ORIGINAL ARTICLE

# Impact of highly active antiretroviral therapy on salivary flow in patients with human-immuno deficiency virus disease in Southern India

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## ABSTRACT

**Aims:** To ascertain and compare between highly active antiretroviral therapy (HAART) and non-HAART patients, the stimulated salivary flow rates and unstimulated salivary flow rates (USFR and SSFR) and to correlate the salivary flow rates with immune suppression. **Materials and Methods:** One hundred human-immuno deficiency virus seropositive patients attending RAGAS-YRG CARE were examined and divided into two groups, a HAART group (patients on combination antiretroviral therapy) comprising 50 patients and a non-HAART group comprising 50 patients. The HAART group was followed every 3 months after the baseline visit (0) for a period of 9 months, during which a clinical oral examination and collection of unstimulated and stimulated saliva was done. Their salivary gland function was assessed using a xerostomia inventory during each visit. The study on non-HAART group was cross-sectional. **Statistical Analysis:** Statistical analysis were performed with the aid of the Statistical Package for the Social Sciences (SPSS version 10.05) software. **Results:** There was no significant difference in mean SSFR and USFR between the two groups at baseline. In the HAART group, the mean stimulated salivary flow rate increased from baseline to 3 months ($P = 0.02$), with the increase being maintained at 6 months and 9 months. When salivary flow rates were correlated with Cluster of Differentiation, CD4 counts, patients in the HAART group with a CD4 ≤ 200 at 6 months visit had a higher mean stimulated salivary flow rate when compared with patients with CD4 ≥ 200 ($P = 0.02$). The xerostomia inventory did not reveal any significant difference between the two groups and HAART was not significantly associated with xerostomia. **Conclusion:** In our study HAART was neither associated with xerostomia nor a reduction in salivary flow rate and immune suppression was not a significant factor for decreasing the salivary flow rate.

***Key words:*** **Cluster of differentiation 4 (CD4) count, highly active antiretroviral therapy, human-immuno deficiency virus, salivary flow rates**

## INTRODUCTION

Saliva plays an important role in maintaining the oral health status. Human-immuno deficiency virus (HIV) infection affects salivary gland function. Salivary gland disease which include xerostomia, cysts and Sjogren's syndrome-like condition with persistent glandular enlargement and secretory hypofunction have been reported in HIV-infected individuals.[1-3]

HIV-salivary gland disease (SGD) includes lymphoepithelial lesions and cysts involving the salivary gland tissue and/or intra-glandular lymph nodes, Sjogren's syndrome-like condition and diffuse infiltrative CD8 Lymphocytosis syndrome (DILS).[4] The introduction of highly active antiretroviral therapy (HAART) which includes a combination of antiretroviral drugs in the treatment of HIV infected has led to a significant decrease in oral manifestations.[5-7] However, adverse effects like xerostomia and an increase in salivary gland disease have been reported with HAART.[8,9] The present study was done to ascertain and compare between HAART

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and non-HAART patients, the occurrence of salivary gland disease, unstimulated salivary flow rates and stimulated salivary flow rates (USFR and SSFR) and their relationship to CD4 count and the perception of xerostomia.

## MATERIALS AND METHODS

The study was carried out on 100 confirmed HIV seropositive patients attending RAGAS-YRG CARE, Chennai, India. The patients were divided into two groups, HAART group comprising 50 patients initiated on HAART. The patients were on a combination of two nucleotide reverse transcriptase inhibitors and one non-nucleotide reverse transcriptase inhibitor. After the baseline (0) examination, they were followed-up in the consecutive 3rd, 6th, and 9th month. At the baseline visit, 50 patients were examined. Subsequently, 44, 35, and 20 patients were followed-up at 3, 6, and 9 months respectively as patients were lost to follow-up. During each visit, clinical oral examination, collection of unstimulated and stimulated saliva was carried out. A "multi-item" xerostomia inventory comprising a set of 19 questions was used to assess salivary gland function during each visit.[10] EC-Clearing house criteria was used to diagnose oral lesions.[11] The "spitting method" proposed by Navazesh *et al.*,[12] was used for the collection of unstimulated saliva. Stimulated saliva was collected by applying 2% citric acid on the dorsolateral surface and tip of the tongue every 30 seconds and the patient was asked to spit saliva into a sterile graduated container. This was done for 10 min and the total volume of saliva was recorded and expressed in ml/min. Fifty patients not on HAART (with age and CD4 count matched as closely as possible with those in the HAART group) comprised the non-HAART group. The study on non-HAART patients was cross-sectional.

### Statistical analysis

Data entry, database management, and all statistical analysis were performed with the aid of the Statistical Package for the Social Sciences (SPSS version 10.05) software. Student *t*-test was carried out to compare the mean differences in normally distributed data. Mann-Whitney U test was applied to assess the statistical differences between the groups of patients when the data were non-normal. ANOVA (one-way) test was used to compare the mean unstimulated salivary flow rate and stimulated salivary flow rate within the HAART group at 0, 3, 6, and 9 months. A $P$ of $< 0.05$ was considered statistically significant.

## RESULTS

The study population comprised 100 HIV seropositives, 50 in the HAART group and 50 in the non-HAART group. There were 76 males (HAART group = 36, non HAART group = 40) and 24 females (HAART group = 14, non-HAART group = 10). The mean age in the HAART group was 34 ± 6.3 (males = 35.1 ± 5.9; females = 30.7 ± 6.5). The mean age in non-HAART group was 35.2 ± 7.6 (males = 36.3 ± 7.5; females = 30.7 ± 6.2) [Table 1]. The mean CD4 count in HAART and non-HAART groups were 255 ± 110 and 200 ± 90 respectively. Forty one patients had a CD4 count ≤ 200 (HAART group = 36% and non-HAART group = 46%) and 59 had a CD4 count > 200 (HAART group = 64% and non-HAART group = 46%) [Table 2]. When the salivary flow rates between the two groups were compared, the mean unstimulated salivary flow rate in HAART group at baseline was 0.61 ± 0.18 and in the non-HAART group was 0.65 ± 0.29. [Table 3; Figure 1].The mean stimulated salivary flow rate in HAART group at baseline and non-HAART groups was 1.24 ± 0.50 and 1.37 ± 0.53 respectively. [Table 3; Figure 2]. The mean unstimulated salivary flow rate in the HAART group at baseline (0), 3, 6, and 9 months was 0.61 ± 0.18, 0.62 ± 0.27, 0.69 ± 0.25, and 0.68 ± 0.27 respectively [Table 4; Figure 1]. The mean stimulated salivary flow rate at baseline was 1.24 ± 0.50 at 3 months 1.57 ± 0.51, at 6 months 1.49 ± 0.73, and at 9 months 1.23 ± 0.57 ($P = 0.02$) [Table 4; Figure 2].

The mean unstimulated salivary flow rate in HAART patients with a CD4 count ≤ 200 at baseline (0) was 0.56 ± 0.13 ml/min, whereas in patients with a CD4 count > 200, the mean unstimulated salivary flow rate was 0.64 ± 0.1 ml/min. At 3 months, the mean unstimulated salivary flow rate in patients with a CD4 count ≤ 200 was 0.61 ± 0.27 ml/min and 0.63 ± 0.27 ml/min in patients with a CD4 count > 200. The mean unstimulated salivary flow rate in patients with a CD4 ≤ 200 at 6 months and 9 months was 0.86 ± 0.38 ml/min and 0.68 ± 0.28 ml/min respectively, whereas in patients with a CD4 > 200, the mean un-stimulated salivary flow rate was 0.66 ± 0.23 ml/min at 6 months and 0.68 ± 0.28 ml/min at 9 months. The mean

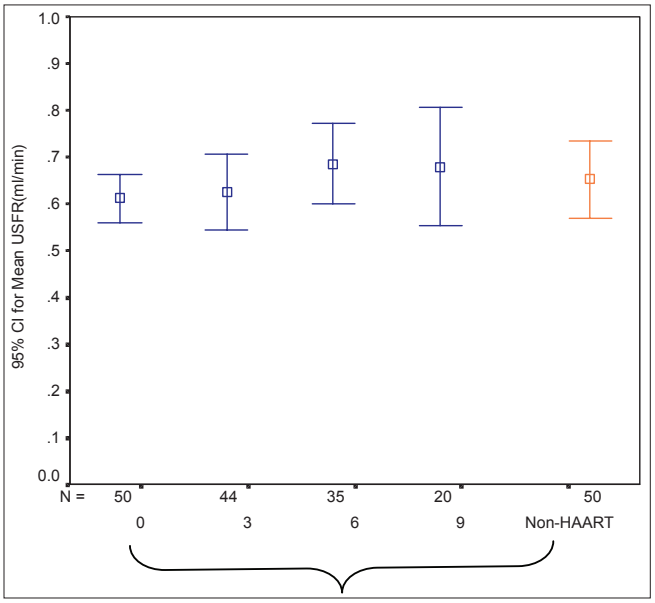


**Figure 1:** Mean and 95% confidence interval for mean unstimulated salivary flow rate in highly active antiretroviral therapy at baseline (0), 3, 6, and 9 months and non-HAART groups

**Table 1: Age and gender distribution**

| Group | Males *n*=76 | Females *n*=24 | Mean age | Mean age (males) | Mean age (females) | M:F |
|---|---|---|---|---|---|---|
| HAART | 36 | 14 | 34±6.3 | 35.1±5.9 | 30.7±6.5 | 2.6:1 |
| Non-HAART | 40 | 10 | 35.2±7.6 | 36.3±7.5 | 30.7±6.2 | 4:1 |

HAART: Highly active antiretroviral therapy

**Table 2: CD4 count in the study population**

| Group | CD4≤200 *n*=41% | CD4>200 *n*=59% | Mean CD4 count |
|---|---|---|---|
| HAART | 36 | 64 | 255±110 |
| Non-HAART | 46 | 54 | 200±90 |

HAART: Highly active antiretroviral therapy, CD4: Cluster of differentiation 4

**Table 3: Mean unstimulated and stimulated salivary flow rates in highly active antiretroviral therapy (at baseline) and non-HAART groups**

| Mean salivary flow rate ml/min | HAART *n*=50 | Non-HAART *n*=50 | *P* |
|---|---|---|---|
| USFR ml/min | 0.61±0.18 | 0.65±0.29 | 0.40 |
| SSFR ml/min | 1.24±0.50 | 1.37±0.53 | 0.20 |

HAART: Highly active antiretroviral therapy, USFR: Unstimulated salivary flow rates, SSFR: Stimulated salivary flow rates

**Table 4: Mean unstimulated and stimulated salivary flow rates in highly active antiretroviral therapy group at baseline (0) 3, 6, 9 months**

| Mean salivary flow rate ml/min | 0 *n*=50 | 3 *n*=44 | 6 *n*=35 | 9 *n*=20 | *P* |
|---|---|---|---|---|---|
| USFR ml/min | 0.61±0.18 | 0.62±0.27 | 0.69±0.25 | 0.68±0.27 | 0.43 |
| SSFR ml/min | 1.24±0.50 | 1.57±0.51 | 1.49±0.73 | 1.23±0.57 | 0.02* |

USFR: Unstimulated salivary flow rates, SSFR: Stimulated salivary flow rates, *$P$<0.05

stimulated salivary flow rate in HAART patients with a CD4 count ≤ 200 at baseline (0) was 1.06 ± 0.26 ml/min and those with a CD4 count > 200 had a mean stimulated salivary flow rate of 1.34 ± 0.59 ml/min. At 3 months, the mean stimulated salivary flow rate in patients with a CD4 ≤ 200 and CD4 > 200 was 1.54 ± 0.49 ml/min and 1.6 ± 0.54 ml/min respectively. The mean stimulated salivary flow rate at 6 months in patients with a CD4 ≤ 200 was 2.25 ± 0.98 ml/min and in those with a CD4 count > 200 was 1.39 ± 0.64 ml/min ($P$ = 0.02). At 9 months, the mean stimulated salivary flow rate in HAART patients with a CD4 count ≤ 200 was 1.15 ± 0.19 ml/min and 1.25 ± 0.64 ml/min in those with a CD4 count > 200 [Table 5; Figure 3].

The mean unstimulated salivary flow rate in non-HAART patients with a CD4 count ≤ 200 was 0.60 ± 0.26 ml/min and 0.69 ± 0.31 ml/min in patients with a CD4 count > 200. In patients with a CD4 count ≤ 200, the mean stimulated salivary flow rate was 1.24 ± 0.40 ml/min and in patients with a CD4 > 200, the mean stimulated salivary flow rate was 1.48 ± 0.6 ml/min [Table 6; Figure 4].

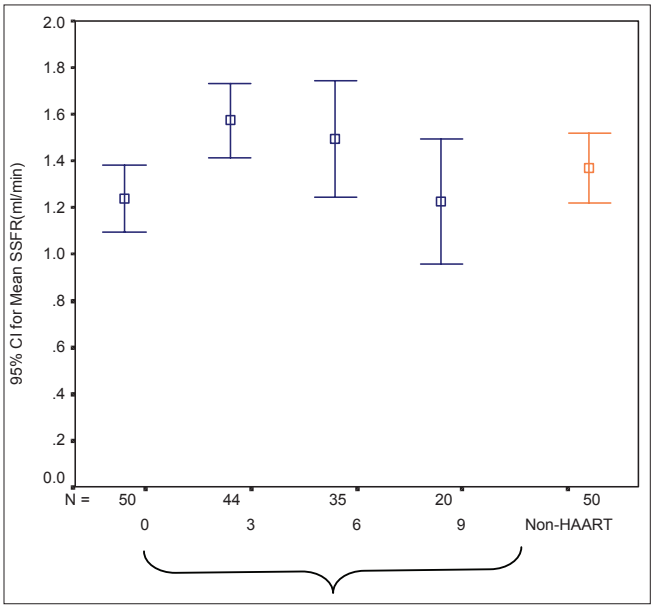


**Figure 2:** Mean and 95% confidence interval for mean stimulated salivary flow rate in highly active antiretroviral therapy at baseline (0), 3, 6, and 9 months and non-HAART groups

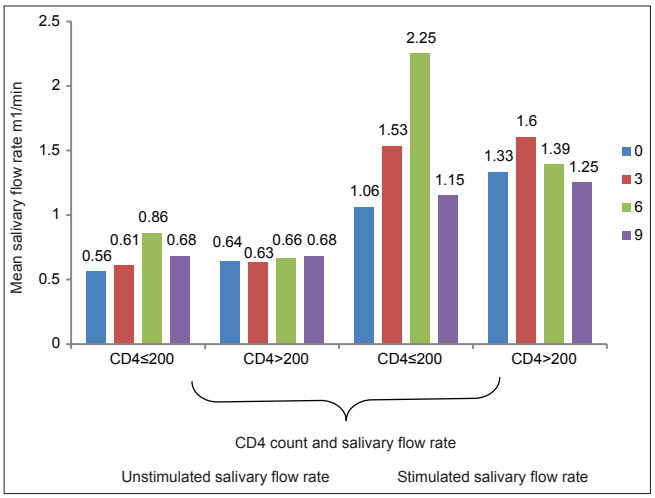


**Figure 3:** Mean salivary flow rates in highly active antiretroviral therapy group with CD4≤200 and CD4>200 at baseline (0), 3, 6, and 9 months

The results of the subjective symptoms of dry mouth perceived by HAART and non-HAART patients are listed in Table 7.

## DISCUSSION

HIV infection affects salivary gland function. Xerostomia with a Sjogren's syndrome-like condition with persistent glandular enlargement and secretory hypofunction have been

**Table 5: Mean salivary flow rates in highly active antiretroviral therapy patients with CD4≤200 and CD4>200 at baseline (0), 3, 6, 9 months**

| Visit | *n* | Mean USFR ml/min | | | | *P* | Mean SSFR ml/min | | *P* |
|---|---|---|---|---|---|---|---|---|---|
| | | CD4≤200 | *n* (%) | CD4>200 | *n* (%) | | CD4≤200 | CD4>200 | |
| 0 | 50 | 0.56±0.13 | 36 | 0.64±0.10 | 64 | 0.13 | 1.06±0.26 | 1.34±0.59 | 0.07 |
| 3 | 44 | 0.61±0.27 | 45 | 0.63±0.27 | 54 | 0.87 | 1.54±0.49 | 1.6±0.54 | 0.70 |
| 6 | 35 | 0.86±0.38 | 11.4 | 0.66±0.23 | 88.5 | 0.16 | 2.25±0.98 | 1.39±0.64 | 0.02* |
| 9 | 20 | 0.68±0.28 | 20 | 0.68±0.28 | 80 | 0.97 | 1.15±0.19 | 1.25±0.64 | 0.77 |

USFR: Unstimulated salivary flow rates, SSFR: Stimulated salivary flow rates, *$P$<0.05

**Table 6: Mean salivary flow rates in non-highly active antiretroviral therapy patients with CD4≤200 and CD4>200**

| Mean USFR ml/min | | | | *P* | Mean SSFR ml/min | | *P* |
|---|---|---|---|---|---|---|---|
| CD4≤200 | *n* (%) | CD4>200 | *n* (%) | | CD4≤200 | CD4>200 | |
| 0.60±0.26 | 46 | 0.69±0.31 | 54 | 0.31 | 1.24±0.40 | 1.48±0.6 | 0.12 |

USFR: Unstimulated salivary flow rates, SSFR: Stimulated salivary flow rates

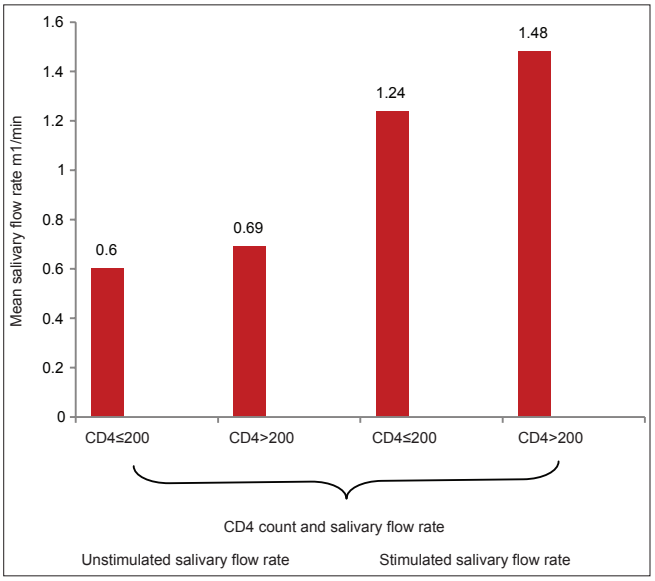


**Figure 4:** Mean salivary flow rates in non-highly active antiretroviral therapy group with CD4≤200 and CD4>200

reported.[13] HIV-SGD includes lymphoepithelial lesions and cysts involving the salivary gland tissue and/or intra-glandular lymph nodes, Sjogren's syndrome-like condition, and DILS. In the present study, the mean USFR and SSFR in HAART and non-HAART groups were compared. The "spitting method", proposed by Navazesh,[12] was used for collecting saliva as it is an inexpensive, simple, and an easily reproducible procedure. There was no significant difference in the salivary flow rates between the two groups at baseline. When the mean unstimulated salivary flow rate in HAART group at baseline (0), 3, 6, and 9 months was compared, there was no statistically significant difference. The mean stimulated salivary flow rate increased from baseline to 3 months and this increase was statistically significant ($P$ = 0.02). This increase was maintained at 6 months and 9 months. This is in contrast to that reported by Navazesh *et al.*,[14] who identified HAART as a significant risk factor for low unstimulated (≤0.1 ml/min) and low stimulated (≤0.7 ml/min) salivary flow rate. In the present study, neither the HAART nor non-HAART patients had an unstimulated salivary flow rate ≤0.1 ml/min and a stimulated salivary flow rate ≤0.7 ml/min**.** Greenspan *et al.*,[5] and Patton *et al.*,[6] observed an increase in HIV salivary gland disease following HAART and attributed this increase to lympho-proliferative reactivation stimulated by HAART. This was not seen in this study. In HIV salivary gland disease, the infiltrate is composed predominantly of lymphocytes of the CD8 (suppressor) subtype. The increased numbers of circulating CD8 T-cells that infiltrate salivary glands in HIV infection is designated DILS.[1] The increase in mean stimulated salivary flow rate observed in patients on HAART during follow up may be attributed to the immune reconstitution following HAART, which probably reduces the CD8 lymphocytosis in salivary glands. To ascertain if immune suppression influences salivary flow rate, the mean USFR and SSFR in HAART and non-HAART patients with a CD4 ≤ 200 and CD4 > 200 were compared. The mean USFR and SSFR in non-HAART patients with a CD4 ≤ 200 and CD4 > 200 were not statistically significant. In the HAART group at baseline (0), patients with CD4 ≤ 200 had a lower mean stimulated salivary flow rate when compared with patients with CD4 > 200 ($P$ = 0.07). Navazesh *et al.*,[15] in their study on 733 HIV-positive and at risk HIV-negative women observed that HIV-positive women with a CD4 ≤ 200 had a higher prevalence of zero unstimulated saliva, suggesting that immunosuppression affects salivary gland function. In yet another study**,** Mulligan *et al.*,[16] found that HIV-positive women had higher rates of salivary gland tenderness and absence of saliva on palpation that was significantly associated with a low CD4 count. In the HAART group at 6 months, patients with CD4 count ≤ 200 had a higher mean stimulated salivary flow rate when compared with patients with CD4 > 200 and this was statistically significant ($P$ = 0.02). Since there were only four patients with CD4 ≤ 200 out of the 35 patients followed-up at 6 months, these results will have to be confirmed with larger samples.

Antiretroviral drugs like didanosine, zidovudine, lamivudine, and protease inhibitors (indinavir, nelfinavir,

**Table 7: Subjective symptoms of dry mouth perceived by highly active antiretroviral therapy and non-HAART patients (% of patients who gave a positive response)**

| Xerostomia inventory questionnaire | HAART *n*=50 (%) | | | | Non-HAART *n*=50 (%) |
|---|---|---|---|---|---|
| | 0 *n*=50 | 3 *n*=44 | 6 *n*=35 | 9 *n*=20 | |
| Often my mouth feels dry | 26 | 15.9 | 2.85 | - | 36 |
| I sip liquids to aid swallowing | - | - | 2.85 | - | - |
| I get up in night to drink water | 28 | 6.8 | 17.1 | - | 24 |
| My mouth feels dry while eating | 4 | - | 2.85 | - | 4 |
| My mouth feels dry always | 16 | 2.2 | 2.85 | - | 6 |
| Difficulty while eating | 2 | - | 2.85 | - | 2 |
| I suck cough lollies | 2 | - | - | - | 8 |
| Difficulty in swallowing certain foods | - | - | 5.7 | - | 4 |
| Skin of my face feels dry | 4 | - | 2.85 | - | - |
| My eyes feel dry | 4 | - | 2.85 | - | - |
| My lip feel dry | 8 | 15.9 | 8.5 | - | 26 |
| The inside of my nose feels dry | - | - | 2.85 | - | - |
| Burning sensation in gums | - | - | - | - | - |
| Burning sensation in tongue | 4 | 4.5 | 2.85 | - | 8 |
| I feel itching sensation in tongue | - | - | - | - | - |
| I feel itching sensation in gums | - | - | - | - | - |
| I feel burning sensation in mouth | 2 | 2.2 | - | - | 6 |
| I feel taste alterations | 10 | - | 5.7 | - | 12 |
| I feel pain in jaws while eating | - | - | - | - | - |

HAART: Highly active antiretroviral therapy

ritonavir and saquinavir) have been reported to cause xerostomia.[8,9] In this study xerostomia was evaluated using a "multi-item" inventory comprising a set of 19 questions proposed by Thomson *et al.*[10] A greater number of patients in the non-HAART group perceived dryness of lips when compared with HAART patients at baseline and this was statistically significant ($P = 0.02$). Out of the 19 questions, only 3 questions "Does your mouth feel dry?" ($P = 0.00$), "Do you get up in the night to drink water?" ($P = 0.00$), and "Does your mouth feel dry always?" ($P = 0.01$) were statistically significant in the HAART group at baseline (0), 3, 6, and 9 months. In the HAART group, the percentage of patients who perceived xerostomia at 3, 6, and 9 months was less than the percentage of patients who perceived xerostomia at baseline (0). This correlates with the increase in mean stimulated salivary flow rate observed from baseline to 3 months which was maintained at 6 months and 9 months. In this study population HAART was not significantly associated with xerostomia.

Sreebny *et al.*,[17] classified USFR that were ≤0.1 ml/min as "abnormal", between 0.11 ml/min and 0.2 ml/min as "low normal," and greater than 0.2 ml/min as "normal." In their study, subjects who complained of dry mouth had USFR ≤ 0.1 ml/min and hence they concluded that the subjective feeling of xerostomia is usually associated with a marked decrease in the rate of whole saliva. In the present study, the HAART and non-HAART patients had "low normal" to "normal" salivary flow rates. Fox suggested that dry mouth symptoms are not reliable indicators of diminished salivary flow rates.[13] Narhi *et al.*,[18] stated that not all patients who complain of dry mouth have salivary gland hypo-function. Although some of the HAART and non-HAART patients perceived xerostomia, their salivary flow rates were normal in the present study.

In the present study, there was no difference in the salivary flow rates (unstimulated and stimulated) between the two groups. In the HAART group, there was an increase in the mean stimulated salivary flow rate from baseline (0) to 3 months and this increase was maintained at 6 months and 9 months. As the salivary flow rates were within normal limits, the xerostomia questionnaire did not reveal any difference between the two groups. Since many patients were lost to follow up in the HAART group in the present study, a long-term follow-up study with a larger sample is required for conclusive evidence on salivary flow rates.

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