pseudomembranous candidiasis	1 (2%)	2 (4%)	0 (0%)	0 (0%)
Hairy leukoplakia	3 (5%)	0 (0%)	1 (2%)	0 (0%)
Aphthous ulcers	2 (3%)	2 (4%)	1 (2%)	2 (4%)
Linear gingival erythema	2 (3%)	1 (2%)	0 (0%)	0 (0%)
Traumatic ulcers	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Frictional hyperkeratosis	0 (0%)	1 (2%)	1 (2%)	0 (0%)
Smoker hyperkeratosis	0 (0%)	1 (2%)	1 (2%)	0 (0%)

<sup>a</sup>Some subjects had more than one lesion.

numbers of HIV-infected subjects receiving PI-based therapy and the low prevalence of OC in our study.

In our study, hyperpigmentation was found to be the most common oral complications observed in HIV-infected subjects who were on HAART. A study by Sharma et al. (31) also reported that melanotic hyperpigmentation was predominant in Indian patients on HAART ( $P < 0.05$ ). This is not surprising as hyperpigmentation is a known side effect of HAART. Zidovudine can also give rise to mucocutaneous hyperpigmentation (32, 33).

Of interest, no oral warts were observed in our study. The lesions have never been reported from studies in other Asian countries (31, 34). In contrast, an increased prevalence of oral warts in subjects on HAART has been reported mainly from western countries (11, 35–38). An increase in benign human papilloma virus (HPV)-associated oral neoplastic lesions including papillomas, condylomas, and focal epithelial hyperplasia in patients on HAART has been observed (11, 35, 39). However, in a Mexican population, similar detection rates of oral warts were documented in subjects on HAART compared with those who were not on therapy (16). Another study also reported that there was no change in the incidence of oral warts with the initiation of HAART (40). It has been proposed that the development of HPV-related oral mucosal lesions in HIV-infected individuals may be related to a decreased HIV viral load (37) and/or CD4 cell count (37, 41). The mechanism by which a reduction in HIV viral load may lead to an increased risk of oral warts remains unclear, but may represent a form of immune reconstitution syndrome (37, 42).

A previous study demonstrated that HPV, which is the cause of oral warts, is more commonly isolated from the oral cavity of HIV-infected individuals than from that of immunocompetent individuals (41). It remains unclear if long-term use of HAART will lead to an increased incidence of HPV-related oral malignancies, particularly if the HPV subtypes carried are high-risk

subtypes such as HPV-16, which have been associated with oral malignancy (43). It is not known why oral warts are uncommon in Asian population. Further studies should be performed to determine whether there is a difference in the prevalence of oral HPV in Asian population compared with western people, which may imply a role for differences in genetics and host susceptibility to the virus.

In our study, HIV-infected subjects who were not on HAART showed greater risks of having orofacial pain, oral dryness, and oral lesions than those with HAART. A previous study by Patton et al. (44) reported that oral symptoms were frequently observed among HIV-infected individuals. Most people with HIV had oral discomfort that needed treatment (45). In addition, it has been reported that patients with HIV experienced more social impact of oral disease than did a comparable sample of the general population (46). The presence of oral symptoms has been shown to have a significant impact on health-related quality of life (21, 22). An improvement in oral health was significantly associated with improvements in both physical and mental health (22). Thus, the oral health-care professional plays an important role in improving and maintaining health-related quality of life in HIV-infected subjects.

Our study demonstrated that HIV-infected subjects who were not on HAART had a greater risk of having periodontal pockets of depth  $\geq 4$  mm than those with HAART. The prevalence of HIV-associated periodontal disease was reported to decrease significantly with HAART (11, 14, 15, 47). It has been reported that greater levels of periodontal destruction were associated with higher HIV viral loads (48). However, a biological explanation for the association remains unclear. Further extensive studies are needed to clarify these relationships.

In our study, HIV-infected subjects without HAART and those who were on long-term use of HAART seemed to have a greater risk of developing cervical

**Table 3** Oral health status of HIV-infected subjects with and without HAART and non-HIV individuals

Oral health status	HIV status		P-value	HAART status of HIV-infected subjects			P-value
	HIV-infected subjects (n = 157)	Non-HIV individuals (n = 50)		No HAART (n = 58)	Short-term HAART (< 3 years) (n = 45)	Long-term HAART (≥3 years) (n = 54)	
Orofacial pain							
Yes	49 (31%)	22 (44%)	0.137	27 (47%)	7 (15%)	15 (28%)	0.002
No	108 (69%)	28 (56%)		30 (53%)	39 (85%)	39 (72%)	
Oral dryness							
Yes	72 (46%)	16 (32%)	0.118	35 (61%)	16 (35%)	21 (39%)	0.012
No	85 (54%)	34 (68%)		22 (39%)	30 (65%)	33 (61%)	
Oral burning sensation							
Yes	26 (17%)	9 (18%)	0.984	13 (23%)	6 (13%)	7 (13%)	0.283
No	131 (83%)	41 (82%)		44 (77%)	40 (87%)	47 (87%)	
Presence of oral lesions							
Yes	110 (70%)	21 (42%)	< 0.001	46 (81%)	26 (57%)	38 (70%)	0.029
No	47 (30%)	29 (58%)		11 (19%)	20 (43%)	16 (30%)	
Presence of cervical caries							
Yes	29 (23%)	14 (28%)	0.617	12 (22%)	5 (16%)	12 (30%)	0.372
No	97 (77%)	36 (72%)		43 (78%)	26 (84%)	28 (70%)	
Presence of periodontal pockets							
Yes	127 (82%)	41 (85%)	0.734	51 (89%)	31 (69%)	45 (85%)	0.022
No	28 (18%)	7 (15%)		6 (11%)	14 (31%)	8 (15%)	
Presence of bleeding on probing							
Yes	146 (94%)	46 (96%)	0.736	57 (100%)	38 (83%)	51 (96%)	< 0.001
No	10 (6%)	2 (4%)		0 (0%)	8 (17%)	2 (4%)	
Salivary flow rates (ml/min)							
Unstimulated saliva							
Range	0.1–0.4	0.2–0.6	< 0.001	0.1–0.4	0.1–0.3	0.1–0.4	0.026
Median	0.2	0.4		0.2	0.2	0.3	
Stimulated saliva							
Range	0.9–2.2	1.4–2.7	< 0.001	0.9–2.3	0.7–2.1	1.2–2.4	0.089
Median	1.5	1.9		1.3	1.4	1.7	

**Table 4** Effects of long-term use of HAART on oral health status of HIV-infected subjects based on logistic regression<sup>a</sup>

Oral health status	Adjusted odds ratios (95% confidence interval) <sup>b</sup>	
	No HAART	Long-term use of HAART
Orofacial pain	4.88 (1.81, 13.2)**	1.39 (0.45, 4.26)
Oral dryness	3.5 (1.49, 8.26)**	1.12 (0.45, 2.83)
Oral burning sensation	1.78 (0.59, 5.32)	0.84 (0.22, 3.15)
Oral hygiene status	0.84 (0.33, 2.14)	1.57 (0.57, 4.33)
Presence of oral lesions	4 (1.5, 10.69)**	2.84 (1.06, 7.61)*
Presence of periodontal pockets	4.67 (1.56, 13.99)**	2.92 (0.96, 8.87)
Presence of cervical caries	1.71 (0.49, 6.01)	2.45 (0.61, 9.82)

<sup>a</sup>After controlling for duration of HIV infection, CD4 cell count, smoking habit, and alcohol consumption.

<sup>b</sup>Short-term HAART was used as a reference.

\*P-value < 0.05.

\*\*P-value < 0.01.

caries than those with short-term use of the medication. These findings are consistent with a previous study by Glick et al. (49) that revealed a relationship between HAART and increased risk of dental caries. However, a study by Phelan et al. (50) showed no significant difference in coronal or root caries by HIV status, nor did the results support a relationship between HAART and increased dental caries risk. In contrast, a study by Bretz et al. (51) reported that HIV-infected individuals receiving HAART had a lower occurrence of dental caries than did patients not taking these medications.

An association between decreased salivary flow and HAART has been reported as a factor for increased caries risk (52). Our results supported this finding because we found that both unstimulated and stimulated salivary flow rates of HIV-infected subjects with HAART were significantly lower than in those without HAART.

In our study, no salivary gland enlargement was observed in HIV-infected subjects receiving HAART. Before HAART era, no salivary gland enlargement was observed among Thai people with AIDS (10). Parotid

**Table 5** Effects of long-term use of HAART and other variables on salivary flow rates of HIV-infected subjects

Predictors for salivary flow rate	Adjusted coefficient (95% confidence interval)	
	Unstimulated salivary flow rate	Stimulated salivary flow rate
Duration of HAART (reference = short-term HAART)		
No HAART	0.15 (0.03, 0.27)*	0.59 (0.08–1.1)*
Long-term HAART	0.06 (–0.07, 0.19)	0.2 (–0.36–0.76)
Duration of HIV infection (reference = < 5 year)		
5–10 years	0 (–0.11, 0.11)	0.45 (0, 0.9)
> 10 years	–0.08 (–0.25, 0.09)	–0.17 (–0.89, 0.55)
CD4 count (reference = > 200 cell/cm <sup>3</sup> )		
< 200	–0.11 (–0.22, 0)	0.15 (–0.32, 0.63)
Smoking		
Yes vs. no	0.03 (–0.09, 0.15)	0.26 (–0.25, 0.77)
Alcohol		
Yes vs. no	0.08 (–0.04, 0.21)	0.13 (–0.41, 0.66)

\**P*-value < 0.05.

gland enlargement had been infrequently observed in HIV-infected subjects in the developed world before the advent of HAART, with the prevalence rate of 5–10% (53–55). With the introduction of HAART, previous studies in the developed countries reported that HIV-related salivary gland disease was increased (11, 39, 40, 56). A study by Patton et al. (11) reported a significant increase in the prevalence of HIV-associated salivary gland disease from 1.8% to 5%. A study by Navazesh et al. (57) demonstrated that PI-based HAART is a significant risk factor for developing enlarged salivary glands. In addition, the study indicated that women with an AIDS outcome were shown to have a 60% greater risk for having enlarged salivary glands (57). It has been shown that the glandular enlargement was correlated with decreased CD4 counts and advanced stages of HIV infection (58). Parotid gland swelling has been attributed to the increase in the CD8 lymphocyte count with CD8 lymphocytic infiltration into the intra-parotid lymph nodes in patients receiving HAART. In addition, intra-parotid lymph nodes may undergo a significant hyperplastic response and lead to visible parotid enlargement (55, 59).

In contrast, a study in developing countries reported that no changes in the prevalence of salivary gland enlargement were observed (16). A study by Nicolatou-Galitis et al. (47) reported that there was no change in the prevalence of salivary gland disease in HIV-infected individuals on PI-based HAART. Thus, it remains unclear whether salivary gland enlargement, especially of the parotid glands, is on the rise in HIV-infected individuals on HAART.

Saliva plays a significant role in oral and systemic health and its absence affects the quality of life. Individuals who suffer from salivary gland dysfunction are at risk for development of dental caries, periodontal diseases, and fungal infection (60). Xerostomia and salivary gland hypofunction have been shown to be associated with HIV infection (17, 19). In our study, salivary flow rates of both unstimulated and stimulated saliva were found to be significantly decreased in HIV-infected subjects compared with non-HIV controls. This may imply that salivary gland function can be compro-

mised by HIV infection. This finding is consistent with that of our previous study, in which salivary flow rate of HIV-infected subjects in Thailand was found to be affected by HIV infection and was significantly decreased with advanced stage of the disease (19). A study by Navazesh et al. (52) also reported that HIV-infected women are at a significantly higher risk of xerostomia and salivary gland hypofunction than are non-infected women. A study by Lin et al. (18) revealed that salivary gland function is adversely affected in the early stage of HIV infection. Thus, a vigorous prophylactic regimen could be beneficial to prevent oral disease associated with reduced salivary gland function in this group of subjects.

In our study, both unstimulated and stimulated salivary flow rates of HIV-infected subjects who were on HAART were significantly lower than in those who were not on HAART. With the advent of HAART, a study by Navazesh et al. (57) revealed that PI-based HAART was significantly associated with a decrease in both unstimulated and stimulated salivary flow rates of HIV-infected subjects. Xerostomia and lipodystrophic changes of the salivary glands have been previously reported as potential adverse effects of PI therapy (61, 62). It is not known why PI-based HAART produces a significant decrease in the salivary flow rates. It has been proposed that the chemical structure of the PI may alter the structure and composition of saliva thereby decreasing the salivary flow (52). In contrast, a study by Lin et al. (63) revealed that no changes were observed in the salivary flow rates between HIV-positive men on HAART and those not on HAART. In our study, PI-based HAART was not found to be significantly associated with a decrease in salivary flow rates of the subjects. These contradictory findings may be a result of the differences in definition of a HAART user, the method of saliva collection, study design, and analysis of results in each study.

With respect to the feeling of oral dryness (xerostomia), HIV-infected subjects without HAART showed a greater risk of feeling dry in the mouth than those with short-term HAART. A previous study by Silverberg et al. (64) reported that prevalence of xerostomia was

increased in patients who had discontinued HAART and those who had switched HAART regimens. Those patients with stable HAART showed the lowest prevalence of xerostomia (64). Similar findings were observed in a study by Navazesh et al. (57) where continued HAART usage for at least 6 months decreased the risk for developing a complaint of too little saliva.

In our study, CD4 cell count and viral load were not found to be significantly associated with salivary flow rates. A study by Navazesh et al. (57) indicated that the reduction in CD4 cell counts and the increased HIV RNA levels were significantly associated with reduced salivary flow rates of HIV-infected individuals. It has been proposed that the lymphoproliferative response as a result of high levels of HIV p24 antigen may have been an important risk factor for developing reduced salivary flow rates (65–67). The exact nature of associated changes in salivary gland structure and function with HAART remains unknown. Further studies should be conducted to gain insights into the effects of long-term use of HAART on salivary gland structure and function.

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