EFFECTS OF PERIODONTAL TREATMENT ON SERUM INFLAMMATORY MARKERS AND CD4+ LYMPHOCYTE CELL COUNT IN PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Summary
Introduction. Several studies have reported reduction in the serum concentration of systemic inflammatory markers upon completion of periodontal therapy. However, no studies have been conducted on the effects of periodontal therapy on systemic inflammation in human immunodeficiency virus-positive patients. The aim of this study was to investigate the effects of periodontal therapy on the serum levels of systemic inflammatory biomarkers and CD4+ lymphocyte cell count in human immunodeficiency virus-positive patients. Material and Methods. The study included 34 human immunodeficiency virus-positive patients with chronic periodontitis receiving antiretroviral therapy. Periodontal parameters (plaque index, gingival index, papilla bleeding index, probing depth and clinical attachment level) and serum samples, assessed for the levels of interleukin-1β, tumor necrosis factor-α, and C-reactive protein, were evaluated at baseline, 1- and 3-months upon completion of the non-surgical periodontal therapy. The CD4+ lymphocyte count was measured at baseline and three months after treatment completion. Results. Significant reduction in the values of plaque index, gingival index, papilla bleeding index, and probing depth was noted (p < 0.001), whereas the reduction in the median clinical attachment level value did not reach a statistically significant level (F = 1.321; p = 0.261). Local inflammation reduction was accompanied by a significant decrease in serum C-reactive protein (F = 5.765; p = 0.014) and a CD4+ lymphocyte count increase (t = 2.321; p = 0.027). Serum interleukin-1β and tumor necrosis factor-α did not change significantly as a result of periodontal treatment. Conclusion. Periodontal therapy contributes to the reduction of C-reactive protein and improvement of general health in human immunodeficiency virus-positive patients receiving highly active antiretroviral therapy. Key words: Periodontal Diseases; CD4-Positive T-Lymphocytes; Biomarkers; HIV Infections; C-Reactive Protein; Tumor Necrosis Factor-alpha; Interleukin-Ibeta; Treatment Outcome;

Sažetak
Uvod. U više naučnih radova objavljeno je da koncentracija serumskih inflamatornih markera značajno opada nakon parodontološke terapije. Međutim, do danas nema podataka u literaturi o uticaju lečenja parodontopatije na sistemsku inflamaciju kod pacijenata pozitivnih na virus humane imunodeficiencije. Cilj ovog istraživanja bio je da se ispitaj učinak parodontološke terapije na serumsku koncentraciju markera sistemskog inflamacije i broj CD4+ limfocita kod pacijenata pozitivnih na virus humane imunodeficiencije. Materijal i metode. U istraživanje je uključeno 34 ispitanika pozitivnih na virus humane imunodeficiencije koji primaju antiretroviralnu terapiju i boluju od kronične parodontopatije. Klinički parodontološki parametri (plak indeks, gingivalni indeks, indeks krvenja papile, dubina sondiranja i nivo pripojnog epitelja) i serumske koncentracije interleukina-1β, faktor nekrozne tumorne alfa i C-reaktivni protein posmatrani su na početku, kao i jedan i tri meseca nakon završetka kauzalne parodontološke terapije. Broj CD4+ limfocita ispitan je na početku i tri meseca posle lečenja. Rezultati. Nakon parodontološkog tretmana došlo je do značajnog pada vrednosti plak indeksa, gingivalnog indeksa, indeksa krvenja i dubine sondiranja (p < 0,001), dok pad srednje vrednosti nivoa pripojnog epitelja nije dostigao statistički značajan nivo (F = 1,321; p = 0,261). Smirivanje lokalne inflamacije bilo je praćenje značajnim smanjenjem serumske koncentracije C-reaktivnog proteina (F = 5,765; p = 0,014) i značajnim porastom broja CD4+ limfocita (t = 2,321; p = 0,027). Koncentracije interleukina-1β i faktor nekrozne tumorne alfa u serumu nisu se značajno promenile nakon lečenja parodontopatije. Zakučak. Klinički uspešna parodontološka terapija praćena je značajnim padom serumske koncentracije C-reaktivnog proteina i poboljšanjem opšteg zdravlja pacijenata pozitivnih na virus humane imunodeficiencije koji koriste antiretroviralnu terapiju. Ključne reči: parodontopatije; CD4+ limfociti; biomarkeri; HIV infekcija; C reaktivni protein; tumor nekrozni faktor alfa; interleukin Ibeta; ishod lečenja

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Introduction

Although it is known that human immunodeficiency virus (HIV) infection affects the periodontal condition, the inverse relationship, i.e., impact of periodontal disease on HIV, has only recently emerged as a topic of interest [1].

Few studies have shown that periodontal infection can cause reactivation of latent HIV in infected cellular reservoirs [2, 3].

While the focus of HIV-related research is increasingly shifting towards early diagnosis of comorbidities [4] and the development of strategies for controlling the residual systemic inflammation and immune activation [5], the aim of the present study was to test the hypothesis that non-surgical periodontal therapy may impact the levels of systemic proinflammatory cytokines, interleukin-1β (IL-1β) and tumor necrosis factor-α (TNFα) in HIV-positive patients receiving highly active antiretroviral therapy (HAART). These two cytokines were selected due to their link with the biological aspects of periodontal disease [6] and their role in the reactivation of the HIV virus in the latently infected cells [7]. We also monitored the C-reactive protein (CRP) serum levels, as this is a highly sensitive indicator of systemic inflammatory response. Furthermore, another objective was to evaluate the influence of periodontal therapy on CD4T-lymphocytes cell count and the HIV viral load.

Material and Methods

A prospective cohort intervention design was used. The study protocol was approved by the Ethical Committee of the Clinic of Dentistry of Vojvodina in Novi Sad, Serbia (Ethical number 02-3/15-2010).

Patients with HIV-infection were selected from a group of 158 individuals who visited the Clinic for Infectious Diseases of the Clinical Centre of Vojvodina for routine check-up between December 2010 and November 2011. The inclusion criteria were as follows: (1) receiving HAART for more than 6 months, without change in the dose or medication protocols in the three preceding months; (2) having at least 20 natural teeth; (3) clinically diagnosed periodontal disease; and (4) volunteering for participation and a signed informed consent. Patients who met any of the following criteria were excluded from the study: (1) any systemic antibiotic therapy within the last 3 months, (2) use of anti-inflammatory drugs within the previous 3 months, (3) periodontal therapy within the preceding 6 months, and (4) diagnosis of any serious uncontrolled systemic conditions.

### Table 1. Demographic data, smoking habit, HIV infection characteristics and antiretroviral parameters of the study group

| Parameter | Description | Value |
|-----------|-------------|-------|
| Age (years) | Mean (SD) | 38.26 ±10.361 |
| Sex | Male/female | 31 (91.18%)/3 (8.82%) |
| Smokers (%) | | 22 (64.7%) |
| Years since HIV infection was diagnosed | Mean (SD) | 5.37 ± 3.29 |
| Risk behavior | MSM | 25 (73.5%) |
| Duration of HAART | Mean (SD) | 3.36 ± 2.58 |

### Abbreviations

- HIV: human immunodeficiency virus
- TNF-α: tumor necrosis factor-α
- IL-1β: interleukin-1β
- CRP: C-reactive protein
- HAART: highly active antiretroviral therapy
- PI: plaque index
- GI: gingival index
- PBI: papilla bleeding index
- PD: probing depth
- CAL: clinical attachment level
- MSM: men who have sex with men
- HS: heterosexuals
- IVDU: intravenous drug users
- OR: other reasons
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After the inclusion and exclusion criteria were applied, 39 individuals remained. However, five patients were subsequently excluded, due to the initiation of systemic antibiotic therapy during the period of investigation. Thus, the final sample included 34 subjects, all of whom completed the study. The clinical aspect of the study measured parameters that indicate the level of oral hygiene, inflammation and destruction of periodontal tissue, i.e., plaque index Silness-Löe (PI) [6], gingival index Löe-Silness (GI) [8], papilla bleeding index – Mühlemann (PBI) [9], probing depth (PD) and clinical attachment level (CAL). All dental variables were assessed at four sites (mesiobuccal, midbuccal, distobuccal, and midlingual) of each tooth, except the wisdom teeth. All assessments were carried out using the Williams periodontal probe. The definition of periodontitis used in this study was proposed by a work group with representatives from both the Centers for Disease Control and Prevention and the American Academy of Periodontology [10]. All clinical data were collected at baseline, at 1- and 3-months after periodontal treatment completion (allowing its efficacy to be assessed).

Blood analysis was conducted in order to determine CD4 lymphocyte count (quantified by flow cytometry analyzer, Becton Dickinson, USA) and HIV viral load (RT PCR Amplicor, Roche Diagnostics Corporation, Indianapolis, USA), both of which were assessed at baseline and three months after completion of therapy. Serums were separated from parts of blood samples and immediately stored at -70°C until required for analyses aiming to establish concentrations of IL-1β (R&D System, Quantikine HS, Human IL-1β Immunoassay, Minneapolis, MN, USA), TNFα (R&D System, Quantikine HS, Human TNFα Immunoassay, Minneapolis, MN, USA) and CRP (Immunoassay, Minneapolis, MN, USA), and IL-1β (R&D System, Quantikine HS, Human IL-1β Immunoassay, Minneapolis, MN, USA) and CRP (Immunoturbidimetric assay, Cobas Integra, Roche AG Diagnostics, Mannheim, Germany). All serum samples were blind tested at the end of the study.

The standard non-surgical, cause-related periodontal therapy was tailored to individual patient needs without any time limitations. Study participants were examined at baseline and at one and three months following the completion of periodontal therapy. The therapy included oral hygiene instructions, extraction of teeth with poor prognosis, ultrasonic (miniPiezon by EMS, Electro Medical System S.A., Nyon, Switzerland) removal of supra- and sub-gingival plaque and calculus, and root planing under local anesthesia using an Gracey curettes (Kohler, Germany).

The clinical data significant for the study objectives were calculated for each parameter by computing the full-mouth mean scores. The analyses included repeated measures analysis of variance (RM ANOVA) in the general linear module of the Statistical package for the social sciences (SPSS) software package. The observed parameters PI, GI, PBI, PD, G, and serum concentrations of IL-1β, TNFα and CRP were used as dependent variables. The within-subjects factors were the three-stage assessments, performed at baseline, as well as at 1- and 3-months post-treatment follow-ups. When the Mauchly’s test indicated that the assumption of sphericity had been violated ($\chi^2 (2) = 10.310, p =$.
0.006), the Greenhouse-Geisser $\varepsilon < 0.75$, Huynh-Feldt correction was used.

A t-test was used to determine changes in the CD4 cell count and the HIV viral load, which were analyzed at baseline and 3 months after therapy.

### Results

The study sample included 34 HIV-positive patients, 31 male and only 3 female with a mean age 38.26 ± 10.36. The general characteristics of subjects and their respective HIV infection parameters are shown in Table 1.

At baseline, most participants showed a widespread inflammation, but limited periodontal tissue destruction. The estimated marginal means of periodontal indices at baseline, and at one and three months post-treatment are shown in Table 2. The RM ANOVA determined that the values of all periodontal indices were statistically significantly low (PI: $F = 54.192; p < 0.001$, GI: $F = 66.60; p < 0.001$, PBI: $F = 49.106; p < 0.001$, PD: $F = 30.673; p < 0.001$) with the exception of CAL ($F = 1.312; p = 0.26$).

The mean (± SD) values of IL-1β at baseline and one and three months after treatment were 0.37 (± 1.49) pg/ml, 0.09 ± 0.25 pg/ml and 0.08 ± 0.22 pg/ml, respectively. In addition, the mean (± SD) values of TNFα at baseline and one and three months after treatment were 1.13 (± 0.87) pg/ml, 1.02 ± 0.59 pg/ml and 1.22 (±0.69) pg/ml, respectively. The RE ANOVA showed that the reduction in both parameters was not statistically significant (IL-1β: $F = 1.715; p = 0.200$; TNFα: $F = 0.530; p = 0.591$). On the other hand, reduction in periodontal inflammation was accompanied by a continued decline in the mean value of serum CRP (at baseline 4.51 (± 6.82) mg/l; one month after therapy: 2.83 ± 3.24 mg/l and 3 months later: 2.30 (± 2.03) mg/l) which reached a statistical significance ($F = 5.765, p = 0.014$).

Before the beginning of periodontal therapy, the CD4 lymphocyte values ranged from 92.00/ml to 1289.00/ml, corresponding to the mean of 575.41 ± 287.83/ml. At the 3-month follow-up, the mean CD4 lymphocyte values increased by 78.41 ± 196.99 on average, reaching 653.82 ± 278.10, which corresponded to a statistically significant improvement ($t = 2.321; p = 0.027$).

In the majority of patients that took part in the present study, the HIV viral load was adequately controlled. At baseline, detectable HIV viral load levels were noted in 6 patients (17.65%), whereas the remaining 28 (82.35%) participants had a non-detectable number of HIV RNA copies per ml of blood. More specifically, the initial mean HIV viral load was 537.00 ± 278.10 copies /ml. Three months after completing the periodontal therapy, only four patients had a detectable HIV viral load, and the mean value declined to 65.51 ± 252.75 copies /ml. However, due to the extremely high standard deviation, the differences in the HIV viral load measured pre- and post-treatment were not statistically significant ($t = 1.101 p = 0.279$).

### Discussion

To the best of our knowledge, thus far, no studies have been conducted on the impact of periodontal therapy on the level of systemic inflammation in population of HIV-positive patients. The aim of the present study was to address this gap in the extant knowledge by assessing the effects of causal periodontal therapy on serum concentrations of proinflammatory cytokines IL-1β and TNFα and serum levels of CRP, along with CD4 count and HIV viral load as the markers of HIV infection. Our results indicate that the serum IL-1β and TNFα values were not significantly changed by the periodontal treatment. These findings are consistent with those reported in systemically healthy patients by Ide [11] and Yamazaki et al. [12]. These authors also noted no statistically significant changes in serum CRP upon therapy completion, despite significant clinical improvements in the condition of periodontal tissues [11, 12]. Conversely, in our population of HIV-positive patients, periodontal treatment contributed to a significant decline in serum CRP.

A significant reduction in the serum CRP level following periodontal therapy was reported in numerous studies conducted in systemically healthy individuals [13 - 15]. However, a meta-analysis conducted by Demmer et al., showed that anti-infective periodontal treatment can reduce serum CRP by approximately 0.4 mg/l [16]. According to the findings yielded by the same study, periodontal therapy that includes use of antibiotics can produce a post-treatment decline in serum levels of CRP to about 0.75 mg/l [16]. In our study, however, we noted an unexpectedly large reduction in the mean CRP level after periodontal treatment, in particular, given the predominance of localized periodontal tissue destruction. Studies have shown that, in HIV-positive patients, including those undergoing HAART treatment, CRP levels tend to be higher compared to HIV-negative individuals [17, 18]. Given that this is the first study on the effects of periodontal therapy on systemic inflammation in HIV-positive patients, it is not possible to compare our results with those reported in similar extant works. Nonetheless, empirical evidence suggests that, in patients with systemic comorbidities, such as diabetes mellitus, anti-infective periodontal treatment results in a somewhat higher CRP reduction in relation to that achieved in systemically healthy cohort. This argument is supported by the results reported by Erciyas et al. [19], who showed that, in patients with active rheumatoid arthritis, periodontal treatment alone (i. e., without any changes in anti-rheumatic therapy) resulted in a decline in CRP level, from 17.00 (6.52–27.30) mm/dl to 8.00 (3.54–12.50) mm/dl ($p < 0.001$). Thus, it can be assumed that periodontal therapy contributes to the reduction of systemic inflammation in HIV-positive patients receiving HAART.

One of the findings that emerged from our research pertains to a significant increase in the mean CD4 values three months after periodontal therapy. In addition,
we also noted a decline in the number of HIV RNA copies in the blood (however, it regard to the baseline values, this change was not statistically significant). Given that none of the study participants reported a change in systemic HIV-related drug therapy during the course of the study, we can suppose that the combination of periodontal and antiretroviral therapy has contributed to the significant overall improvement in the health of HIV-positive patients. Our results support those reported by Noro-Filho et al., who reported that, in their study sample, periodontal treatment was associated with a decline in HIV viral load and a significant increase in the CD4 lymphocyte count [20].

The results of this study indicate that adequate treatment to HIV-positive patients with chronic periodontal disease is important, as it can lead not only to significant local improvements, but also contribute to the overall enhancement of their systemic health. In addition, our findings emphasize the importance of treatment of periodontal disease in the overall health status and outcomes of HIV-positive patients.

**Conclusion**

Based on our findings, non-surgical periodontal treatment leads not only to a significant clinical improvement of periodontal disease status, but also contributes to the improvement in the general health of human immunodeficiency virus-positive patients receiving highly active antiretroviral therapy.

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