Periodontal Conditions in Human Immunodeficiency Virus–Positive Patients Under Highly Active Antiretroviral Therapy From a Metropolitan Area of Rio De Janeiro

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Background: The aim of this study is to evaluate the periodontal status and the presence of opportunistic oral lesions in human immunodeficiency virus–positive (HIV+) patients under highly active antiretroviral therapy (HAART) and their association with cluster of differentiation (CD)4+ and CD4+ nadir T-cell counts and viral load levels.

Methods: Clinical periodontal parameters and the presence of opportunistic oral lesions along with records of CD4+ counts and viral load levels were evaluated in 29 individuals (16 females; mean age: 42.7 years) with previous serologic diagnosis of HIV, from the acquired immunodeficiency syndrome program of the Health Center of Duque de Caxias, Rio de Janeiro, Brazil.

Results: All individuals presented gingivitis or periodontitis. A higher non-significant prevalence of periodontitis was found in smokers (93.8%) compared with non-smokers (76.9%). A significant weak positive correlation was observed between CD4+ counts and missing teeth ($\rho = 0.380$, $P < 0.05$), CD4+ nadir and periodontal diagnosis ($\rho = 0.418$, $P < 0.005$), and CD4+ nadir and moderate probing depth (PD) ($\rho = 0.424$, $P < 0.05$). When only non-smokers were analyzed, a significant moderate positive association was found between viral load and moderate clinical attachment level (CAL) ($\rho = 0.638$, $P < 0.05$), CD4+ nadir and diagnosis ($\rho = 0.586$, $P < 0.05$), and CD4+ nadir and moderate CAL ($\rho = 0.680$, $P < 0.05$). Analysis considering only smokers found no correlations between serologic parameters and demographic or clinical parameters.

Conclusions: The current investigation demonstrates that HIV+ individuals under HAART presents a high prevalence of mild to moderate periodontal disease. Viral load levels, CD4+ nadir, and CD4+ counts may present a weak to moderate correlation to the number of missing teeth, periodontal diagnosis, moderate PD, and moderate CAL, which may also reflect some effect of these systemic conditions on the periodontal status. *J Periodontol 2016;87:338-345.*

KEY WORDS

Antiretroviral therapy, highly active; CD4-positive T-lymphocytes; HIV; periodontal diseases; viral load.

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doi: 10.1902/jop.2015.150345

Human immunodeficiency virus (HIV) infection is still an important and prevalent medical condition. There are an estimated 35 million people living with HIV/acquired immunodeficiency syndrome (AIDS) worldwide in 2012.[1] In Brazil, the estimated prevalence is ≈718,000 individuals.[2] HIV is an RNA virus that has an affinity for the cluster of differentiation (CD)4 molecule present on the surface of some cells, mainly in T lymphocytes, monocytes, and macrophages.[3]

In the past, severe manifestations of AIDS that used to lead infected individuals to death have become manageable chronic conditions. This change in clinical outcome was possible because of the introduction of the highly active antiretroviral therapy (HAART).[3] HAART has allowed HIV-infected individuals to have a better quality of life associated with increased life expectancy.[4]

The aim of HAART is to reduce HIV-associated morbidity, prolong and improve the quality of life of HIV-positive (HIV+) individuals, restore and preserve their immune function, decrease their viral load, and prevent the transmission of HIV.[5] The availability of this therapy resulted in dramatic reductions in mortality and morbidity related to HIV.[6] HAART is a combination of at least three antiviral drugs.[7] It may be composed of two nucleoside analog reverse transcription (RT) inhibitors, a non-nucleoside RT inhibitor, or a protease inhibitor.[8]

Monitoring clinical and immunologic status of the HIV+ patients is crucial, and the most commonly used parameters for this purpose are the CD4+ (CD4+) T-lymphocyte count and viral load measurements.[9] The CD4+ T lymphocytes are the main targets of infection, and their counts are used to assess the level of immunosuppression.[10,11] Furthermore, this is the most reliable method for monitoring HIV+ patients.[5,12]

Conversely, viral load assessment is proportional to the total number of infected cells.[10] Moreover, it indicates, through the average rate of increase in the number of infected cells, how fast the patient may progress to AIDS.[10] The count is considered high if it ranges from 100,000 to 1 million copies/mL.[5] The primary goal of HAART is to lower this number to 20 to 70 copies/mL, which is considered undetectable by most available assays. By 2020, the Joint United Nations Program on HIV/AIDS (UNAIDS) hopes to diagnose 90% of all those with unknown HIV infection, treat 90% of those diagnosed, and achieve 90% of undetectable viral loads in those treated to curb the HIV epidemic.[13] Still, a high viral load is a strong indication for starting HAART.[9] Asymptomatic patients with CD4+ counts <500 cells/mm^3 are considered at risk for HIV infection progression, especially if the viral load is >100,000 copies/mL.[5]

The oral lesions are an important part of the complex of diseases associated with AIDS, especially candidiasis, hairy leukoplakia, Kaposi sarcoma, non-Hodgkin lymphoma, and necrotizing periodontal disease.[3-5] Nevertheless, the introduction of HAART promoted a stabilization of CD4+ counts and the reduction of viral load, and consequently, the reduction of the total prevalence of oral lesions.[14] Oral lesions in HIV+ patients are opportunistic conditions, and their presence is correlated closely with viral load and CD4+ cell counts. It has being suggested that the absence of those lesions could be used as a marker for the efficacy of HAART, especially in developing countries.[15] The first periodontal manifestations in HIV+ patients, including linear gingival erythema, necrotizing ulcerative gingivitis, and necrotizing ulcerative periodontitis, were described in the late 1980s.[16] After the introduction of HAART, a decline in the frequency of destructive forms of periodontal disease in HIV+ patients has been observed in both developed and developing countries.[17] Low prevalence of oral lesions in patients under HAART has been described recently.[18] In immunocompromised patients, preexisting periodontitis can show worsening of clinical periodontal parameters.[19] Therefore, HIV infection could be considered a modifier of periodontal disease severity.[19,20] Conversely, some findings have suggested that HIV infection may not increase periodontal probing depth (PD), attachment loss, or tooth loss.[21]

In Nigeria, a study[22] including 120 HIV+ patients observed that the prevalence of periodontitis was 64%. However, there was no association between periodontitis and CD4+ counts. In contrast, a study from India showed a negative significant association between immune status (CD4+ cell counts) and periodontal status (presence of supragingival or subgingival calculus).[23] These contrasting findings regarding the relation between chronic periodontitis (CP) and/or the presence of opportunistic oral lesions in HIV+ patients may raise many questions, indicating that the oral status of HIV+ after the introduction of HAART is not completely elucidated. Therefore, the aim of this study is to evaluate the periodontal status and the presence of opportunistic oral lesions in HIV+ patients under HAART and their association with CD4+ and CD4+ nadir counts and viral load levels.

MATERIALS AND METHODS

Study Population

The studied population consisted of individuals with previous serologic diagnosis of HIV from the AIDS Healthcare Center of Duque de Caxias, Rio de Janeiro, Brazil, under HAART treatment. Individuals were enrolled in the study from March to August 2014. The study protocol was reviewed and approved by the Ethics Review Committee for Human Subjects of the University of Grande Rio, Rio de Janeiro, Brazil, under 30279114.0.0000.5283.

Of 70 individuals screened to participate in this study, 29 females (aged 32 to 62 years; mean age: 42.7 years) agreed to participate after meeting the following inclusion criteria: 1) had at least 15 teeth, and 2) were older than 18 years. Participants were informed about the nature of the study protocol and signed an informed consent form before enrollment.

Clinical Data

Through anamnesis questionnaires, data regarding age, sex, and smoking habits were obtained. The following information was collected from the medical chart: current CD4+ and CD4+ nadir (lowest-ever levels of CD4+) counts and viral load levels. These tests are usually performed every 6 months, and the most recently included was performed within the 6 months before periodontal examination done in the study.

The CD4+ counts were categorized by absolute numbers as low if <350 cells/mm^3, medium if between 350 and 500 cells/mm^3, and high if >500 cells/mm^3.[5,9]

The viral load level was categorized as high if from 100,000 to 1 million copies/mL, low if <10,000 copies/mL, and as undetectable if from 20 to 70 copies/mL.[5,9]

A single calibrated examiner (LPDB) conducted the periodontal examination. The periodontal parameters measured were PD, clinical attachment level (CAL), and bleeding on probing (BOP) at six sites per tooth with a periodontal probe.‖ Clinical diagnosis of periodontal status was established for all participants based on the following criteria: 1) periodontal health, ≤10% of sites with BOP, no PD or CAL >3 mm, although PD or CAL = 4 mm in up to 5% of the sites without BOP was allowed; 2) gingivitis, >10% of sites with BOP and no PD or CAL >3 mm, although PD or CAL = 4 mm in up to 5% of the sites without BOP was allowed; and 3) periodontitis, >10% of teeth with PD and/or CAL ≥5 mm and BOP.[24] After periodontal examinations, the patients diagnosed with periodontal disease were treated.

The oral mucosa was evaluated by visual inspection for the presence of oral lesions associated with HIV infection, such as candidiasis, necrotizing lesions, tumoral lesions, and other opportunistic conditions.

Statistical Analyses

Statistical analyses were performed using a statistical software package.¶ Participants were divided in two groups: 1) smokers, and 2) non-smokers. Frequency of males/females, gingivitis, and periodontitis was calculated according to smoking status. Mean missing teeth and mean percentage of BOP, moderate PD (>4 to 6 mm), severe PD (>6 mm), moderate CAL (>4 to 6 mm), and severe CAL (>6 mm) were also calculated according to smoking status. Values of current CD4+ and CD4+ nadir were compared and the differences tested by Wilcoxon test. Bivariate Spearman correlation was calculated to evaluate associations among viral load, CD4+ nadir, and CD4+ counts with demographic (age, sex, and smoking habit) and clinical (missing teeth, BOP, diagnosis of gingivitis or periodontitis, moderate and severe PD, and moderate and severe CAL) variables. Significant differences for variables between different smoking statuses were sought by χ^2 and Mann-Whitney *U* tests. Statistical significance was reached at a 5% level.

RESULTS

No opportunistic oral lesion associated with HIV infection was detected in the study population.

Table 1 displays demographic data of the study population. There were 16 smokers, who were mostly females (11 females and five males). The participants showed a mean ± SD age of 39.54 ± 5.07 and 45.31 ± 9.21 years for non-smoker and smokers, respectively. Those differences were not statistically significant.

Regarding the type of HAART, 69% of the patients were being treated with efavirenz backbone therapy and 31% with protease inhibitors. Four (14%) patients had diabetes, and they were females. Medical history was pulmonary tuberculosis in seven (24%), oral candidiasis in six (21%), including two cases associated with esophageal involvement, and neurotoxoplasmosis in three patients (10.5%). One patient had a history of Kaposi sarcoma involving skin and mucosae. Only six (21%) individuals were asymptomatic. Regarding sexual behavior, six (21% overall, 46% of males) were males who were homosexual, one was a transsexual, and the remaining were heterosexual. None of them were illicit intravenous drug users, and one inhaled cocaine.

Clinical parameters are presented in Table 1. All individuals presented periodontal disease, either gingivitis or periodontitis. The majority presented periodontitis, which was more prevalent in smokers (93.8%) compared with non-smokers (76.9%), although the difference was not statistically significant. Despite the higher presence of periodontitis in the smokers group, BOP tended to be lower in smokers (62.58% ± 20.23%) compared with non-smokers (74.36% ± 21.12%). Regarding PD and CAL distribution, both groups presented similar frequency of moderate and severe PD and CAL.

The viral load of ≤10,000 copies/mL detected in non-smokers and smokers was 100% and 81.3%, respectively. Moreover, a viral load of >10,000 copies/mL was not detected in non-smokers, whereas in smokers it

‖ UNC periodontal probe, Hu-Friedy, Chicago, IL.
¶ SPSS Statistics v.19, IBM, São Paulo, São Paulo, Brazil.

Table 1.

Demographic, Clinical, and Serologic Data According to Smoking Status of Study Population

Parameters	Non-Smokers (n = 13)	Smokers (n = 16)	*P**
Females, %	38.5	68.8	>0.05*
Age, years (mean ± SD)	39.54 ± 5.07	45.31 ± 9.21	>0.05*
Mean missing teeth	4.54 ± 3.82	5.37 ± 4.47	>0.05*
With gingivitis, %	23.1	6.3	>0.05†
With periodontitis, %	76.9	93.8	>0.05†
Mean ± SD, %			
BOP	74.36 ± 21.12	62.58 ± 20.23	>0.05*
PD >4 to 6 mm	16.24 ± 13.05	18.19 ± 13.70	>0.05*
PD >6 mm	1.01 ± 1.32	0.89 ± 1.23	>0.05*
CAL >4 to 6 mm	3.18 ± 3.51	6.67 ± 6.93	>0.05*
CAL >6 mm	0.64 ± 1.23	1.32 ± 2.14	>0.05*
Viral load (copies/mL)			>0.05†
≤10,000	100	81.3	
>10,000 copies	0	18.8	
CD4+ (cells/mm^3)			>0.05†
≤350	7.7	25.0	
>350 to 500	38.5	25.0	
>500	53.8	50.0	

* Mann-Whitney *U* test.
† χ^2 test.

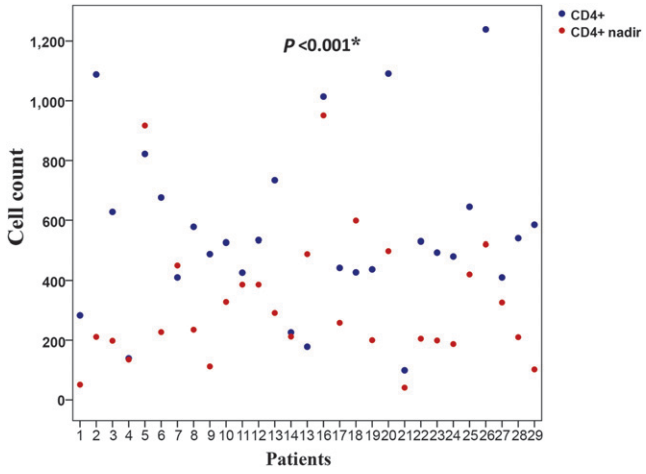

Figure 1.
*CD4+ and CD4+ nadir counts for each studied individual. *Wilcoxon test.*

was 18.8%. The distribution of participants according to CD4+ cells counts in the categories of up to 350, from 350 to 500, and >500 cells/mm^3 were 7.7%, 38.5%, and 53.8% in non-smokers and 25%, 25%, and 50% in smokers, respectively. None of these differences found in serologic parameters between groups were statistically significant.

Values of cell counts of CD4+ and CD4+ nadir for each participant is displayed in Figure 1. CD4+ nadir and CD4+ counts were significantly different within patients (P <0.001, Wilcoxon test).

Table 2 shows a bivariate analysis: Spearman correlation coefficient among viral load, CD4+ nadir, CD4+, and demographic and clinical data of the study population. Weak positive correlations, although significant, were observed between CD4+ and missing teeth (ρ = 0.380, P<0.05), CD4+ nadir and periodontal diagnosis (ρ = 0.418, P <0.005), and CD4+ nadir and moderate PD (ρ = 0.424, P<0.05). When only non-smokers were analyzed, a significant moderate positive association was found between viral load and moderate CAL (ρ = 0.638, P<0.05), CD4+ nadir and diagnosis (ρ = 0.586, P <0.05), and CD4+ nadir and moderate CAL (ρ = 0.680, P <0.05). Analysis considering only smokers found no correlations among serologic parameters and demographic or clinical parameters.

DISCUSSION

The aim of this study is to investigate the periodontal condition and the presence of opportunistic oral

Table 2.

Correlations Among Viral Load, CD4+ Nadir, CD4+, and Demographic and Clinical Data of Study Population

	Spearman Correlation Coefficient								
	Viral Load			CD4+ Nadir			CD4+		
	Non-Smokers	Smokers	All	Non-Smokers	Smokers	All	Non-Smokers	Smokers	All
Sex	0.336	0.403	0.192	–0.127	–0.102	–0.099	–0.465	–0.278	–0.249
Age	–0.070	0.054	0.138	0.052	–0.075	–0.011	0.072	0.298	0.177
Missing teeth	0.313	–0.025	0.104	0.166	–0.066	0.056	0.510	0.293	0.380*
Diagnosis	0.233	–0.093	0.109	0.586*	0.196	0.418*	0.293	0.028	0.120
BOP	0.074	0.360	0.146	0.226	0.302	0.217	0.195	0.006	0.164
Moderate PD	0.515	0.250	0.354	0.544	0.352	0.424*	0.379	0.324	0.296
Severe PD	0	0.204	0.109	0.208	–0.418	–0.093	0.176	0.058	0.116
Moderate CAL	0.638*	–0.136	0.226	0.680*	–0.211	0.169	0.501	0.255	0.333
Severe CAL	–0.277	–0.139	–0.095	–0.134	–0.184	–0.179	–0.054	–0.049	–0.093

* $P < 0.05$.

lesions in HIV+ patients under HAART from a metropolitan area of Rio de Janeiro. Moreover, correlations among periodontal status and CD4+ nadir and CD4+ counts and viral load levels were investigated. The current periodontal clinical data showed that all studied individuals presented some degree of periodontal disease. In addition, a non-significant higher prevalence of periodontitis was found in smokers (93.8%) compared with non-smokers (76.9%). However, the participants presented mild to moderate periodontitis, and none of them presented it in a severe form. Importantly, there is evidence that HIV+ patients under HAART are less likely to present severe periodontal disease when compared with HIV+ individuals without HAART.[25] It has been reported previously that patients under HAART present an increase in CAL, frequently as a result of necrotizing lesions.[26] Previously, pre-HAART studies in this field showed that necrotizing periodontal disease was present in 28%,[27] 52%,[28] and 48%[29] of the HIV+ patients analyzed.

In Brazil, the presence of opportunistic oral lesions may be associated with CD4+ <200 cells/mm^3 and viral load >3,000 copies/mL.[30] In contrast, in the individuals in this study, no opportunistic oral lesions are detected, although some of them had medical history of oral candidiasis and Kaposi sarcoma before treatment. This finding is in agreement with other studies that evaluated patients treated with HAART, which found a relatively low prevalence of opportunistic oral lesions.[31,32] In the study of Dongo et al.,[31] it was found that only 5% of individuals, from a total of 987 HIV+ individuals, had some opportunistic oral lesion. Furthermore, Ramos et al.[32] evaluated 1,232 HIV+ patients and found only 1.2% of necrotizing periodontal disease cases. These findings may suggest that the introduction of HAART has led to a decrease in the prevalence of such clinical oral conditions. In fact, there are reports showing that individuals who regularly use antiretroviral drugs present a lower prevalence of oral lesions compared with patients without HAART.[14,18] However, one can speculate that patients who volunteer to participate in clinical studies may be more likely to have a greater sense of self-care. Ultimately, it would imply that they might have better general health, a satisfactory immune status, and as a result, a lower chance to present opportunistic oral lesions. In fact, the effectiveness of HAART in the study population was found to be significant (Fig. 1). A significant improvement in the counts of CD4+ compared to CD4+ nadir was observed, which may be responsible for the absence of opportunistic oral lesions. In conformity with this finding, Pavan et al.[33] attributed the use of HAART to a low frequency of oral lesions in HIV+ patients. Moreover, measurements of PD in HIV+ without HAART might be higher compared with HIV+ patients using HAART with CP.[34] In addition, increased PD in HIV+ patients may be more frequent in patients without HAART.[21]

In the current study population, the mean age was 42.7 years when all patients were grouped, 39.54 years

for non-smokers and 45.31 years for smokers. These values correspond to data reported in Brazil that show the average age of HIV+ patients ranges from 30 to 49 years.[2] The relatively young age of studied participants may be reflected in the periodontal clinical status that was found, which was a mild to moderate degree of periodontitis. It is known that with increasing age, there is an increase in the risk for severe periodontal breakdown.[35] However, the current findings show that periodontal disease, including both gingivitis and periodontitis, is common in the studied patients. In a representative study of a young population in Brazil,[36] it has been demonstrated that young Brazilian individuals (aged 25 to 29 years) present a frequency of CAL ≥6 mm of 0.7%. This frequency is similar to the one reported in the current study for non-smoker individuals. Conversely, BOP reported in the same study ranged from 25% to 30%, depending on the group. Therefore, the currently reported BOP of 74.36% and 62.58% is definitely relatively high. These findings are also consistent with those reported by Gonçalves et al.,[37] in which the authors reported a prevalence of BOP of 13% (periodontal health) and 29% (periodontitis).

Regarding associations among serologic parameters and demographic and periodontal clinical diagnosis, it was found that there might be a significant weak positive correlation between CD4+ cell counts and missing teeth. It might indicate that higher levels of CD4+ may be detected in individuals with a higher number of missing teeth. Conversely, CD4+ nadir presented a moderate positive association with periodontal diagnosis (worst degree: periodontitis) and moderate PD, which might explain that worse immunologic conditions are associated with worse periodontal conditions. Interestingly, other periodontal parameters were not correlated to serologic parameters. Additionally, when only non-smokers were evaluated for correlation, a significant positive association was found between viral load and moderate CAL, CD4+ nadir and diagnosis, and CD4+ nadir and moderate CAL. Surprisingly, no significant correlations were detected for smokers. Those findings are somehow in agreement with Vernon et al.,[38] who showed a negative relation between CD4+ cell counts and higher levels of CAL. However, no correlation was found for PD. Conversely, another study demonstrated that lower levels of CD4+ were not associated with more periodontal disease, including HIV+ with or without HAART.[39] As remarked above, the increase in the frequency of BOP was not correlated to higher levels of CD4+, which is in agreement with the findings from other studies.[33,34,40,41] It should also be stressed that in the current analysis, when smokers and non-smokers were examined together, no tested parameter correlated with viral load. This finding may corroborate what was demonstrated by other studies, which have shown that viral load, detectable or not, was not associated with the presence or progression of periodontal disease.[21,33]

The current study has found a high prevalence of mild to moderate periodontal disease in HIV+ patients. However, the studied individuals may not have enough age to present advanced forms of periodontal disease. Conversely, results have shown that even when using HAART, HIV+ patients are more prone to develop periodontal disease. The associations found between CD4+/CD4+ nadir counts and periodontal clinical parameters indicate that good oral care must be provided to HIV+ individuals. Furthermore, it might be especially important in those that are not under HAART. Therefore, more studies, including a larger number of patients, are needed to confirm the trend that shows HIV+ patients using HAART may not be at a higher risk for advanced oral/periodontal diseases.

CONCLUSIONS

The current investigation demonstrated that HIV+ patients under HAART presented a high prevalence of mild to moderate periodontal disease. The studied serologic parameters, viral load levels, CD4+ nadir, and CD4+ counts may present a weak to moderate correlation to the number of missing teeth, periodontal diagnosis, moderate PD, and moderate CAL, which might show some effect of the systemic conditions on the periodontal status.

ACKNOWLEDGMENTS

The authors thank the patients who participated in this study and the staff of the AIDS Healthcare Center of Duque de Caxias, Rio de Janeiro, Brazil, for their support. The authors report no conflicts of interest related to this study.

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Submitted June 4, 2015; accepted for publication October 23, 2015.