



Stage II and stage III periodontitis clinical burdens of HIV-1 undergoing antiretroviral therapy

Lucio Souza Gonçalves¹ · Dennis de Carvalho Ferreira^{1,2} · Fabio Vidal¹ · Rodrigo Carvalho Souza¹ · Cristiane Gonçalves¹ · Priscila Pavan¹ · Florence Carrouel³ · Denis Bourgeois³ · Gregory J. Seymour⁴

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Abstract

Objectives The aim of this retrospective cross-sectional study was to estimate the association of HIV-1 infection under highly active antiretroviral treatment (HAART) on the clinical parameters of periodontitis.

Materials and methods A total of 205 patients were divided in two groups: 74 HIV + and 131 HIV – . Periodontal probing depth (PPD), clinical attachment loss (CAL), bleeding on probing (BOP), and visible supragingival biofilm (VSB) were recorded. The association of HIV-1 infection with the presence of at least 3 sites with PPD \geq 5 mm and/or CAL \geq 4 mm in non-adjacent teeth was estimated using binary logistic regression models.

Results The variables HIV-1 infection (OR = 5.53, $p < 0.0001$, 95% CI: 2.45–13.64), age [range 35–50 years old (OR = 5.73, $p < 0.0001$, 95% CI: 2.49–13.20); > 50 years old (OR = 6.29, $p = 0.002$, 95% CI: 1.94–20.42)], and VSB (OR = 23.68, $p < 0.0001$, 95% CI: 8.07–69.53) showed a significant direct association with BOP outcome.

Conclusions HIV-1 infection under HAART did not have association with the presence of at least 3 sites with PPD \geq 5 mm and/or CAL \geq 4 mm. However, HIV patients on HAART had direct association of HIV-1 infection with BOP and an inverse association with PPD.

Clinical relevance These results support that monitoring gingival bleeding associated with oral prophylaxis would be beneficial in the prevention and management of periodontitis in HIV-1 patients on HAART.

Keywords HIV-1 infection · Periodontitis · HAART

Introduction

Although global attention is dominated by COVID-19, the HIV/AIDS pandemic, as it enters its fifth decade, is far from over [1] despite the success of antiretroviral therapy which has led some people to now ask whether the end of AIDS is possible. For patients who have access to effective

antiretroviral treatment especially after 1995, a new set of HIV-associated complications have emerged, resulting in a novel chronic disease that for many will span several decades of life [2]. A direct consequence is that people living with HIV/AIDS (PLWH) have a growing life expectancy especially in the developing countries [3]. Highly active antiretroviral treatment (HAART) has significantly altered HIV infection and reduced AIDS-related morbidity and mortality [4].

This has resulted in increasing exposure to age-related chronic illness that may be exacerbated by HIV/AIDS or antiretroviral treatment. Moreover, HIV suppression with antiretroviral therapy may decrease inflammation and immune activation thought to contribute to higher rates of cardiovascular and other co-morbidities reported in HIV-infected cohorts. Treatment does not fully restore immune health; as a result, several inflammation-associated or immunodeficiency complications such as cardiovascular disease and cancer are increasing in importance [2]. HIV/AIDS

✉ Lucio Souza Gonçalves
lucioconcalves@yahoo.com.br

¹ Postgraduation Programa in Dentistry, Estácio de Sá University, Avenida das Américas 700, Loja 218, Bloco 8 do Conjunto Comercial Cittá – Barra da Tijuca, Rio de Janeiro, RJ 22640-100, Brazil

² Universidade Veiga de Almeida, Rio de Janeiro, Brazil

³ University Claude Bernard Lyon 1, Laboratory “Health Systemic Process”, EA4129, 69008 Lyon, France

⁴ School of Dentistry, The University of Queensland, Brisbane, Australia

conditions, such as cardiovascular disease, diabetes, osteoporosis, and dementia, are more prevalent in older than in young adult HIV-infected subjects [5].

Periodontal diseases are completely within the framework of the potential consequences of HIV [6, 7]. They are multifactorial chronic infectious diseases, classically occurring around the age of 35–40 years old and are part of a rationale of co-morbidities. It is important to control for chronic comorbidities — a feature that prior studies have typically not examined — as many chronic conditions may interact [8]. For instance, periodontal diseases may elevate the risk of diabetes and cardiovascular disease; chronic illnesses can exacerbate cognitive impairment or vice versa [9]. In this perspective, HIV-associated periodontal diseases (PD) could serve as a source of chronic inflammation [10]. Persons infected with HIV are particularly vulnerable to a variety of oral microbial diseases [6, 7]. HIV infection and CD4 cell loss can disrupt the oral symbiosis, which can lead to significant changes in the composition and diversity of the periodontal microbiota with an increased susceptibility to pathogenic microorganisms. [11]. In addition, the dysbiosis associated with periodontitis may contribute to systemic inflammation, predisposing to viral replication and thus influencing the status of HIV infection. Furthermore, mononuclear inflammatory cells in periodontitis lesions may act as a reservoir for HIV-1 leading to further viral replication [12]. However, despite a number of studies, the extent to which HIV infection and immune suppression with HAART impact the oral microbiota is still unclear. No consensus has been achieved in all the research, and, collectively, these studies are not conclusive [11].

The classification criteria of the European Community Clearing house identified periodontitis as a condition strongly associated with HIV [13]. In the 1990s, periodontal diseases at a global level were about 25% more likely to be encountered in the groups under ART compared to those who were not under treatment, with obvious biases related to the inequalities of antiretroviral therapy use. Thirty years later, the evolution of knowledge, the evolution of periodontal disease classifications, the novel modalities for the treatment of HIV-PD, and the increasing evolution of patients under ART in industrialized countries suggest that this condition would be associated with aging rather than HIV [14]. As well, the diagnosis and management of HIV disease and spectrum of opportunistic infection has changed over the past 30 years as our understanding of the infection has evolved [15, 16]. And this, in a research context where the studies on highly active antiretroviral therapy and periodontal diseases over the last 10 years are extremely limited [17] and thus may not be representative [18]. So, 24 studies were identified in the last 10 years on PubMed with keywords relating to HIV-1 periodontal diseases ("hiv 1" [MeSH Terms] OR "hiv 1" [All Fields] OR "hiv 1" [All

Fields]) AND ("periodontal diseases" [MeSH Terms] AND "diseases" [All Fields]) OR "periodontal diseases" [All Fields]). To date, no studies have been published concerning the association between HIV-1/HAART and conventional periodontal disease in these HIV-infected populations.

Our research focused on the following controversial topic: Are periodontal manifestations of HIV in 2020 still relevant after the introduction of highly active antiretroviral therapy (HAART)? The purpose of the present study was to compare the periodontal clinical conditions in HIV-positive persons under HAART to an HIV-negative group. One specific question is addressed as follows according to the PICO principles: Do HIV-positive patients (population) receiving HAART therapy (intervention) have a similar risk of stage II and III periodontitis (outcome) compared to non-HIV-positive patients (control)?

Materials and methods

Study design and ethical approval

This study was designed as a cross-sectional study conducted at the Estácio de Sá University, Brazil. A simple random sample without replacement of patients was obtained from a pool of 16,106 individuals in attendance at the School of Dentistry. This research was performed in accordance with the STROBE guidelines. The study protocol was approved by the Review Committee for Human Subjects of the Estácio de Sá University (CAE 59,875,316.7.0000.5284) and performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients.

Study population

The study comprised 207 patients, aged 18 to 75 years, from a pool consulting to the School of Dentistry, between March 2018 and February 2020. All consecutive HIV-infected individuals (aged ≥ 18 years) who had confirmed HIV-1 were included. A total of 74 HIV-1 infected on HAART patients were recruited during the period. Meanwhile, 133 non-HIV-1-infected subjects were also recruited and assigned to the control group for a comparative study (ratio HIV – :HIV-1 = 2). The control group was matched to cases on age (within 5 years). The HIV-negative group was selectively recruited to match the HIV-positive group on demographic and health factors. HIV-1 patients were defined with positive HIV serology by ELISA and confirmed by the Western blot test, while non-HIV-1 group were patients who self-declared as non-HIV-1 infected.

Inclusion criteria were patients: age between 18 and 75 years old, more than 15 natural teeth excluding the 3rd

molars, ability and willingness to give written informed consent, and written agreement to participate in the study.

Exclusion criteria were patients with the following: inflammatory periodontal diseases requiring immediate and independent medical attention, need of antibiotic prophylaxis for dental procedures, pregnancy, diabetes, autoimmune diseases, necrotizing periodontal diseases, having used antibiotics and/or anti-inflammatory drugs in the last 6 months, and periodontal treatment in the last 6 months. Patients who were undergoing a course of dental or orthodontic treatment were also excluded.

Determination of medical history and immunological status

A self-administered questionnaire was used to obtain socio-demographic characteristics (smoking, age and gender) and medical records (medical history, diabetes, hypertension, heart disease, use of ARV drugs or not) of the participants. HIV characteristics (antiretroviral therapy, T-CD4 + lymphocyte counts, viral load and antiretroviral therapy) were collected from medical charts.

Classification of subjects with stage II or III periodontitis

The diagnosis of periodontal lesions of stage II or III was assigned to subjects presenting PD ≥ 5 mm and/or CAL ≥ 4 mm, in at least 3 sites in non-adjacent teeth and $\geq 10\%$ of sites with bleeding on probing (BOP) after 30 s [19].

Clinical record

Periodontal measurements at the School of Dentistry at the Estácio de Sá University were recorded at six sites per tooth (distobuccal, buccal, mesiobuccal, distolingual, lingual, and mesiolingual) in all teeth, excluding third molars. Standardized periodontal monitoring was performed by one experienced periodontist observer (intra-class correlation coefficient of 0.86 for probing depth and 0.80 for clinical attachment loss). Screening of the clinical assessments were evaluated (periodontal probing depth (PPD) (mm), clinical attachment loss (CAL) (mm), bleeding on probing (BOP) (presence/absence)) using a periodontal probe with a diameter of 0.5 mm (PCV12, HuFriedy, Chicago, IL, USA).

The level of oral hygiene and the severity of gingival inflammation were respectively determined using the visible supragingival biofilm (VSB) [20] and the BOP [21].

Sample size calculation

Sample size calculation was performed using the G*Power 3.1 Program for binary logistic regression [22]. The following parameters were established to calculate the sample size for estimate the effect of independent variable HIV infection (1 = “yes” and 2 = “no”) on a binary outcome (the detection of at least 3 sites with PPD ≥ 5 mm and/or CAL ≥ 4 mm in non-adjacent teeth) (0 = “no” and 1 = “yes”), probability of error $\alpha = 5\%$ ($\alpha = 0.05$), power = 0.95, R² other X = 0.1, odds ratio = 1.5, and event rate under H₀ = 0.5, with two-tailed analysis. The results suggested a total number of 190 subjects.

Statistical analysis

Statistical software (Statistical Package for the Social Sciences 21.0; IBM, Armonk, NY) was used for all statistical analyses. In the bivariate analysis, the difference between groups (HIV-1 infected and non-HIV-1 infected) was compared using the chi-square test or Fisher exact test. After applying the statistical test for the comparison between the groups (obtaining the level of significance for each analysis), the effect size for each variable was calculated. The following interpretation criteria were used for the effect size (*d*): no effect 0–0.1; small effect 0.2–0.4; intermediate effect 0.5–0.7; large effect ≥ 0.80 [23].

The association of HIV-1 infection with the periodontal clinical parameters, such as BOP (0 = “< 10%” and 1 = “ $\geq 10\%$ ”), mean of PPD (0 = “ ≤ 3 mm” and 1 = “> 3 mm”), and mean of clinical attachment loss (CAL) (0 = “ ≤ 2 mm” and 1 = “> 2 mm”), was assessed using binary logistic regression models. The detection of at least 3 sites with PPD ≥ 5 mm and/or CAL ≥ 4 mm in non-adjacent teeth was also analyzed using a binary logistic regression model (0 = “no” and 1 = “yes”). Correlation between BOP and CD4 counts was performed. Multicollinearity analysis among independent variables was tested, using as reference tolerance (TOL) < 0.1 and the variance inflation factor (VIF) > 5. Variables influenced by outcome are inappropriate for control of confounding and, therefore, were excluded. For the four models, the following independent variables were included in the multiple regression analyses: gender, age, smoking, visible supragingival biofilm (VSB) (1 = “< 10%” and 2 = “ $\geq 10\%$ ”), and HIV infection. All data were considered statistically significant at $p < 0.05$.

Results

Of the 205 subjects who participated in this study, 52.7% were males, 65.2% were not smoking, and 52.2% were 36–50 years of age. The variables “gender” ($p = 0.006$),

“smoking” (≥ 1 cigarette by day) ($p = 0.018$), “BOP” ($p = 0.003$), and “PPD” ($p < 0.0001$) showed statistically significant difference between HIV-1-infected group and non-HIV-1-infected group. Thirty percent of patients with CD4 counts had AIDS. Correlation between BOP and CD4 counts including all infected patients did not show statistically significant results.

The most frequently used antiretrovirals were respectively lamivudine (66.7%), zidovudine (43.5%), tenofovir (36.6%), and lopinavir (27.5%). Tuberculosis (33.8%), pneumocystis pneumonia (28.8%), herpes zoster (24.7%), and oral herpes simplex (19.2%) were the most frequent clinical conditions. The immunological data demonstrated that HIV-1 plasmatic viral load ranged from 0 to 1000 copies/mL in 58.3% and

47.5% had a T-CD4+ lymphocytes range of 200–500 cells/mm³ (Table 1).

The variables HIV-1 infection (OR = 5.53, $p < 0.0001$, 95% CI: 2.45–13.64), age [range 35–50 years old (OR = 5.73, $p < 0.0001$, 95% CI: 2.49–13.20); > 50 years old (OR = 6.29, $p = 0.002$, 95% CI: 1.94–20.42)], and VSB (OR = 23.68, $p < 0.0001$, 95% CI: 8.07–69.53) showed a significant direct association with BOP outcome, in the multiple regression model (adjusted) (Table 2). In the multiple binary regression model between HIV-1 infection (exposure) and BOP (outcome), CD4 counts were not considered a confounder ($p = 0.369$).

At least 3 sites with PPD ≥ 5 mm and/or CAL ≥ 4 mm in non-adjacent teeth were detected in 53.2% of patients (37 in

Table 1 Descriptive features of the studied groups (HIV (+) and HIV (-))

Variable	HIV (+) (N = 74)	HIV (-) (N = 131)	Total (N = 205)	<i>p</i>	<i>d</i>
Gender				0.006	0.388
Male	48 (64.9)	59 (45.0)	107 (52.2)		
Female	26 (35.1)	72 (55.0)	98 (47.8)		
Age¹				0.328	0.212
18 – 35	25 (34.2)	42 (32.8)	67 (33.4)		
36 – 50	41 (56.2)	64 (50.0)	105 (52.2)		
>50	7 (9.6)	22 (17.2)	29 (14.4)		
Smoking²				0.018	0.342
Yes	32 (45.7)	37 (28.9)	69 (34.8)		
No	38 (54.3)	91 (71.1)	129 (65.2)		
≥ 3 sites with PPD ≥ 5 mm and/or CAL ≥ 4 mm				0.494	0.096
Yes	37 (50.0)	72 (55.0)	109 (53.2)		
No	37 (50.0)	59 (45.0)	96 (46.8)		
VSB				0.407	0.116
< 10%	16 (21.6)	22 (16.9)	38 (18.6)		
$\geq 10\%$	58 (78.4)	108 (83.1)	166 (81.4)		
BOP				0.003	0.420
< 10%	17 (32.0)	57 (43.5)	74 (36.1)		
$\geq 10\%$	57 (77.0)	74 (56.5)	131 (63.9)		
HIV viral load³					
≤ 1000	21 (58.3)	-	-	-	-
1001 – 10000	7 (19.5)	-	-	-	-
> 10000	8 (22.2)	-	-	-	-
TCD4+ lymphocytes⁴					
< 200	12 (30.0)	-	-	-	-
200 – 500	19 (47.5)	-	-	-	-
> 500	9 (22.5)	-	-	-	-

Data are presented as n (%).

VSB visible supragingival biofilm, BOP bleeding on probing, PPD periodontal probing depth, CAL clinical attachment loss.

¹Data refers to 201 patients [HIV (+) = 73; HIV (-) = 128].

²Data refers to 198 patients [HIV (+) = 70; HIV (-) = 128].

³Data refers to 36 patients HIV (+).

⁴Data refers to 40 patients HIV (+). Effect size (d): small ($0.20 \leq d < 0.50$), medium ($0.50 \leq d < 0.80$), and large ($d \geq 0.80$) [21]

Table 2 Multiple binary logistic regression model between HIV-1 infection (exposure) and bleeding on probing (BOP) $\geq 10\%$ (outcome) adjusted for potential confounders (age, gender, VSB, and smoking) ($R^2=0.430$)

Predictor variables	BOP $\geq 10\%$		Total ($n=205$)	β	SE	p	aOR	95% CI
	No ($n=74$)	Yes ($n=131$)						
Age ¹								
18–35	37 (50.7)	30 (23.4)	67 (33.3)				1	
36–50	29 (39.7)	76 (59.4)	105 (52.2)	1.75	0.426	< 0.0001	5.73	2.49–13.20
> 50	7 (9.6)	22 (17.2)	29 (14.5)	1.84	0.601	0.002	6.29	1.94–20.42
Gender								
Male	32 (43.2)	75 (57.3)	107 (52.2)				1	
Female	42 (56.8)	56 (42.7)	98 (47.8)	-0.05	0.374	0.887	0.95	0.46–1.97
VSB ²								
< 10%	30 (41.1)	8 (6.1)	38 (18.6)				1	
$\geq 10\%$	43 (58.9)	123 (93.9)	166 (81.4)	3.17	0.550	< 0.0001	23.68	8.07–69.53
Smoking (≥ 1 cigarette by day) ³								
Yes	20 (27.8)	49 (38.9)	69 (34.8)				1	
No	52 (72.2)	77 (61.1)	129 (65.2)	0.01	0.403	0.976	1.01	0.46–2.23
HIV-1 infection ²								
Yes	17 (23.0)	57 (43.5)	74 (36.1)	1.71	0.460	< 0.0001	5.53	2.45–13.64
No	57 (77.0)	74 (56.5)	131 (63.9)				1	

β regression coefficient, aOR adjusted odds ratio, SE standard error, VSB visible supragingival biofilm.

¹Data refers to 201 patients.

²Data refers to 198 patients.

³Data refers to 205 patients.

the HIV group and 72 in the non-HIV group). According to the multiple logistic regression (adjusted), HIV-1 infection did not show a significant association with the detection of at least 3 sites with PPD ≥ 5 mm and/or CAL ≥ 4 mm in non-adjacent teeth (Table 3).

Discussion

The aim of the study was to specify the risk factors of periodontal clinical conditions and to provide estimates of the importance of common risk factors. Globally, our results do not suggest the relevance of the identification of periodontal disease in patients under HAART treatment, for the screening of immune suppression in developed countries. Additionally, being a common condition casts doubt on whether periodontal conditions should be included as strongly indicative of HIV [18]. The pattern of HIV-1 infection has changed from a deadly disease to a manageable chronic disease since the introduction of HAART. Therefore, the relationship between HIV-1 infection and oral disease manifestations, especially periodontal disease, has shifted [12]. In the current study, the frequency of detection of at least 3 sites with PPD ≥ 5 mm and/or CAL ≥ 4 mm in non-adjacent teeth in HIV-1-infected patients was 50%, while in the non-HIV infected controls, it was 54.9% ($p=0.499$), showing that

the infection does not appear to influence the detection of this level of periodontitis in those taking HAART. In terms of the latest classification of periodontitis [24], the level of periodontitis chosen in the present study would be classified as stage II and above. It represents moderate to severe periodontitis and is clearly clinically relevant. It was specifically chosen as previous studies have shown that the prevalence of severe periodontitis in HIV-1-infected patients can be almost twice as high as that in the control group [25].

Since the years 1995, as the infection by the HIV became gradually a chronic disease characterized by persistency of the virus in the infected host, the evolution in the patients infected by the HIV of the oral manifestations such as linear gingival erythema, necrotizing ulcerative gingivitis, erythematous candidiasis, oral herpes, Kaposi sarcoma, and oral hairy leukoplakia has required more detailed researches [26]. The literature indicates that there has been a significant decrease in the prevalence of the oral manifestations of HIV documented in Europe and the USA in response to antiretroviral therapy (ART) [27–30]. If the prevalence and progression of periodontal disease has been modified with the advent of HAART [31], it concerns especially the reduced incidence of necrotizing periodontal disease [4, 32]. So, periodontitis, which is one of the major elements of the oral lesions, under the HAART period, was little studied [33]. Regarding periodontal disease, the findings are not

Table 3 Multiple binary logistic regression model between HIV-1 infection (exposure) and detection of ≥ 3 sites with PPD ≥ 5 mm and/or CAL ≥ 4 mm (outcome) adjusted for potential confounders (age, gender, VSB and smoking) ($R^2 = 0.461$)

Predictor variables	≥ 3 sites with PPD ≥ 5 mm and/or CAL ≥ 4 mm		Total ($n=205$)	β	SE	p	aOR	95% CI
	No ($n=96$)	Yes ($n=109$)						
Age ¹								
18–35	50 (53.2)	17 (15.9)	67 (33.3)				1	
36–50	35 (37.2)	70 (65.4)	105 (52.2)	2.19	0.418	< 0.0001	8.95	3.94–20.31
> 50	9 (9.6)	20 (18.7)	29 (14.5)	2.16	0.571	< 0.0001	8.65	2.83–26.47
Gender								
Male	46 (47.9)	61 (56.0)	107 (52.2)				1	
Female	50 (52.1)	48 (44.0)	98 (47.8)	0.316	0.384	0.411	1.37	0.65–2.91
VSB								
< 10%	34 (35.8)	4 (3.7)	38 (18.6)				1	
$\geq 10\%$	61 (64.2)	105 (96.3)	166 (81.4)	3.14	0.601	< 0.0001	23.18	7.13–75.31
Smoking (≥ 1 cigarette by day) ²								
Yes	22 (23.7)	47 (44.8)	69 (34.8)	0.90	0.400	0.025	2.46	1.12–5.38
No	71 (76.3)	58 (55.2)	129 (65.2)				1	
HIV-1 Infection								
Yes	37 (38.5)	37 (33.9)	74 (36.1)	−0.24	0.392	0.542	0.79	0.37–1.70
No	59 (61.5)	72 (56.5)	131 (63.9)				1	

β regression coefficient, aOR adjusted odds ratio, SE standard error, VSB visible supragingival biofilm.

¹Data refers to 201 patients.

²Data refers to 198 patients.

clear [34]. But it should be mentioned that the classification of the periodontal diseases has undergone several revisions over this period [19, 24]. This has resulted in frequent revisions and changes [35]. The heterogeneity of the clinical manifestations, disease progression of periodontitis from the 1999 classification to the 2017 one proved problematic and was an exacerbating element to the development of collaborative research as well as after the introduction of HAART, findings from relevant studies also vary and cannot be compared, partly because of the different types of therapy received by participating patients. Our study included both HIV + and HIV – patients with varying degrees of PD. The results showed significant results in favor of the group on HAART with lower prevalence for stage II or III periodontitis, which might occur because of the improvement in immunity provided by the therapy. Age and dental biofilm accumulation are recognized factors associated with periodontal disease [36, 37] and explain the direct association of age on the outcome BOP, while VSB showed an association on both BOP. It was also interesting to note that in the present study, patients in the HIV-1 group on HAART had increased BOP compared with the non-HIV group but at the same time they appeared to have reduced PPD (data not shown). While smoking and age can explain the direct impact of these variables on PPD [36, 38], the inverse relationship between HIV-1 infection and PPD in patients on HAART has not

previously been reported and the mechanisms underlying this remains to be determined although it could be related to a restoration of T cell function in these patients.

Ferreira et al. (2016) have demonstrated that HIV-1-infected patients have significantly less visible supragingival plaque, as well as less periodontal inflammation and tissue destruction compared with non-HIV-1-infected patients [39]. The periodontal clinical parameters were also less severe in these HIV-infected patients than in non-HIV-1-infected patients, confirming previous data reported by other studies on the same population [40, 41]. It is possible to speculate that as HIV-1-infected individuals are normally more cautious about their general health and are more exposed to a range of health care professionals [12], as well as to the effect of long-term use of HAART [42, 43], their overall oral health care could be better than those non-HIV-1-infected patients not exposed to these influences. This could partially explain the inverse association of HIV-1 infection on PPD (data not shown).

A crucial role for oral bacterial communities in long-term systemic immune activation in patients on HAART is suggested. For oral lesions, Greenspan et al. (2004) have reported a lack of reduction despite a higher mean CD4 + count and a lower mean viral load, with HAART treatment. Despite evidence of a chronic inflammatory phenotype in PLWH on antiretroviral therapy, the role of oral

microbiota in chronic immune activation has not been fully explored. More broadly, these findings can bolster general models of microbiome-mediated chronic systemic immune activation and aid the development of precise microbiota-targeted interventions to reverse chronic inflammation [8]. Thus, interventions targeting both inflammation and the microbiome, particularly in the oral cavity, may be necessary to reduce chronic immune dysregulation in patients with HIV. Recently, the increase in the prevalence of HPV-related oral conditions has been attributed to the immune reconstitution status [44] or age-related immune insufficiency, rather than as direct consequence of using antiretroviral therapy [45].

Interventions targeting both inflammation and microbial diversity are needed to mitigate oral inflammation-related comorbidities, particularly in HIV-positive patients. HAART increases CD4+ cell count and decreases levels of HIV RNA. All these inflammatory mediators or cytokines have the capacity to operate alone in concert or alone, to induce periodontal disease and collagen damage through the use of tissue-derived matrix metalloproteinases, a characteristic of periodontitis evolution as a process presenting a significant host immune and inflammatory response to the bacterial challenges which determine the propensity to induce destructive/progressive periodontitis [46]. Antiretroviral therapy may decrease inflammation and immune activation thought to contribute to higher rates of cardiovascular and other co-morbidities reported in HIV-infected cohorts [47]. HIV-HAART-associated PD could serve as a source of chronic inflammation. In the presence of inflammation, there is evidence of up-regulation of various receptors, including HIV receptors, on the surface of oral epithelium, and the epithelium may become more permeable [48].

One of the strengths of our trial is, in an adequate sample size, with a calculated *p*-value presented which can support powerful statistical conclusions. Eligible subjects were primary consultants recruited from the pool of hospital consultation without relation with oral health content. A matching of controls was used on age, a variable scientifically known to have an impact on the incidence and prevalence of periodontal diseases. Gender was not retained as a matching variable. The effect of the smoking variable, known to be a major confounder, was adjusted in the multiple binary regression model for all outcomes.

Our study has several potential limitations, such as selection bias, but we have made a significant effort to overcome subjectivity by obtaining information in a standardized way. Potential confounding biases were controlled through multivariate analysis. Furthermore, the TCD4 lymphocytes data were not available for all patients with possible impacts of the study outcomes. Ideally, the data should have been reanalyzed with only HIV and AIDS cases separately. At least, determination of medical history and immunologic status of

HIV patients targeted antiretroviral therapy, T-CD4+ lymphocyte count, and viral load and antiretroviral therapy. However, it would have been logical to include “dynamic” data of the disease, not available in the medical data record, such as duration and active phase. Similarly, the quality of compliance with the HAART medication was not assessed.

Conclusions

With the necessary caution in the causal interpretation of the observed associations, our findings indicated that the detection of clinically relevant stage II or III periodontitis in PLWH undertaking HAART is similar to non-HIV-1-infected patients. Accordingly, oral health practitioners could consider conventional periodontitis in HIV-1-infected patients on HAART the same as they would a non-HIV-1-infected patient. Furthermore, the current study has shown a direct association of HIV-1 infection with BOP and an inverse association with PPD in those on HAART; however, due to the cross-sectional design of the study a cause-and-effect relationship should be considered with caution. Additional research is required regarding biological issues such as the role of oral immune factors and periodontal disease in the persistency of HIV infection, the possibility of oral transmission, and the re-emerging of HIV infection. Prospective studies with adequate controls are needed to estimate the effect of HIV-1 infection under HAART on different outcomes related to periodontal disease, clinical parameters, and subgingival microbiota over the years of the PLWH.

Author contribution Conceptualization: L.S.G., D.C.F., and F.V.; methodology: L.S.G., D.C.F., and F.V.; formal analysis: L.S.G. and C.G.; investigation: P.P. and R.C.S.; data curation: L.S.G., P.P., and R.C.S.; writing—original draft preparation: L.S.G., C.G., and P.P.; writing—review and editing: D.B., F.C., L.S.G., and G.J.S.; supervision: L.S.G., D.C.F., and F.V.; project administration: L.S.G., D.C.F., and F.V.; resources: L.S.G. and D.C.F.

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Declarations

Conflict of interest The authors declare no competing interests.

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