CLINICS

BASIC RESEARCH

Periradicular lesions in HIV-infected patients attending the faculty of dentistry: clinical findings, socio-demographics status, habits and laboratory data - seeking an association

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OBJECTIVE: The purpose of this study was to estimate the prevalence of periradicular lesions in HIV-infected Brazilian patients and to assess the correlation of several factors with the periradicular status.

METHOD: One hundred full-mouth periapical radiographs were evaluated. A total of 2,214 teeth were evaluated for the presence of periradicular lesions, caries lesions, coronal restorations, pulp cavity exposure and endodontic treatment.

RESULTS: The prevalence of periradicular lesions was 46%. There were no significant differences between individuals with or without periradicular lesions with respect to their socio-demographic status, habits, laboratory data and route of HIV infection. However, the presence of a periradicular lesion was statistically correlated with the number of teeth with endodontic treatment ($p = 0.018$), inadequate endodontic treatment ($p = 0.025$), images suggesting pulp cavity exposure ($p = 0.002$) and caries lesions ($p = 0.001$).

CONCLUSIONS: The prevalence of periradicular lesions in HIV-infected individuals was 46% and was not related to HIV infection.

KEYWORDS: HIV; Root Canal Filling; Endodontic Treatment; Periradicular Status; Apical Periodontitis.

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INTRODUCTION

Recently, the human immunodeficiency virus (HIV) and AIDS disease, which were characterized by a rapidly progressive course of immunodeficiency leading to death, evolved to a chronic pattern of disease as a consequence of the new therapeutic regimen that was introduced in 1996 (1). This new therapy, known as highly active antiretroviral therapy (HAART), decreased the viral load, which resulted in the absence of detectable virus as well as in reduced morbidity and mortality related to AIDS. Additionally, after the introduction of HAART, there was a significant decrease in the rate of opportunistic infections in HIV-infected patients, such as oral candidiasis (2) and herpesviruses (3,4).

With respect to periodontal disease, HIV-infected patients have increased chances of developing a more aggressive form of chronic periodontitis (5). Recently, Gonçalves et al. (6) demonstrated that the long-term use of HAART in Brazilian HIV-infected individuals resulted in a decrease in the severity of chronic periodontitis.

The human immunodeficiency virus (HIV) can lead to severe depression of the immune system; therefore, HIV infection may be a factor that modifies pathological changes and interferes in the development/repair of periradicular lesions of endodontic origin. In this type of infection, the microorganisms that are in contact with the periradicular tissues stimulate, either directly or indirectly, an inflammatory response, leading to several forms of apical periodontitis

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that spread outward from the infected root canal system (7). Chronic apical periodontitis occurs with persistent exposure to irritants in the root canal and is characterized by a loss of hard tissue and a radiolucent area around the tooth apex (8). Interaction among several immunocompetent cells determines the structural changes in the periradicular bone (9).

Despite our extensive understanding of the role of bacteria and their products in the etiology and persistence of periradicular lesions (10), studies have shown that certain systemic conditions, such as diabetes, herpesvirus infections and genetic polymorphisms, as well as systemic changes caused by smoking, stress and depression, can compromise the host immune response and avoid or delay the healing of periradicular lesions. Thus, the above-mentioned conditions and factors are considered risk factors or disease modifiers (11). In this context, HIV infection is one of these modifying factors that can vary from individual to individual, resulting in different disease progression and having repercussions in the oral cavity.

The impact of HIV infection on the characteristics of periradicular lesions is poorly understood. The histological findings from a case report on the extraction of teeth with periradicular lesions in HIV/AIDS patients showed lesions that were almost devoid of $TCD4^+$ lymphocytes but with an abundance of $TCD8^+$ lymphocytes (12). Additionally, HIV can be detected in the vital dental pulp of these patients, but the pulp tissue's immune response has not yet been determined (12,13). Immunohistological studies, case reports and the principles of basic immunology have shown that treating periradicular lesions could have an unfavorable prognosis in immunocompromised patients, such as those infected with HIV. According to these authors, T cells, which are affected by HIV, play an important role in both the pathogenesis (the balance of protective and tissue-destructive processes) and repair of periradicular lesions (14-17).

Therefore, because there is limited information on periradicular lesions in HIV-infected patients, studies to clarify this issue are warranted. The aim of this study was to estimate the prevalence of periradicular lesions in Brazilian HIV-infected patients and to assess the correlation of several factors with the periradicular status.

MATERIAL AND METHODS

Subject Population

A cross-sectional study was conducted on a convenience sample of subjects who were recruited from a pool of patients from Clementino Fraga Filho University Hospital of the Federal University of Rio de Janeiro, Brazil, from 1997 to 2004. All subjects were informed about the aims, risks and benefits of the study and all signed a consent form. The study protocol was approved by the Review Committee for Human Subjects of the Clementino Fraga Filho University Hospital/UFRJ. Patients were included in the study if they had available full-mouth periapical radiographs. These radiographs were selected according to the required information related to age, gender, education, smoking, socioeconomic level, family income, $CD4^+$ lymphocyte level, viral load, medications used, AIDS-defining diseases (tuberculosis, pneumocystosis, toxoplasmosis, cytomegalovirus and Kaposi's sarcoma), alcohol consumption, drug use and full-mouth periapical radiographs taken a maximum of five months before or after the laboratory tests in patients who had at least 5 teeth in their mouths. The patients included in this study were all undergoing highly active antiretroviral therapy (HAART).

Radiographic evaluation

Periradicular lesions were detected by evaluating of the full-mouth periapical radiographs for each individual. The quality of the root canal filling and the coronal restorations were analyzed according to criteria of the Tronstad et al. (18) with a slight modification, as described below:

Endodontic Treatment

a) Adequate restoration: all canals were filled; lack of empty spaces; root canal fillings ended within 0-2 mm of the radiographic apex.

b) Inadequate restoration: root canal filling ended more than 2 mm from the radiographic apex, or the apex was overfilled; root canal filling showed empty spaces, inadequate density, unfilled canals and/or poor condensation.

Coronal Restoration

a) Adequate: any permanent restoration that appeared well adapted to the edge of the tooth upon radiographic examination;

b) Inadequate: any overhanging permanent restoration, any restoration poorly adapted to the edge; presence of recurrent caries or of temporary coronal restoration upon radiographic examination; teeth that appeared to be in need of restoration.

The endodontic treatment was categorized according to the Strindberg (19) criteria as follows:

Success: normal width of the periodontal ligament space and normal appearance of the surrounding bone.

Failure: periradicular radiolucency.

Caries lesion

A caries lesion was defined as a radiolucency identified in the coronal tooth surface.

Image suggesting pulp exposure

Pulp exposure was defined as a radiolucency identified in the coronal tooth surface in contact with the pulp cavity in a tooth with or without root canal filling.

Two independent endodontic specialists, using an endodontic illuminator with an attached magnifier (4x) (*Endo Gold line*), analyzed all radiographs. There was no disagreement between the observers; however, had there been disagreement, a third endodontic specialist would have been consulted. The two observers were previously calibrated and the kappa coefficient was used to analyze agreement regarding the presence/absence of a periradicular lesion ($\kappa = 0.89$).

Data analysis

A statistical software package (SPSS, Statistical Package for the Social Sciences, version 17.0, Chicago, IL, USA) was used for all of the analyses. Descriptive analysis was performed for the socio-demographic features, the health-related behaviors, the radiographic data, the route of HIV-infection and the laboratory data. The normality of the distribution of continuous variables was tested using the graphic method. We performed bivariate analysis comparing the presence of a periradicular lesion with several of

the studied variables using the Mann-Whitney test for continuous data and the Chi-squared test or Fisher's exact test for categorical data. The threshold of statistical significance was set at 5% ($p \leq 0.05$).

RESULTS

In the current study, we enrolled 100 patients; most were male (64%). The prevalent age range was from 45 to 49 years (67.7%). Considering the household income and education the lowest levels in most individuals, who reported 0-2 minimum wage (61.1%) and 50% who had a maximum of a high school education. Most of the individuals did not smoke (65.3%), 83.9% did not consume alcohol and 91.8% were not drug users. The comparison between individuals with and without periradicular lesions with respect to socio-demographic and health-related behavior data did not reveal statistically significant differences for any of the studied variables ($p>0.05$; Chi-squared test and Fisher's exact test) (Table 1).

The immunological data for the HIV-infected individuals indicated a population with advanced immunodeficiency with average lymphocyte TCD4$^+$ counts <300 cells/mm^3 and a high prevalence of individuals with a viral load $>10{,}000$ copies/mL (40.7%). The most frequent route of HIV transmission was sexual (84.7%). With regard to the oral and systemic manifestations studied, herpes simplex (41.7%) and herpes zoster (28%) were the most common systemic manifestations, and pseudomembranous candidiasis (14%) and erythematous candidiasis (11%) were the most common oral manifestations (data not shown). All individuals included in this study were receiving HAART; zidovudine was the most frequently used drug (62.0%), followed by stavudine (46%), didanosine (37%), lamivudine (23%) and indinavir (23%) (data not shown). There was no statistically significant difference between individuals with or without periradicular lesions when the laboratory data and the route of HIV infection (Table 2) were compared; the same was true for all oral and systemic manifestations and antiretrovirals (data not shown) ($p>0.05$; Mann-Whitney test and Fisher's exact test).

Table 1 - Bivariate analysis between periradicular lesions and the socio-demographic/health-related characteristics of the study population.

VARIABLE	PERIRADICULAR LESIONS		*p*-value
	Yes	NO	
	N (%)	N (%)	
Gender*			
Male	26 (56.5)	38 (70.4)	0.150
Female	20 (43.5)	16 (29.6)	
Education¶			
Illiterate	3 (6.5)	3 (5.3)	0.562
Family income (wages)¶			
0-2	24 (55.8)	34 (65.4)	0.297
3-4	10 (23.3)	13 (25.0)	
≥5	9 (20.9)	5 (9.6)	
Smoking (cigarettes)			
No	29 (65.9)	33 (64.7)	0.446
1-20	12 (27.3)	17 (33.3)	
>20	3 (6.8)	1 (2.0)	
Alcohol consumption¶			
No	34 (73.9)	39 (72.2)	0.941
1-2 times/week	6 (13.0)	6 (11.1)	
≥3 times/week	1 (2.2)	1 (1.9)	

*Chi-squared test.
¶Fisher's exact test.

Table 2 - Bivariate analysis between periradicular lesions and the laboratory data of the study population.

VARIABLE	PERIRADICULAR LESIONS		*p*-value
Laboratory Data	Yes	No	
TCD4 lymphocytes§- Mean (sd)	281.7 (191.1)	315.7 (267.3)	0.997
Total leukocytes§ - Mean (sd)	5369.8 (2010.5)	6942 (9743.2)	0.521
Neutrophils§ - Mean (sd)	2639.3 (1487.4)	2827.3 (1488.8)	0.405
Total lymphocytes§- Mean (sd)	1658.1 (762.6)	1976.2 (1052.9)	0.177
Viral load¶ - N (%)			0.319
0-1000	10 (29.4)	20 (42.6)	
1001-10000	10 (29.4)	8 (17)	
>10000	14 (41.2)	19 (40.4)	
Route of HIV infection-N (%)			0.222
Transfusion	1 (2.3)	4 (7.8)	
Sexual	38 (86.4)	45 (88.2)	
Intravenous drug user	0	1 (2.0)	
Mother to child transmission	1 (2.3)	0	
Do not know	4 (9.0)	1 (2.0)	

§Mann-Whitney test.
¶Fisher's exact test.
sd (standard deviation).

Table 3 - Radiographic characteristics of the study population.

VARIABLE	RESULTS
Total number of studied teeth	2214
Mean (± dp) of teeth/individual	22.1±6.4
Periradicular lesion - N (%)	
Yes	46 (46.0)
No	54 (54.0)
N (%) of individuals with:	
Number of periradicular lesions	
0	49 (49.0)
1-2	39 (39.0)
≥3	12 (12.0)
Caries lesions	
0	8 (8.0)
1-5 lesions	66 (66.0)
>5 lesions	26 (26.0)
Inadequate coronal restorations	
No	38 (38.0)
1-4 restorations	51 (51.0)
>4 restorations	11 (11.0)
Images suggesting pulp cavity exposure	
0	20 (20.0)
1-3 teeth	56 (56.0)
>3 teeth	24 (24.0)
Endodontic treatment	
0	68 (68.0)
1-2	26 (26.0)
≥3	6 (6.0)
Inadequate endodontic treatment	
0	72 (72.0)
1	17 (17.0)
≥2	11 (11.0)

Table 4 - Bivariate analysis between periradicular lesions and the radiographic characteristics of the study population.

VARIABLE	PERIRADICULAR LESIONS		*p*-value
	Yes	No	
Caries lesions	2 (4.3)	6 (11.1)	0.117
0	28 (60.9)	38 (70.4)	
1-5 lesions	16 (34.8)	10 (18.5)	
>5 lesions			
Inadequate coronal restorations			0.749
0	16 (34.8)	22 (40.7)	
1-4 restorations	24 (52.2)	27 (50.0)	
>4 restorations	6 (13.0)	5 (9.3)	
Images suggesting pulp cavity exposure			0.245
0	6 (13)	14 (25.9)	
1-3 teeth	27 (58.7)	29 (53.7)	
>3 teeth	13 (28.3)	11 (20.4)	
Endodontic treatment			0.124
0	28 (60.9)	40 (74.1)	
1-2	13 (28.3)	13 (24.1)	
≥3	5 (10.9)	1 (1.8)	
Inadequate endodontic treatment			0.156
No	30 (65.2)	42 (77.8)	
1	8 (17.4)	9 (16.7)	
≥2	8 (17.4)	3 (5.5)	

p-values refer to the Fisher's exact test.

Radiographic characteristics

Table 3 presents the radiographic features of the study sample (100 individuals and 2,214 teeth). The prevalence of periradicular lesions was 46%. More than 50% of the individuals had 1-4 inadequate restorations and 66% and 56% had 1-5 caries lesions and 1-3 teeth with images suggestive of pulp cavity exposure, respectively. Approximately 70% of the study participants had not undergone any endodontic treatment and only 12% had more than 1 tooth with inadequate endodontic treatment.

There were no statistically significant differences between individuals with or without periradicular lesions when the radiographic characteristics were compared ($p>0.05$; Chi-squared test and Fisher's exact test) (Table 4). Logistic regression showed no significant associations between periradicular lesions and all radiographic variables considered in this study. Nevertheless, periradicular lesions, categorized as ''no lesion'', ''1-2 lesions'' and ''≥3 lesions'', were statistically correlated with the number of teeth with endodontic treatment (ET) ($p=0.018$) (Figure 1), the number of teeth with inadequate endodontic treatment (IET) ($p=0.025$) (Figure 2), images suggesting pulp cavity exposure (PCE) ($p=0.002$) (Figure 3) and caries lesions (CL) (data not shown) ($p=0.001$, Fisher's exact test). The number of teeth with inadequate restorations was not statistically correlated with periradicular lesions ($p>0.05$) (data not shown).

DISCUSSION

Since the beginning of the HIV epidemic, few studies have evaluated the possible relationship between HIV and endodontic infections. HIV infection is a transient symptomatic disease characterized by high HIV replication and severe immune response suppression (20). The main targets of HIV-infection are $TCD4^+$ cells, leading to a rapid depletion of the T cell repertoire and to functional damage of $TCD4^+$ cells in the weeks following infection. These cells work as a marker of immunodeficiency (21). In the current study, the participants demonstrated signs of advanced immunodeficiency with mean $TCD4^+$ levels <300 cells/mm^3 and most had a viral load >10,000 copies/ml. The laboratory data was not significantly different for individuals with and without periradicular lesions. Suchina et al. (1) reported that a mean $TCD4^+$ cell count = 240 cells/mm^3 does not significantly influence the success of endodontic treatment. Nevertheless, de Brito et al. (21) reported that 79.2% of individuals in need of endodontic treatment had a $TCD4^+$ cell level <500 cell/mm^3 even though most of them were receiving HAART, suggesting poor compliance with the antiretroviral treatment.

When first receiving antiretroviral therapy, most patients develop inflammatory or cellular proliferative diseases because of T and B cell depletion or because of residual dysfunction in association with an opportunistic infection

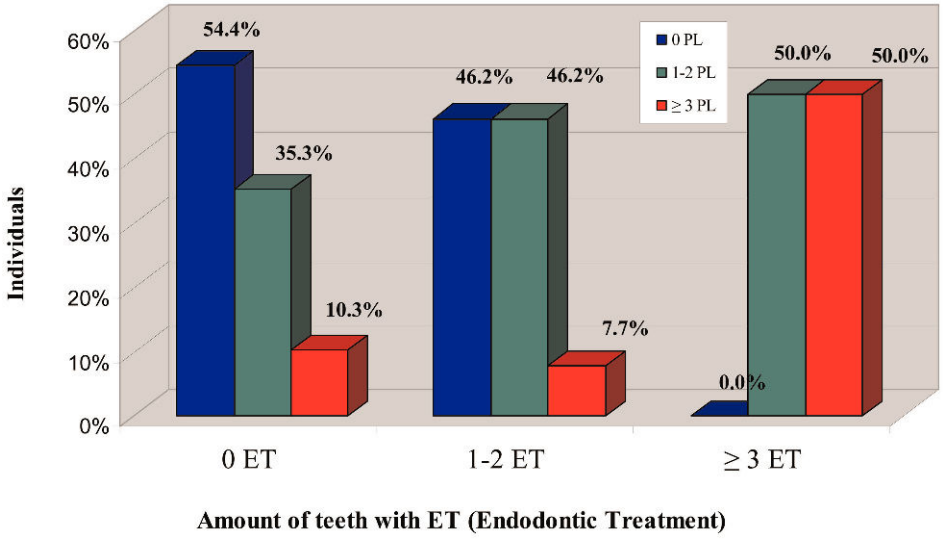

Figure 1 - Bivariate analysis between the number of teeth that underwent endodontic treatment (ET) (categorized as 0, 1-2 and ≥3) and the frequency (%) of individuals with periradicular lesions (PL) (categorized as 0, 1-2 and ≥3) ($p=0.018$; Fisher's exact test).

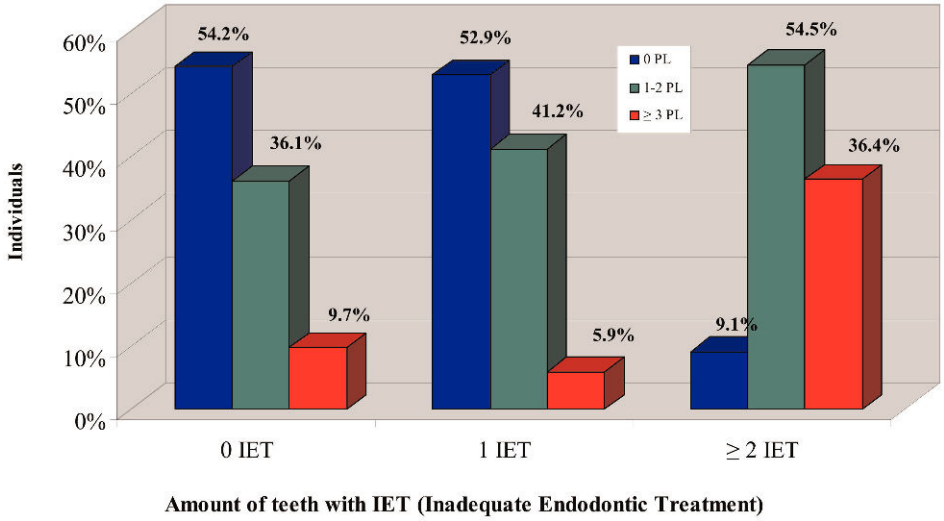

Figure 2 - Bivariate analysis between the number of teeth with inadequate endodontic treatment (IET) (categorized as 0, 1 and ≥2) and the frequency (%) of individuals with periradicular lesions (PL) (categorized as 0, 1-2 and ≥3) ($p = 0.025$; Fisher's exact test).

(22,23). However, no previous reports exist regarding whether patients requiring endodontic therapy have periradicular lesions. HAART can decrease the viral load to undetectable levels (<50 copies/mL) (24) and can decrease the morbidity and mortality associated with HIV; this treatment has also improved the quality of life and has restored and preserved the immunological functions of HIV-infected patients (25). Additionally, HAART has reduced the incidence of periodontitis in the HIV-infected population (26). It is also worth noting that the few studies on HAART in the current era that have compared successful endodontic treatments between HIV-infected and non-HIV infected patients have reported no statistically significant differences (17,27-30).

However, the risk of caries lesions is likely increased because some antiretroviral medications may induce xerostomia (26). In the present study, a high prevalence of caries was observed: 66% of 100 individuals (all undergoing HAART) had 1 to 5 caries lesions. Zidovudine (AZT) was the most frequently prescribed antiretroviral for patients undergoing HAART (62.0%); this was also true in a study by de Brito et al. (21) (50.6%), whereas Gonçalves et al. (31) reported that lamivudine (3TC) was the most frequently prescribed drug (45.9%), followed by zidovudine (36.5%).

In the current study, radiographic evaluation was used as a criterion for determining the presence of periradicular lesions in HIV-infected patients. We evaluated 2,214 teeth and 46% of the study participants had periradicular lesions. The presence of a periradicular lesion was correlated with the number of teeth with endodontic treatment, the number of teeth with possible pulp exposure and the number of teeth with caries lesions as well as with inadequate endodontic treatment. The number of inadequate coronal restorations did not have a significant correlation with the presence of periradicular lesions. Several studies have

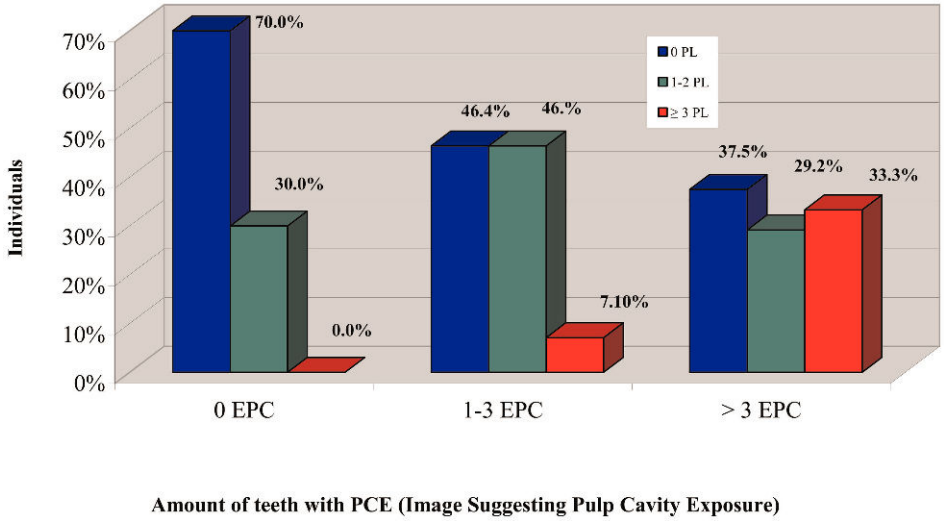

Figure 3 - Bivariate analysis between the number of teeth with images suggesting pulp cavity exposure (PCE) (categorized as 0, 1-3 and >3) and the frequency (%) of individuals with periradicular lesions (PL) (categorized as 0, 1-2 and ≥3) ($p = 0.002$; Fisher's exact test).

demonstrated the influence of endodontic treatment quality on periradicular tissue (10,32-36). In fact, inadequate endodontic treatment quality may be the main factor responsible for the high prevalence of poor outcomes (12,37-40).

The prevalence of periradicular lesions (46%) in the present study was as high as that observed in other countries, such as Belgium (40%) (32), Denmark (52%) (33), Canada (44% to 51%) (34), Spain (64.5%) (35), Lithuania (39%) (41), Germany (61%) (42), Scotland (51%) (43) and the United States (39%) (44). However, it is important to note that the present study has a cross-sectional design and some limitations should be considered. For example, the data were obtained in the absence of longitudinal follow-up and the sample size is not representative of the HIV-infected adult population in Brazil. Radiolucent images associated with teeth that underwent endodontic treatment were classified as persistent periradicular lesions; however, they might be considered periradicular lesions in the healing phase (45). Another limitation of this study is that the information was based only on radiographs, increasing the possibility of an incomplete diagnosis. In some cases, periradicular lesions are restricted to the cancellous bone; as a result and they would not be detectable by conventional radiographic examination (46). Additionally, radiographs do not completely show the quality of the canal seal (47). However, a cross-sectional study has a reduced chance of researcher bias compared with a longitudinal study.

In conclusion, the prevalence of periradicular lesions (46%) in HIV-infected individuals that was observed in this study is similar to that reported in studies of HIV-seronegative subjects. These lesions were not correlated with the HIV infection data (laboratory exams, routes of infection, antiretrovirals and systemic/oral manifestations) or with the number of inadequate coronal restorations. However, the lesions were correlated with the number of teeth that underwent endodontic treatment, the number of teeth with possible pulp exposure and the number of teeth with caries lesions as well as with inadequate endodontic treatment. Further studies should be performed to test additional relevant hypotheses and to address specific questions.

AUTHOR CONTRIBUTIONS

Fontes TV, Ferreira SM, Noce CW and Gonçalves LS conceived and designed the study. Fontes TV, Marotta PS and Noce CW collected the data. Marotta PS, Noce CW, Ferreira SM, Silva Jr A, Ferreira DC and Gonçalves LS analyzed the data. Fontes TV, Ferreira SM, Silva Jr A, Ferreira DC and Gonçalves LS wrote the paper. Ferreira SM, Silva Jr A, Ferreira DC and Gonçalves LS reviewed the manuscript.

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