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ORAL DISEASES

HIV-infection and periodontal diseases: an overview of the post-HAART era

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3 HIV-infection and periodontal diseases: an overview of the post-HAART
4 era
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8 Running head:HIV-infection and periodontal diseases
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ABSTRACT

HIV infection remains a global health problem of unprecedented dimensions, although the development of highly active antiretroviral therapy (HAART) has significantly modified the course of HIV disease into a manageable chronic disease with longer survival and improved quality of life in HIV-infected subjects. Among the HIV-associated infections, oral lesions have been recognized as prominent features since the beginning of the epidemic and continue to be important. Periodontal diseases strongly associated with HIV infection are classified as Linear Gingival Erythema (LGE), Necrotizing Ulcerative Gingivitis (NUG), and Necrotizing Ulcerative Periodontitis (NUP), and are included among the cardinal oral lesions. Although oral candidiasis appears to be the infection more significantly decreased after the introduction of HAART, the current literature suggests that the prevalence and course of periodontal lesions have also been modified. Higher prevalence of opportunistic microorganisms has been frequently detected in the subgingival flora of HIV-infected individuals, probably due to the immune status of those patients, as colonization and overgrowth of atypical pathogenic species is facilitated by immunosuppression. 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.

INTRODUCTION

HIV infection remains a global health problem of unprecedented dimensions. Unknown 27 years ago, HIV has already caused an estimated 25 million deaths worldwide and has generated profound demographic changes in the most heavily affected countries. While the percentage of people living with HIV has stabilized since 2000, the overall number of people living with HIV has steadily increased, as new infections occur each year, HIV treatments extend life, and in addition, new infections still outnumber AIDS deaths.

The development of highly active antiretroviral therapy (HAART) especially after 1995, has significantly modified the course of HIV disease, at least in the industrialized world, into a manageable chronic disease with longer survival and improved quality of life in HIV-infected subjects.

HAART generally consists of a dual nucleoside analogue reverse transcriptase inhibitor (NRTI) "backbone" and a third or "cornerstone" drug, such as a nonnucleoside inhibitor (NNRTI) or a protease inhibitor (PI), usually a "boosted" one. The use of a NNRTI as a third drug is less potent and therefore, in most settings not a preferred option, and it is recommended that baseline resistance testing should guide the specific regimen design.

HAART increases CD4+ cell count, decreases levels of HIV RNA, and extends AIDS-free survival, at least in the short term. 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.

Eradication of HIV infection cannot be achieved with available antiretroviral regimens. This is mainly attributed to the fact that the pool of latently infected CD4+ T-cells is established during the earliest stages of acute HIV infection and persists with a long half-life, even with prolonged suppression of plasma viremia.

It is known that HAART is associated with significant problems, including toxic side effects, development of virological resistance and great financial expense. Up to half of patients on antiretroviral therapy may experience adverse effects of the medications (Fellay *et al*, 2001). Common side-

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3 effects vary depending on the drug regimen, but can include
4 hypersensitivity, lactic acidosis, increases in blood lipids, bleeding events,
5 anaemia, neuropathy, lipodystrophy, and pancreatitis (UNAIDS, 2008).
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7 While most side-effects diminish over time, some can be life-threatening,
8 underscoring the importance of careful patient monitoring (UNAIDS,
9 2008).

10
11 Due to the intensity of combined antiretroviral treatment and widespread
12 use of HAART, the incidence of many AIDS-related opportunistic infections
13 in patients with advanced HIV infection has significantly decreased but
14 despite dramatic declines in the incidence of opportunistic infections in
15 many resource-rich nations, opportunistic infections remain a leading
16 cause of hospitalization and death for persons with HIV infection.

17
18 Among the HIV-associated infections, oral lesions have been recognized
19 as prominent features of HIV infection since the beginning of the epidemic
20 and continue to be important.

21
22 Purpose of the present review is to overview the features, prevalence,
23 bacteriology and host response characteristics of periodontal infections in
24 HIV patients, especially as modified during the HAART era.

25 26 27 28 29 30 31 32 33 34 35 36 FEATURES OF PERIODONTAL LESIONS IN HIV INFECTED PATIENTS

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39 HIV infection in adults is linked with the expression of various types of
40 periodontal lesions, which include specific forms of gingivitis and
41 necrotizing periodontal diseases, as well as with possible exacerbation of
42 preexisting periodontal disease (Winkler *et al*, 1992; Robinson *et al*,
43 2002; EC-Clearinghouse, 1993). Periodontal diseases strongly associated
44 with HIV infection are classified as Linear Gingivitis Erythema (LGE),
45 Necrotizing Ulcerative Gingivitis (NUG), and Necrotizing Ulcerative
46 Periodontitis (NUP) and are included among the seven cardinal oral
47 lesions, which have been identified and recognized internationally, as
48 follows: oral candidiasis, oral hairy leukoplakia, Kaposi sarcoma, LGE,
49 NUG, NUP and non-Hodgkin lymphoma (Armitage, 1999; EC-
50 Clearinghouse, 1993; Coogan *et al*, 2005).

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60 The criteria for diagnosis of HIV-related oral lesions are not well defined in
children. Orofacial manifestations have been categorised into three

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3 groups: those less commonly, commonly, and strongly but rarely
4 associated with pediatric HIV infection. LGE has been reported between
5 those commonly associated (Ramos-Gomez *et al*, 1999; Coogan *et al*,
6 2005)
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10 Together with other oral infections, HIV-associated periodontal diseases
11 are regarded as serious complications of HIV infection and have an
12 important diagnostic and prognostic value (EC-Clearinghouse, 1993; Glick
13 *et al*, 1994a; Shangase *et al*, 2004; Coogan *et al*, 2005). They belong
14 among the earliest clinical features of the infection and could predict
15 progression of HIV disease to AIDS. (Robinson *et al*, 2002; Coogan *et al*,
16 2005). It should also be mentioned that for patients on antiretroviral
17 therapy, HIV-related oral lesions in general, may suggest possible
18 treatment failure as will be further discussed in the present review.
19 (Margiotta *et al*, 1999; Ramirez-Amador *et al*, 2007; Gaitan-Cepeda *et al*,
20 2005; Eyeson *et al*, 2002; Flint *et al*, 2006). However, HIV-associated
21 periodontal infections are less common than oral candidiasis and oral hairy
22 leukoplakia and thus not included as criteria in the Centers for Disease
23 Control (CDC) classification (CDC, 1992). HIV-associated periodontal
24 infections have characteristic clinical appearance which has been well
25 described (Winkler *et al*, 1992; Greenspan & Greenspan, 2008; Reznik,
26 2006; Murray 1994).
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30 *Linear Gingival Erythema (LGE)* is a form of gingivitis characterized by a
31 distinct fiery red band along the margin of the gingiva (EC-Clearinghouse,
32 1994). It is usually associated with anterior teeth, commonly extended to
33 the posterior teeth, accompanied in some cases by bleeding and
34 discomfort (Reznik, 2006). In other cases it presents as petechia-like
35 patches on attached or free gingiva. Currently, *Candida* species have been
36 implicated to the aetiopathology of LGE as well as other HIV-associated
37 periodontal pathology.
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41 *Necrotizing Ulcerative Gingivitis (NUG)* is characterized by rapid onset and
42 acute painful inflammation of gingiva with rapid destruction of soft
43 tissues, while *Necrotizing Ulcerative Periodontitis (NUP)* is escorted by
44 bleeding, sharp pain, ulcerated gingival papillae, rapid and extensive soft
45 tissue necrosis and advanced loss of periodontal attachment, frequently
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3 leading to bone exposure (Murray, 1994; Greenspan & Greenspan,
4 2008; Reznik, 2006).

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7 The rapid establishment and course of necrotizing forms of periodontal
8 disease in patients with HIV/AIDS infection, contrary to the gradually
9 progressing periodontal disease in adults in the general population has
10 been outlined in many studies and had not been reported before AIDS
11 epidemic. (Murray *et al*, 1989; Murray, 1994; Barr *et al*, 1992; Yeung *et*
12 *al*, 1993a) HAART appears to have profoundly influenced the prevalence,
13 severity and course of periodontal lesions as will be further discussed in
14 the next section of the present review (Parveen *et al*, 2007).

15
16 Risk factors for periodontal disease in HIV-infected individuals besides the
17 general factors of age, smoking, preexisting gingivitis, poor oral hygiene
18 and poor diet, include counts of CD4+ cells (Glick *et al*, 1994b), viral load
19 and specific species of microbiota.

20
21 Oral opportunistic infections, mainly oral candidiasis (OC) and oral hairy
22 leukoplakia, (OHL) have been associated with CD4+ count in both the pre-
23 HAART and the HAART era in several studies. Based on these findings, low
24 CD4+ counts are now considered as the main risk factor associated with
25 the development of oral lesions and especially of oral candidiasis
26 (Margiotta *et al*, 1999).

27
28 Regarding periodontal disease, there is little and unclear data, especially
29 during the HAART era. In 1994, Glick and coworkers have reported an
30 association between NUP and CD4+ count below 200 cells/mm³ in HIV-
31 infected patients and suggested that NUP may be a good marker of
32 immune deterioration. The same authors reported in another 1994 study
33 a positive predictive value (95.1%) for periodontal diseases, which was
34 higher than the values reported for oral hairy leukoplakia (70.1%) and
35 oral candidiasis (69.9%) (Glick *et al*, 1994a). High positive predictive
36 values have also been reported for necrotizing ulcerative periodontitis
37 (80%) and a moderate (54.5%) one for LGE. (Begg *et al*, 1996; Patton
38 2000). In agreement with the previous studies, Margiotta *et al* (1999)
39 reported that NUP and NUG were significantly associated with CD4+
40 counts lower than 200 cells/mm³ in a cohort of Italian subjects infected
41 with HIV. In contrast to these reports, Schuman *et al*, in a study
42 conducted in a US population, after the introduction of HAART, reported
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3 that LGE and NUG were not related to HIV serostatus or CD4+ lymphocyte
4 count (Schuman *et al*, 1998).
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7 Contradictory results have also been reported in a 2000 study by Patton.
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9 The author reported that the viral load was significantly related to the
10 presence of strongly HIV-associated oral lesions (Patton, 2000) but that
11 among periodontal lesions, only LGE has a significant predictive value
12 (70%) for immune suppression when measured by CD4 cell counts below
13 200 cells/mm³. In the same study, the predictive value for necrotizing
14 ulcerative diseases was lower (47.4%) compared to the values reported
15 previously, a finding which could be attributed to the improved
16 antiretroviral management of HIV disease of the population under
17 investigation. A significant correlation between necrotizing ulcerative
18 diseases and CD4+ T cells number below 200/mm³ was also reported in a
19 study from South Africa, with a positive predictive value of 69.6% for HIV
20 infection in otherwise asymptomatic subjects (Shangase *et al*, 2004).
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22
23 As HIV infection gradually becomes a chronic disease, the features and
24 course of chronic periodontal disease in HIV infected patients require more
25 extensive investigation. The "conventional" periodontal diseases in the
26 HAART era have been mentioned in very few studies. (Kroidl *et al*, 2005;
27 Alpagot *et al*, 2004). Conventional periodontitis progresses gradually,
28 causing no or minimal pain or discomfort, being thus undiagnosed, until
29 considerable tissue loss occurs. (Alpagot *et al*, 2004). Generally,
30 periodontal inflammation seems to be more severe in cases where CD4+
31 counts are low (Kroidl *et al*, 2005) and research nowadays is focused on
32 the accelerated rate with which chronic adult periodontitis presents in
33 seropositive patients. (Lamster *et al*, 1997)
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36 Overall, findings from the above mentioned studies suggest the value of
37 the identification of periodontal disease, even in patients on HAART
38 therapy, in screening the immune suppression, both in diagnosed and
39 undiagnosed HIV infection in adults.
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42 The relation between oral lesions in general and immune and virologic
43 status is still not well established in children. No association was found
44 between the prevalence of oral lesions and immunological status or viral
45 load in children, while there are no data for periodontal diseases (Gaitan-
46 Cepeda *et al*, 2002).
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PREVALENCE OF PERIODONTAL DISEASES IN HIV-INFECTED INDIVIDUALS

The prevalence of periodontal diseases in HIV-infected individuals remains a controversial issue. Data from relevant studies vary widely due to several factors. Many studies refer to HIV-infected individuals, without mentioning the stage of AIDS or the use and the type of antiretroviral therapy, the use of protease inhibitors or not, as well as the use of adjunctive antimicrobials (antibiotics, antifungals). Factors which influence the prevalence of periodontal disease such as age, immune system competence, smoking habits, oral hygiene level, are not always taken into consideration (Barr *et al*, 1992; Alpagot *et al*, 2004). The type of lesion is often not mentioned, while there is some confusion with the terminology. Additionally, it is usually unclear whether diagnosis is made by trained examiners or if universally accepted criteria are used. (EC-Clearinghouse, 1993).

Introduction of antiretroviral therapies and mainly the HAART in 1995 has changed the epidemiology of opportunistic infections in HIV-infected patients (Holtzer *et al*, 1998; Paul *et al*, 2002), and has decreased the mortality and morbidity of HIV infection (Pallela *et al*, 1998). A significant decrease of the overall prevalence of oral lesions from 47-85%, before the introduction of HAART, to 32-46%, post-HAART has been reported (Schmidt-Westhausen *et al*, 2000; Patton *et al*, 2000; Gaitan-Cepeda *et al*, 2008). Oral manifestations significantly decreased in patients on dual and triple therapy in comparison with patients on monotherapy and those on no antiretroviral therapy (Tappuni & Fleming, 2001). Moreover, a lower prevalence (32%) of oral lesions was found in patients on HAART, including efavirenz, compared to patients on HAART including a PI (63%). (Aquino-García *et al*, 2008). Recently, in a retrospective epidemiological analysis performed in Brazil from 1988 to 2004, HAART was found to be associated with significantly lower prevalence of oral manifestations (Ferreira *et al*, 2007). Among oral manifestations, oral candidiasis appears to be the lesion most significantly decreased after the introduction of HAART as shown by several studies.

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3 Regarding the prevalence of HIV-associated periodontal diseases in the
4 pre-HAART era, data vary widely both in developed and developing
5 countries. Indicatively, reported rates of prevalence for LGE range
6 between 9 and 50%, for NUG between 11 and 25% and for NUP between
7 1 and 18% (Laskaris *et al*, 1992; Masouredis *et al*, 1992; Tukutuku *et al*,
8 1990; Glick *et al*, 1994b).

9
10 After the introduction of HAART, findings from relevant studies also vary
11 and cannot be compared, partly because of the different types of therapy
12 received by participating patients. Data from representative studies in
13 developed and developing countries concerning adult and pediatric
14 populations are shown in Table1. The effect of HAART on prevalence of
15 HIV-associated periodontal disease is shown in Table 2. It appears that
16 HAART is associated with a lower prevalence of HIV-associated periodontal
17 disease in adults. The difference between pre- and post-HAART in most of
18 the studies was found to be statistically significant.

19
20 On the contrary, HAART does not appear to significantly affect the
21 prevalence of periodontal disease in children (Flanagan *et al*, 2000;
22 Khongkuntian *et al*, 2001; Parveen *et al*, 2007)

23 24 BACTERIA ASSOCIATED WITH PERIODONTAL DISEASE IN HIV -INFECTED 25 PATIENTS

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27 The development of periodontal disease is generally accepted to depend
28 on the interaction between the host response and the resident oral
29 microbiota, which constitutes a complex dynamic biofilm of multiple
30 microbial communities. Considering that it is a microbial community
31 disease, a distinct microbial profile in these patients, if identified, could
32 assist our understanding of the aetiopathological mechanisms (Kuboniva
33 *et al*, 2009).

34
35 Results from studies on the subgingival microbiota in HIV-infected
36 individuals are quite diverse. Some studies have shown that the
37 microbiota is similar in HIV-positive and HIV-negative patients with
38 periodontitis. (Zambon *et al*, 1990; Brady *et al*, 1996; Nakou *et al*, 1997;
39 Tsang & Samaranayake, 2001; Teanpaisan *et al*, 2001). Other studies
40 have shown a higher prevalence of putative periodontal pathogens such
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3 as *Aggregatibacter actinomycetemcomitans*, *Fusobacterium nucleatum*,
4 *Porphyromonas gingivalis*, *Prevotella intermedia*, *Tannerella forsythia* and
5 *Treponema denticola*, in HIV-positive patients, in comparison to HIV-
6 negative patients, (Murray *et al*, 1989; Cross & Smith, 1995; Scully *et*
7 *al*, 1999; Alpagot *et al*, 2004), while there are studies that present the
8 exact opposite, i.e. that putative pathogens are less prevalent in HIV-
9 positive patients. (Tenebaum *et al*, 1997; Paster *et al*, 2002; Patel *et al*,
10 2003; Gonçalves *et al*, 2007; Botero *et al*, 2007)

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18 Several authors agree that certain microbial species such as *Candida spp*
19 (*Jabra-Rizk et al*, 2001), *Enterobacter faecalis* (Gonçalves *et al*, 2004;
20 Zambon *et al*, 1990; Nakou *et al*, 1997; Gonçalves *et al*, 2007),
21 *Clostridium clostridiiforme* (Zambon *et al*, 1990) *Clostridium difficile*
22 (*Zambon et al*, 1990; Nakou *et al*, 1997; Gonçalves *et al*, 2007),
23 *Klebsiella pneumoniae* (Zambon *et al*, 1990; Nakou *et al*, 1997;
24 Gonçalves *et al*, 2007; Botero *et al*, 2007), *Mycoplasma salivarium* (Moore
25 *et al*, 1993; Zambon *et al*, 1990; Nakou *et al*, 1997; Gonçalves *et al*,
26 2007), *Pseudomonas aeruginosa* (Nakou *et al*, 1997; Gonçalves *et al*,
27 2007; Botero *et al*, 2007), *Acinetobacter baumannii* (Nakou *et al*, 1997;
28 Gonçalves *et al*, 2007), *Enterobacter cloacae* (Botero *et al*, 2007; Nakou
29 *et al*, 1997), which are frequently found in the periodontal environment
30 of HIV-positive patients, are uncommon in other individuals. The role of
31 these "uncommon" species in the pathogenesis of periodontal disease in
32 HIV-infected individuals is not yet fully understood, while it is suggested
33 that the higher prevalence of such opportunistic microorganisms is due to
34 the immune status of those patients as colonization and overgrowth of
35 atypical pathogenic species is facilitated by severe immunosuppression.
36 (Gonçalves *et al*, 2004).

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Data from studies in the HAART era, which apply culture-independent
molecular techniques are displayed in Table 3. These techniques as well as
other approaches such as proteomics and the study of biofilms will allow
an extensive investigation of the microbiota in HIV-infected individuals
and the pathogenetic role of "unusual" species.

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3 As shown in Table 3, bacteria that are not usually linked with periodontal
4 disease, such as *Enterococcus faecalis*, *Acinetobacter baumannii*,
5 *Pseudomonas aeruginosa*, *Campylobacter pylori*, were frequently detected
6 in HIV-infected patients, in most of the studies (Gonçalves *et al*, 2004;
7 Gonçalves *et al*, 2007; Aas *et al*, 2007; Gonçalves *et al*, 2009). Putative
8 periodontopathogenic bacteria, such as *T. forsythia*, *P. gingivalis*, *P.*
9 *intermedia*, were associated with periodontitis (Alpagot *et al*, 2004;
10 Gonçalves *et al*, 2004) in HIV-positive patients and were considered as
11 risk factors (Gonçalves *et al*, 2004), whereas in many studies the
12 prevalence of these classical periodontopathogenic bacteria was found
13 smaller in HIV- positive than in HIV- negative subjects (Paster *et al*, 2002;
14 Patel *et al*, 2003; Gonçalves *et al*, 2007; Aas *et al*, 2007; Gonçalves *et al*,
15 2009). Possibly, pathogens such as *P. gingivalis*, that are commonly
16 associated with periodontal disease, do not consist the principle
17 pathogenic factor, while both atypical oral organisms and typical
18 periodontopathogenic bacteria influenced the pathogenesis of periodontitis
19 in HIV-infected patients.
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33 More over the recognition of different microbial profiles in the subgingival
34 area of these patients may be significant. More complex microbial profiles
35 were demonstrated in diseased sites than in healthy periodontium in HIV-
36 infected patients (Paster *et al*, 2002), while certain combinations of
37 microbes were detected exclusively in HIV-infected individuals. These
38 specific "complexes" may be responsible for chronic periodontitis in this
39 group of patients (Patel *et al*, 2003) since it is known that changes in the
40 humoral and cellular immunity can affect the establishment and growth of
41 pathogens and the resultant combination of microbes in the subgingival
42 pockets of HIV-positive subjects.
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52 HIV - HOST INTERACTION IN THE PERIODONTAL ENVIRONMENT

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56 Periodontal disease may result from a loss of regulation of immune
57 responses to oral microbiota (Jotwani *et al*, 2001).

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59 However, in HIV-infected patients, pathogenetic mechanisms involved in
60 immune responses and in tolerance at the oral mucosa in health and

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inflammation remain unclear and studies are required in order to define the interaction between the immuno-compromised host and microbes. In general, it is poorly understood how HIV or HIV-infected cells affect oral mucosal epithelium and influence innate and acquired immunity, and how the altered local or systemic immune response of these patients contributes to the pathogenesis of periodontal disease (Alpagot *et al*, 2004; Challacombe & Naglik, 2006). Subgingival biofilm microorganisms have the capacity to activate inflammatory cells including polymononuclears (PMN), lymphocytes and macrophages, which produce inflammatory mediators, and subsequently induce MMPs and their inhibitors production. It is known that, in periodontal disease, most of the tissue damage is caused by host response (Lamster & Novak, 1992; Van Dyke & Serhan, 2003). In HIV-infected patients with periodontitis an increase of inflammatory mediators has also been detected. Alpagot *et al* (2003) reported that the higher GCF levels of pro-inflammatory cytokine interferon- γ (IFN- γ) is associated with the periodontal disease progression in HIV-positive patients similarly to reports for non-HIV individuals with chronic periodontitis (Dutzan *et al*, 2009). High levels of significant mediators of inflammation involved in the pathogenesis of periodontal disease such as prostaglandin E₂ (PGE₂), (Leibur *et al*, 1999), transforming growth factor-beta (TGF- β 1), matrix metalloproteinase -1 (MMP-1) were also found in gingival crevicular fluid (GCF) of periodontitis sites in HIV/AIDS patients and could serve as prognostic factors for the progression of tissue destruction in HIV-infected adults.

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After the introduction of HAART, HIV-infection is considered as a chronic infection characterized by persistency of the virus in the infected host, and, despite the undetectable plasma levels of the HIV, cessation of therapy results in viral reappearance in circulation. (Chun *et al*, 1999). Persistency of the virus is possibly due to a very low level of replication and continuous secretion of virus by long-lived infected cells, undetectable by conventional assays, or HIV latency and silencing (reviewed in Mok & Lever, 2008; Williams & Greene, 2007; Dahl, 2009; Colin & Van Lint, 2009). The oral cavity seems to be an important reservoir of HIV-1 as the virus is found in saliva, GCF, and oral epithelial cells. To date, HIV-1

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2
3 reservoirs have been identified in the reproductive tract, breast, lung,
4 brain, and gastrointestinal tract (Schrager & D'Souza, 1998)

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6 Therefore, the role of oral immune factors and periodontal disease in the
7 persistency of HIV infection, the possibility of oral transmission and the
8 re-emerging of HIV infection, should be investigated.
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11 The oral cavity has rarely been reported as a site of HIV transmission.
12 (Klein *et al*, 1988; Cohen *et al*, 2000; Jotwani *et al*, 2004; Cutler &
13 Jotwani, 2006). In saliva, HIV is present at very low levels (Spear *et al*,
14 2005) possibly due to low levels of macrophages and lymphocytes and to
15 inhibitory factors in the saliva of HIV-infected patients. A number of host
16 defense factors are present in the saliva including, the hypotonic nature of
17 saliva (Baron *et al*, 1999), endogenous inhibitors of HIV, particularly
18 secretory leukocyte protease inhibitor (SLPI) that blocks HIV infection in
19 several cell-culture systems (Shugars *et al*, 1999), salivary mucins MUC5B
20 and MUC7 which trap and aggregate the virus and can inhibit it by 100%
21 (Habte *et al*, 2006), sIgA antibodies which neutralize HIV,
22 antimicrobial peptides such as α - and β -defensins (Nakashima *et al*, 1993;
23 Jotwani *et al*, 2004; Zhang *et al*, 2002; Mackewicz *et al*, 2003; Quinones-
24 Mateu *et al*, 2003), histatins (Groot *et al*, 2006) and lactoferrin. It seems
25 that the inhibitory factors may act synergistically (Bolscher *et al*, 2002).
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28 Recently, HIV-specific antibody dependent cell-mediated cytotoxicity
29 (ADCC) activity, an important part of cell mediated immunity, was
30 demonstrated in saliva. (Kim *et al*, 2006). More over, studying the
31 possible effect of microbial components on HIV, inhibition of virus entry by
32 a binding domain (HGP44) of *P. gingivalis* was demonstrated (Xie *et al*,
33 2006).
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36 HAART appears not to adversely affect inherent salivary oral host defense
37 in HIV- patients with mild to moderate immune dysfunction. (Lin *et al*,
38 2006)
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41 In many studies RNA (Spear *et al*, 2005; Shugars *et al*, 2001) and DNA of
42 HIV have been detected in saliva (Goto *et al*, 1991; Yeung *et al*, 1993 b;
43 Levy & Greenspan, 1988). Possible sources of infectious virions and
44 proviral HIV-1 DNA in saliva include serum and HIV-containing
45 macrophages and lymphocytes from GCF, which is increased during
46 periodontal infection. In most studies, HIV is present in patients' saliva at
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3 very low levels, lower than blood. However, Shugars *et al* (2001) reported
4 that 5 out of 67 HIV-positive subjects expressed higher levels in saliva
5 than blood and also had more advanced HIV-associated periodontal
6 disease, suggesting that HIV can be produced locally in the oral cavity and
7 may be influenced by oral tissue inflammation.
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10 Although, relatively little and contradictory information on HIV excretion
11 patterns in GCF is available in the literature, however the presence of
12 periodontitis may be a contributing factor. Proviral HIV-1 DNA, viral RNA
13 and p24 antigen has been detected in up to 50% of GCF samples from
14 HIV-infected subjects with periodontitis (Sanz *et al*, 1996; Chebbi *et*
15 *al*,1997; Maticic *et al*, 2000) while in some reports the virus or the p24
16 antigen have not been detected in GCF samples (O'Shea *et al*, 1990;
17 Chebbi *et al*, 1997). These results suggest that infected mononuclear cells
18 present in GCF could be a potential source of HIV-1.
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21 More over it has been demonstrated that HIV-1 infects and replicates in
22 vitro in keratinocytes isolated from normal oral mucosa (Moore *et al.*,
23 2003) as well as in vivo in oral mucosal epithelial cells (Rodríguez-Iñigo *et*
24 *al*, 2005), which could represent a reservoir for the virus, although this is
25 not a universal finding (Quinones-Mateu *et al*, 2003).
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28 Regarding gingival tissues, studies have shown that dendritic cells (DCs)
29 and macrophages in gingiva express C-type lectin receptors DC-SIGN
30 (Dendritic-cell-specific ICAM-3-grabbing non-integrins, CD209), MR
31 mannose receptors, CD206), and Langerin (CD 207), which are targets
32 for HIV and other microbes (van Kooyk *et al*, 2004). Using these receptors
33 HIV could advance by down-regulating intracellular signalling and effective
34 immune response and cause chronic infections that persist for life.
35 However, recent studies showed that, during health, in lamina propria
36 cells usually express the DC-SIGN receptors and mannose receptors, but
37 very few of the cells present the CCR5 on their surface and none present
38 the CXCR4 HIV co-receptors. (Jotwani *et al*, 2004). In the epithelium,
39 cells do not express CD4 but instead glycosphingolipid-galactosylceramide
40 (GalCer) and Langerin receptors (Jotvani *et al*, 2004; Challacombe &
41 Naglik, 2006). HIV co-receptors CCR5 and/or CXCR4 were found closer to
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3 the basal layer far from the surface-associated layers (Jotwani *et al*,
4 2004). So, in health, low expression of CCR5, and restricted expression of
5 CXCR4 in oral mucosa suggest an unfavourable environment for the virus
6 and this may play a significant role in the resistance of gingiva to infection
7 with HIV-1. (Jotwani *et al*, 2004; Jameson *et al*, 2002).

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10 In the presence of inflammation, there is evidence of up-regulation of
11 various receptors, including HIV receptors, on the surface of oral
12 epithelium, and the epithelium may become more permeable.
13 (Challacombe & Naglik, 2006). More over, in patients with chronic
14 periodontitis there is a significant increase in the number of dermal
15 dendritic cells (DDCs) expressing DC-SIGN receptors and a trend for
16 increased mannose receptors identified in the inflamed gingival lamina
17 propria (Jotvani *et al*, 2004). It is suggested that HIV uses both the
18 above C-type lectin receptors to attach to different dentritic cells subsets
19 (Turville *et al*, 2001). It has been shown that dentritic cells, DDCs and
20 LCs, form immune conjugates with CD4+ T cells in the lamina propria
21 (Jotvani & Cutler, 2003) and under these conditions it is possible for
22 dendritic cells to transfer HIV in the T-lymphocytes in the inflamed
23 gingival lamina propria.

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26 It has also been reported that in the presence of oral lesions and
27 periodontal disease there is a continuous shedding of HIV-infected blood
28 into the oral cavity from mucosal and gingival lesions in HIV- infected
29 patients, resulting in the detectable presence of the HIV at a high
30 frequency in the oral cavity, with an increased possibility for HIV
31 transmission. (Bolscher *et al*, 2002).

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34 According to the above mentioned findings, inflammation is considered as
35 a risk factor for HIV infection although defensive mechanisms However,
36 during chronic periodontitis there is a ten fold increase in α -defensin-1
37 (Jotwani *et al*, 2004), known to have potent anti-HIV activity, while HBD2
38 and HBD3 are also up-regulated during inflammation. (Dale *et al*, 2002;
39 Quiñones-Mateu *et al*, 2003).

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42 Notably, co-infection with the endogenous pathogen *P.gingivalis* in vitro,
43 revealed an upregulation of CCR5 receptors of oral keratinocytes, which
44 are not usually expressed in health, through LPS stimulating the Toll-like
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3 receptors and gingipains. The R5-type HIV-1 co-receptors CCR5, is the
4 target of R5-type HIV-1 associated with most primary systemic infections.
5 Thus infection with *P. gingivalis* could increase transmission of HIV
6 infection through the oral cavity. (Giacaman *et al*, 2007).
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10 In addition, periodontal diseases and other oral opportunistic infections in
11 HIV-infected patients could influence HIV reactivation. They represent
12 chronic infections and associated inflammation, with a possibility of
13 latently infected host cell stimulation. Transcription of the HIV-provirus is
14 dependent on the interaction between cellular and viral transcription
15 factors (reviewed in Mok & Lever, 2008; Williams & Greene, 2007).The
16 mechanisms involved in the reactivation of latency remain to be
17 elucidated, however a number of factors such as different cellular
18 environments and LTR (Long Terminal Repeat) variations in different HIV-
19 1 isolates have been proposed that may play a role (Rohr *et al*, 2003).
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27 In vitro exposure of latently infected resting CD4+ cells to a number of
28 cytokines, bacterial antigens, mitogens or monoclonal antibodies directed
29 to T-cell receptors CD3 can induce viral replication, but these findings
30 have not been reproduced in vivo. It is also suggested that in the progress
31 of an opportunistic infection microorganisms or their components, such as
32 LPS, stimulate and activate Toll-like receptors (TLRs), and subsequently
33 NFκB and other transcription factors. In addition, transcription factors can
34 be activated indirectly by the large amounts of pro-inflammatory
35 cytokines and chemokines which are produced during infection (reviewed
36 in González *et al*, 2009). Regarding periodontal pathogens, it has recently
37 been shown that *P. gingivalis* produces high concentrations of butyric
38 acids causing histone acetylation which is involved in repressing HIV
39 transcription and results in virus persistency (Imai *et al*, 2009) The
40 results of the study and the above mentioned possible mechanism of
41 reactivation of HIV, suggest that periodontal disease could act as a risk
42 factor for HIV reactivation in infected individuals and might contribute to
43 the systemic dissemination of the virus.
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56 This hypothesis could be the biological basis linking a chronic
57 infection such as periodontitis to the "immune reconstitution inflammatory
58 syndrome" (IRIS) (Gaitan-Cepeda *et al*, 2008) a situation in which, pre-
59 existing asymptomatic or mildly symptomatic infections or inflammatory
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3 conditions paradoxically worsen with a substantial increase in
4 inflammation during the initial months of host immune reconstitution, as a
5 result of HAART (Feller *et al*, 2007; Murdoch *et al*, 2007).
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8 Opportunistic oral infections have not yet been characterized as IRIS, but
9 Nicolatou-Galitis *et al* (2004) and Greenspan *et al* (2004) have reported a
10 lack of reduction of oral lesions despite a higher mean CD4+ count and a
11 lower mean viral load, with HAART treatment. Recently, Gaitan-Cepeda *et al*
12 (2008) found that HIV+/AIDS patients under HAART who present CD4+
13 lymphocyte counts of >500 cells /ml and undetectable viral loads can
14 suffer opportunistic oral HIV-associated infections. IRIS may lead to
15 increased frequency of periodontal disease as the presence of latent
16 infection(s) has been considered as a risk factor for the syndrome (Crum-
17 Cianflone 2006; Murdoch *et al*, 2007). However, it is not known if the
18 appearance of these lesions is the consequence of a qualitative failure of
19 immune cell response, or examples of de novo infections.
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30 CONCLUSIONS

31 The introduction of highly active antiretroviral therapy (HAART) has
32 significantly modified the course of HIV disease, at least in the
33 industrialized world, into a manageable chronic disease with longer
34 survival and improved quality of life in HIV-infected subjects. Oral lesions
35 are among the clinical manifestations whose prevalence, severity and
36 course have been affected by this treatment. Although oral candidiasis
37 appears to be the infection more significantly decreased after the
38 introduction of HAART, the current literature suggests that the prevalence
39 and course of periodontal lesions have also been modified. Additional
40 research is required regarding biological issues such as the role of oral
41 immune factors and periodontal disease in the persistency of HIV
42 infection, the possibility of oral transmission and the re-emerging of HIV
43 infection.
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Table 1 Prevalence of HIV-associated and conventional periodontal disease in the HAART era

Authors	Country	Subject sample	HIV associated periodontal disease			Conventional	
			LGE	NUG	NUP	GING	PERIO
ADULTS							
Schuman <i>et al</i> (1998)	USA	867 HIV+ 35% on ART	13.6%	11.6%			
Patton <i>et al</i> (2000)	USA	606 HIV+ 30% on HAART/PI	3.3%	NUG/NUP=3.1%			
Ceballos <i>et al</i> (2000)	Spain	154 HIV+ 100% on HAART	0.6%	0.6%			
Eyson <i>et al</i> (2002)	UK	203 HIV+ 69% on HAART	6%	8%	3%		
Reichart <i>et al</i> (2003)	Thailand Cambodia	87HIV+ 63HIV+ non on HAART	Thai 8% Cambodian 12%	Thai 0% Cambodian 27.7%			
Pinheiro <i>et al</i> (2004)	Brazil	161 HIV+ 70.8% on ART	Periodontal disease= 4.4%				
Kroidl <i>et al</i> (2005)	Germany	139 HIV/AIDS 100% on HAART	9%	NUG/NUP=3.6%		28%	30%
Bravo <i>et al</i> (2006)	Venezouela	75 HIV+ 63% on ART 52% on HAART	8%				
Ranganathan <i>et al</i> , (2004)	India	774 HIV+ 11% on ART				72%	33%
Gaitan <i>et al</i> (2008)	Spain	86 HIV/AIDS 100% on HAART	0%	0%	0%	0%	0%
Brady <i>et al</i> (1996)	USA	25 HIV/AIDS				84%	52%
Ceballos <i>et al</i> (1996)	Spain	396 HIV+				Periodontal disease 78.3%	
Alpagot <i>et al</i> (2004)	USA	152 HIV+ patients 63% on HAART				19%	73%
CHILDREN							
Santos <i>et al</i> (2001)	Brazil	80 HIV+				17.5%	
Khongkuntian <i>et al</i> , (2001)	Thailand	45 HIV+ 33.3% on ART		2.2%			
Gaitan <i>et al</i> (2002)	Mexico	48 HIV+	Periodontal/gingival disease 4.2%				
Reichart <i>et al</i> (2003)	Thailand	45 HIV+ 33% on ART		2.2%			

ART=Any type of antiretroviral therapy, HAART=Highly active antiretroviral therapy, HAART/ PI= Highly active antiretroviral therapy with protease inhibitor as the third drug, GING=Gingivitis, PERIO=Periodontitis, LGE= linear gingival erythema, NUG=necrotizing ulcerative gingivitis, NUP= necrotizing ulcerative periodontitis

Table 2 Effect of HAART on prevalence of HIV-associated periodontal disease in HIV-infected adults

Authors	Country	Subject sample	HIV-associated periodontal disease			Effect of therapy
			LGE	NUG	NUP	
Aguirre <i>et al</i> (1999)	Spain	72 HIV+ patients CD4+ <499 on HAART	48.6%		31.9%	LGE are down, NUP has remained steady in comparison to two earlier studies from the Spain
Schmidt <i>et al</i> , (2000)	Germany	103 HIV+ patients one month on HAART	1.9%.		2.9%	After 6 months of therapy, from 61 re-examined patients only one had NUP.
Patton <i>et al</i> (2000)	USA	<i>Pre-HAART</i> , 271 HIV+ 8% on HAART <i>Post HAART</i> , 299 HIV+ 42% on HAART).			4.8% 1.7%	Significant decrease of NUP ($p=0.03$)
Ceballos <i>et al</i> (2000)	Spain	154 HIV/AIDS on HAART /PI for at least 6 months	0.6%	0.6%		More than 30% decrease of HIV associated periodontal disease in comparison with historical controls
Tappuni and Fleming (2001)	UK	195 HIV+ not on ART 89 HIV+ on ART		6% 2%		Decrease of NUG
Ramirez <i>et al</i> (2003)	Brazil	Study of 12 years <i>before HAART</i> (1989-1995) <i>after HAART</i> (1996-2001)	Periodontal disease 4.1% (1989-1991) 1.7% (1992-1995) 0.4% (1996-1998) 0.7% (1999-2001)			Significant decrease of periodontal disease between before and after HAART periods ($p=0.002$)
Ferreira <i>et al</i> (2007)	Brazil	1230 HIV+ (1988-2004) on HAART	2.5%	1.6%	1.3%	HAART associated with a significant lower prevalence of LGE ($p<0.001$)
Nicolatou <i>et al</i> (2004)	Greece	HIV+ not on ART HIV+ on double ART and HAART/PI		8.1% 0%		Decrease of NUG

HAART=Highly active antiretroviral therapy ,HAART/ PI= Highly active antiretroviral therapy with protease inhibitor as the third drug, ART= Any type of antiretroviral therapy, HIV-associated periodontal disease: LGE=linear gingival erythema, NUG=necrotizing ulcerative gingivitis, NUP= necrotizing ulcerative periodontitis

Table 3. Studies of subgingival plaque microbiota in HIV infected patients in HAART era using culture-independent methods

<i>Authors</i>	<i>Subject sample</i>	<i>methodology</i>	<i>Principal findings</i>
Paster <i>et al</i> 2002	8 HIV+/NUP HAART: data not available	Checkerboard DNA hybridization assay Over 200 probes	108 species identified (65 uncultivable) Most frequent: <i>Bulleidia extracta</i> , <i>Dialister</i> , <i>Fusobacterium</i> , <i>Selenomonas</i> , <i>Phylum TM7</i> <i>Peptostreptococcus</i> , <i>Veillonella</i> , Classical periodontal pathogens not detected Different and more complex microbial profiles in periodontitis than in healthy periodontium
Patel <i>et al</i> 2003	20 HIV+/CP HAART: data not available	PCR for <i>P. nigrescens</i> , <i>C.rectus</i> , <i>P.intermedia</i> , <i>P.gingivalis</i> , <i>T.denticola</i> , <i>E.corrodens</i> , <i>A.actinomycetemcomitans</i>	<i>T.denticola</i> and <i>P.gingivalis</i> less prevalent in HIV+ subjects Three microbial profiles exclusively in HIV+ <i>P. nigrescens</i> / <i>C.rectus</i> <i>P. nigrescens</i> / <i>P. gigivalis</i> <i>P. nigrescens</i> / <i>T.denticola</i>
Alpagot <i>et al</i> 2004	152 HIV+/CP 63% HAART	Fluorescent assay for selective Gram-negative species	<i>F.nucleatum</i> , <i>P. intermedia</i> , <i>A. actinomycetemcomitans</i> , <i>P. gingivalis</i> : risk factors for periodontitis in HIV+
Goncalves <i>et al</i> 2004	64 HIV+/CP 100% HAART	Checkerboard DNA hybridization assay Probes for 22 species	Several classical pathogens more prevalent in HIV+/CP than in HIV+/healthy periodontium: <i>E. faecalis</i> , <i>F. nucleatum</i> more prevalent in patients with lower T CD4+cells
Goncalves <i>et al</i> 2007	37 HIV+/CP 35 HIV+/HP 100% HAART	Checkerboard DNA hybridization assay Probes for 33 species	Bacterial species and classical periodontal pathogens less frequent in HIV+/CP, than in HIV- /CP (<i>T. forsythia</i> , <i>S. gordonii</i> , <i>P.gingivalis</i> , <i>S. intermedius</i> ,) Unusual for CP species more commonly in HIV+ (<i>A.baumannii</i> , <i>E. faecalis</i>)
Aas <i>et al</i> 2007	14 HIV+/CP, gingivitis, LGE HAART: data not available	16S and 18S rRNA- cloning and sequencing	109 species (42% uncultivable) were identified <i>Gemella</i> , <i>Dialister</i> , <i>Streptococcus</i> , <i>Veillonella</i> were predominant Classical periodontal pathogens not detected (<i>T.denticola</i> , <i>P.gingivalis</i> , <i>T. forsythia</i>) Unusual for CP microbes (<i>Pseudomonas</i> , <i>Neisseria</i>) more commonly in HIV+ and severe immunosuppression
Goncalves <i>et al</i> 2009	13 HIV+/CP 10 HIV+/HP 100% HAART	PCR for <i>H. pylori</i> , <i>E.faecalis</i> , <i>P.aeruginosa</i>	Unusual for CP microbes more frequent in CP than in healthy periodontium (<i>E.faecalis</i> , <i>E.pylori</i> , <i>P.aeruginosa</i>) <i>E.pylori</i> most prevalent in CP in HIV+
CP= chronic periodontitis NUP= necrotizing ulcerative periodontitis		HP=healthy periodontium HAART=Highly active antiretroviral therapy	LGE= linear gingival erythema

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