ORIGINAL ARTICLE

Relationship of long-term highly active antiretroviral therapy on salivary flow rate and CD4 Count among HIV-infected patients

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ABSTRACT

Objectives: To determine if long-term highly active antiretroviral therapy (HAART) therapy alters salivary flow rate and also to compare its relation of CD4 count with unstimulated and stimulated whole saliva. **Materials and Methods:** A cross-sectional study was performed on 150 individuals divided into three groups. Group I (50 human immunodeficiency virus (HIV) seropositive patients, but not on HAART therapy), Group II (50 HIV-infected subjects and on HAART for less than 3 years called short-term HAART), Group III (50 HIV-infected subjects and on HAART for more than or equal to 3 years called long-term HAART). Spitting method proposed by Navazesh and Kumar was used for the measurement of unstimulated and stimulated salivary flow rate. Chi-square test and analysis of variance (ANOVA) were used for statistical analysis. **Results:** The mean CD4 count was 424.78 ± 187.03, 497.82 ± 206.11 and 537.6 ± 264.00 in the respective groups. Majority of the patients in all the groups had a CD4 count between 401 and 600. Both unstimulated and stimulated whole salivary (UWS and SWS) flow rates in Group I was found to be significantly higher than in Group II ($P < 0.05$). Unstimulated salivary flow rate between Group II and III subjects were also found to be statistically significant ($P < 0.05$). ANOVA performed between CD4 count and unstimulated and stimulated whole saliva in each group demonstrated a statistically significant relationship in Group II ($P < 0.05$). There were no significant results found between CD4 count and stimulated whole saliva in each groups. **Conclusion:** The reduction in CD4 cell counts were significantly associated with salivary flow rates of HIV-infected individuals who are on long-term HAART.

Key words: CD4 count, highly active antiretroviral therapy, human immune deficiency virus, salivary flow rates

INTRODUCTION

Saliva is known to play an important part in the maintenance of 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.[1] A variety of medical conditions and medications can contribute to the development of salivary gland dysfunction. One such medical condition associated with xerostomia (subjective complaint of dry mouth) and salivary gland hypofunction (objective evidence of reduced salivary output) is the human immunodeficiency virus (HIV) infection. The prevalence of xerostomia and salivary gland hypofunction has been reported to be 2–10% in HIV-infected patients.[2-4] Numerous studies have reported an alteration of salivary gland function and composition in HIV patients in both early and advanced stages of infection.

However, the evolution of antiretroviral therapy has altered the management of patients with HIV infection to the extent that HIV infection is now treated as a chronic disease.[5] As of 2008, there are more than 20 approved antiretroviral drugs against HIV infection across five mechanistic classes. These include

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the nucleoside/nucleotide reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors and integrase inhibitors.[6] Only the first three types have well-established information on oral adverse effects. In contrast, there have been no reports on the oral effects of the latter two.[7,8] When several antiretroviral drugs, typically three, are taken in combination to treat HIV infection, the approach is known as highly active antiretroviral therapy (HAART). Principally, HAART increases CD4 + T-cell counts, decreases HIV ribonucleic acid (RNA) viral load, improves immune status and decreases incidence of opportunistic infections.[9] Significant drop in incidence of oral lesions are noted after the introduction of antiretroviral therapy.[10,11] On the negative side, orofacial adverse effects of HAART are more common, especially with the use of nucleoside reverse transcriptase inhibitors (NRTI), particularly, azidothymidine (AZT).[12]

Contemporary studies have disclosed an increased manifestation of oral warts, salivary gland enlargement and dry mouth in association with HAART as a part of new phenomenon called immune restoration or reconstruction disease (IRD).[13,14] Like some other groups of medicines (e. g. antibiotics, antidepressants and antihistamines), xerostomia and lipodystrophic change of the salivary glands have been reported as potential harmful effects of PI therapy.[7,15] However there is no conclusive evidence in the literature as to how these drugs can alter salivary secretion and composition.[16]

Recent studies reveal that HAART has adverse effects on salivary flow rate and yet there is no concrete evidence on salivary flow rate on long-term usage of HAART therapy. Hence, this study was undertaken to mainly emphasize on the long-term effect of HAART therapy on saliva flow rate and its relation to CD4 count with unstimulated whole saliva and stimulated whole saliva.

MATERIALS AND METHODS

A cross-sectional study was performed at an NGO, recognized by Department of Science and Industrial Research (DSIR), Government of India. The study group comprised of 150 individuals divided into three groups with 50 subjects in each group. Group I (50 HIV-seropositive patients, but not on HAART therapy), Group II (50 HIV-infected subjects and on HAART for a period of less than 3 years called short-term HAART), Group III (50 HIV-infected subjects and on HAART for a period of more than or equal to 3 years called long-term HAART). CD4 + cell count and medications taken by the patient were obtained from the medical records. CD4 + cell count values recorded on the day of saliva collection or 1 week prior to the saliva collection were considered. Unstimulated whole saliva and stimulated whole saliva was collected from each patient in all the three groups. Inclusion criteria for study group included seropositive for HIV [as tested by the government, integrated counseling and testing center by three consecutive HIV rapid tests as per guidelines of National AIDS Control Organisation (NACO)], currently on HAART and consented to participate in the study. Exclusion criteria included HIV-infected subjects with a history of local radiation therapy of head and neck and severely-ill HIV-infected subjects who could not cooperate with the study procedure.

Ethical considerations

The study protocol was approved by research committee at Panineeya Mahavidyalaya Institute of Dental Sciences and Research Center, Hyderabad. All the information about the patient identity was innominate.

Measurement of salivary flow rate

Measurement of salivary flow rate was conducted only in the morning between 9 and 12 am. "Spitting method" proposed by Navazesh and Kumar[17] was used for the collection of unstimulated saliva into a sterile preweighted container for 10 min. Stimulated saliva was collected by applying 2% citric acid on the dorsolateral surface and tip of the tongue every 30 seconds and the patient were asked to passively drain the saliva into a sterile preweighted container. This was done for 5 min and the total volume of saliva was recorded and expressed in ml/min.

Clinical examination

History taking and oral examination were performed in all the study subjects. Clinical diagnosis of HIV-related oral lesions (presence of orofacial pain, feeling of oral dryness and oral burning sensation) was made according to the criteria proposed by the EC-Clearinghouse.[18]

Statistical analysis

The data was coded and entered into Microsoft Excel spread sheet. Analysis was done using Statistical Package for Social Sciences (SPSS) version 15 (SPSS Inc, Chicago, IL, USA) Windows software program. The variables were assessed for normality using the Kolmogorov–Smirnov test. Descriptive statistics were calculated. Chi-square test was used for comparing the frequency and analysis of variance (ANOVA) was used for comparing the means of both groups. Level of significance was set at $P < 0.05$.

RESULTS

The study population comprised of 150 HIV-seropositive patients aged between 20 and 50 years. They were divided into three groups of 50 each. Group I (HIV-seropositive patients and not on HAART Therapy) included 21 (42%) males and 29 (58%) females (mean age - 34.22 ± 7.88), Group II (HIV-infected subjects and on HAART for a period

of less than 3 years called short-term HAART) had 15 (30%) males and 35 (70%) females (mean age - 34.92 ± 7.01) and in Group III (HIV-infected subjects and on HAART for a period of more than or equal to 3 years called long-term HAART) comprised of 18 (36%) males and 32 (64%) females (mean age - 36.28 ± 6.72). The distribution was not significant between the groups ($P > 0.05$). Majority of the patients were females (64%), which was statistically significant between the groups ($P < 0.05$). The mean CD4 + count was 424.78 ± 187.03, 497.82 ± 206.11 and 537.6 ± 264.00 in the respective groups which was also statistically significant ($P < 0.05$) [Table 1].

Majority of the patients in all the groups had a CD4 count between 401 and 600. Thirty-two percent of the patients each in Group II and III had a CD4 count of more than 601. The overall frequency distribution was statistically significant ($P < 0.05$) [Table 2]. The comparison of salivary flow rates among the three groups is as shown in Table 3. The mean unstimulated salivary flow rate in Groups I, II and III were 0.31 ± 0.12, 0.28 ± 0.11 and 0.33 ± 0.13, respectively. Similarly, the mean stimulated salivary flow rate in Groups I, II and III were 0.94 ± 0.16, 0.84 ± 0.20 and 0.92 ± 0.22, respectively. Univariate analysis between unstimulated and stimulated salivary flow rates between three groups was statistically significant ($P < 0.05$) [Table 3].

The mean unstimulated whole salivary (UWS) flow rate in all the three groups with CD4 count of more than 601 was 0.34 ± 0.08, 0.34 ± 0.09 and 0.36 ± 0.08 ml/min, respectively. Reduced salivary flow rate was seen in patients having less than 200 CD4 count in all the three groups (0.25 ± 0.08, 0.3 ± 0.09 and 0.2 ± 0.0 ml/min, respectively). The mean stimulated whole salivary (SWS) flow rate in all the three groups with CD4 count of more than 601 was 1 ± 0.13, 0.95 ± 0.25 and 0.99 ± 0.18 ml/min, respectively. Reduced salivary flow rate was seen in Group III (0.78 ± 0.08 ml/min) patients having CD4 count less than 200 and in Group II (0.78 ± 0.02 ml/min) when CD4 count was between 201 and 400 [Table 4]. The

Table 1: Distribution of the study population according to age, gender and CD4 count

Variables	Group I (HIV-infected subjects) *N*=50 (%)	Group II (short-term HAART) *N*=50 (%)	Group III (long-term HAART) *N*=50 (%)	Total *N*=150 (%)	*F*/χ^2-value *P* value
Age in years					
20-30	16 (32)	13 (26)	08 (16)	37 (24.7)	1.415
30-40	20 (40)	24 (48)	27 (54)	71 (47.3)	0.246
40-50	14 (28)	13 (26)	15 (30)	42 (28)	
Mean	34.22±7.88	34.92±7.01	36.28±6.72	35.14±7.22	
Gender					
Male	21 (42)	15 (30)	18 (36)	54 (36)	45.134
Female	29 (58)	35 (70)	32 (64)	96 (64)	0.038*
CD4 count					
Mean	424.78±187.025	497.82±206.11	537.6±264.00	486.73±224.92	279.34
Range	62-797	131-912	40-1,408	40-1,408	0.001*

Test used: ANOVA followed by Bonferroni for analysis of age and CD4 count. Chi-square test for gender. *P<0.05 is considered statistically significant. HAART=Highly active antiretroviral therapy, HIV=Human immunodeficiency virus, ANOVA=Analysis of variance

Table 2: Distribution of frequencies of CD4 count among the study population

CD4 range	Group I (HIV infected subjects) *N*=50 (%)	Group II (short-term HAART) *N*=50 (%)	Group III (long-term HAART) *N*=50 (%)	Total *N*=150 (%)	χ^2-value *P* value
0-200	8 (16)	2 (04)	4 (08)	14 (9.3)	271.00
					0.05*
201-400	12 (24)	15 (30)	11 (22)	38 (25.3)	
401-600	23 (46)	17 (34)	19 (38)	59 (39.3)	
601 and above	07 (14)	16 (32)	16 (32)	39 (26)	

Test used: Chi square test. *P<0.05 is considered statistically significant. HAART=Highly active antiretroviral therapy, HIV=Human immunodeficiency virus

Table 3: Estimation of salivary flow rate in the study subjects

Salivary flow	Group I (HIV-infected subjects)	Group II (short-term HAART)	Group III (long-term HAART)	F-value *P* value
Unstimulated whole saliva (UWS)	0.31±0.12	0.28±0.11	0.33±0.13	1.537
				0.032*
Stimulated whole saliva (SWS)	0.94±0.16	0.84±0.20	0.92±0.22	

Test used: ANOVA. *P<0.05 is considered statistically significant. HAART=Highly active antiretroviral therapy, HIV=Human immunodeficiency virus, ANOVA=Analysis of variance

CD4 count between both unstimulated and stimulated whole saliva was not statistically significant ($P > 0.05$).

ANOVA was performed between CD4 count and UWS and SWS in each group. In Group I, both UWS and SWS ($P > 0.05$) was found to be not so significant with CD4 count. In Group II, UWS ($P < 0.05$) was statistically significant with CD4 count as compared with Group III. There were no significant results found between CD4 count and SWS in each group.

The prevalence of oral lesions among the study subjects is as shown in Table 5. Orofacial pain (28%) and oral burning sensation (26%) were most frequently observed in Group II, whereas, oral dryness (22%) was seen in Group III. The subjects on HAART therapy demonstrated a higher prevalence for these lesions when compared with those infected but not on therapy; however, it was not statistically significant ($P > 0.05$).

DISCUSSION

Various studies have concluded that HAART has adverse effect on salivary gland function and salivary flow rates,[4,19] yet it is not quantified based on duration of HAART therapy. In our present study, UWS and SWS flow rates were compared among short and long duration usage of HAART therapy with HIV infected individuals.

It was found that both UWS and SWS flow rates of HIV-infected subjects without HAART (Group I) were found to be significantly higher than in those with short-term use of HAART (Group II) ($P < 0.05$), whereas, UWS flow rate between subjects with short-term HAART (Group II) and long-term HAART (Group III) were also found to be statistically significant ($P < 0.05$). Results in the present study were not conforming with an earlier study conducted by Lin *et al*., (2006) where there was no significant difference in the salivary flow rates between subjects on HAART and those who are not on HAART therapy.[20] The present study demonstrate duration of HAART as a factor affecting salivary flow which was not considered in previous studies.

Evidence of reduction in salivary flow rate (both stimulated and unstimulated salivary flow rates) were found in HIV-infected subjects in early stages of the disease process by Schiodt.[21] Our study also revealed decreased salivary flow rate in HIV-positive subjects. One recent longitudinal report indicated that HAART was a risk factor for lower flow rates of unstimulated and chewing-stimulated whole saliva in an interagency population of women with HIV. Navazesh *et al*., 2003 have suggested that these types of individuals are at a significantly higher risk for salivary gland enlargement and salivary gland hypofunction which may alter the composition of saliva.[22] This may also be attributed to HIV infection itself and/or due to consequent immunosuppression or the effect of drugs in HAART.[23] In contrast to our observation, a study in developing countries reported no changes in the prevalence of salivary gland enlargement.[11]

A diffuse infiltration of lymphocytes within the salivary gland [also called diffuse infiltrative lymphocytosis syndrome (DILS)] have been reported in patients with Human Immunovirus-associated salivary gland disease (HIV-SGD) process which is responsible for salivary gland dysfunction.[24]

Our study demonstrated that long-term use of HAART had adverse effects on oral health status of the subjects. Oral dryness was found in 22% of the study subjects. This is in accordance with a previous study by Patton *et al*.,[19] who have also reported that oral symptoms were frequently observed among HIV-infected individuals. However, a study by Nittayananta *et al*.,[25] showed greater risks of having orofacial pain, oral dryness and oral lesions in HIV-infected subjects

Table 4: Mean CD4 count vs unstimulated and stimulated whole saliva

CD4 range	Unstimulated whole saliva			F-value *P* value	Stimulated whole saliva			F-value *P* value
	Group I (HIV-infected subjects)	Group II (short-term HAART)	Group III (long-term HAART)		Group I (HIV-infected subjects)	Group II (short-term HAART)	Group III (long-term HAART)	
0-200	0.25±0.08	0.3±0.09	0.2	1.18	0.86±016	0.88±0.21	0.78±0.08	0.13
201-400	0.29±0.07	0.26±0.07	0.28±0.08	0.032*	0.96±0.19	0.78±0.2	0.81±0.18	1.000
401-600	0.28±0.05	0.29±0.05	0.31±0.06		0.95±0.12	0.87±0.2	0.85±0.14	
601 and above	0.34±0.08	0.34±0.09	0.36±0.08		1±0.13	0.95±0.25	0.99±0.18	

Test used: ANOVA followed by Bonferroni. *P<0.05 is considered statistically significant. HAART=Highly active antiretroviral therapy, HIV=Human immunodeficiency virus, ANOVA=Analysis of variance

Table 5: Prevalence of oral lesions in HIV-infected subjects

Oral lesions*	Group I (HIV-infected Subjects) *N*=50 (%)	Group II (short-term HAART) *N*=50 (%)	Group III (long-term HAART) *N*=50 (%)	χ^2 value *P* value
Orofacial pain	13 (26)	14 (28)	10 (20)	7.52
Oral dryness	5 (10)	8 (16)	11 (22)	0.111
Oral burning sensation	6 (12)	13 (26)	12 (24)	

*Some subjects have more than one lesion. Test applied: Chi-square test. HAART=Highly active antiretroviral therapy, HIV=Human Immunodeficiency Virus

who were not on HAART than those with HAART. Similarly, Greenspan *et al*., 2004[10] have reported the effectiveness of HAART in the reduction of incidence of oral damage. This may be attributed to an increase in CD4 cell count, lower viral loads and direct inhibition by PIs.

Among HAART regime, PIs are group of drugs which causes lipodystrophic changes in parotid salivary gland which is ultimately responsible for xerostomia-like symptoms and reduced salivary flow rates.[7] In a study on effect of HAART on salivary gland function in HIV-infected women done by Navazesh *et al*., found that HAART with PIs cause significant reduction in salivary flow rates (both stimulated and unstimulated) when compared to HIV-infected subjects who are not on HAART therapy.[4] The results of present study coincide with that of Nittayananta *et al*., in which most of the subjects on HAART did not have PI in their regime.[25]

But in Indian scenario, PI-based therapy is only used in second regime when first regimen of drugs fails according to Guidelines of NACO. So subjects in the present study were on first-line HAART therapy according to NACO guidelines which mostly uses 2 NRTI + 1 NNRTIs.[26] The most common drugs being used in first-line regime are zidovudine, lamivudine, nevirapine and stavudine.[27] The present study reports for the first time the effect of salivary flow rate in HIV patients on HAART, in relation to duration of usage of the antiretroviral drugs in Indian scenario. However, further studies of patients in the advanced stages of HIV disease and/or a longitudinal evaluation of salivary gland function in HIV patients is necessary to delineate the beneficial/deleterious effects of HAART on salivary gland function and oral health.

CONCLUSIONS

Patients living with the HIV and on HAART had a reduced rate of salivary flow than the group not on HAART. The reduction in CD4 cell counts were significantly associated with reduced salivary flow rates in HIV-infected individuals who are on HAART for duration longer than 3 years.

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