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REVIEW ARTICLE

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

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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, necrotizing ulcerative gingivitis and necrotizing ulcerative periodontitis 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.

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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 non-nucleoside 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 viraemia.

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-effects vary depending on the drug regimen, but can include hypersensitivity, lactic acidosis,

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increases in blood lipids, bleeding events, anaemia, neuropathy, lipodystrophy and pancreatitis (UNAIDS, 2008). While most side-effects diminish over time, some can be life-threatening, underscoring the importance of careful patient monitoring (UNAIDS, 2008).

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

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

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

Features of periodontal lesions in HIV-infected patients

HIV infection in adults is linked with the expression of various types of periodontal lesions, which include specific forms of gingivitis and necrotizing periodontal diseases, as well as with possible exacerbation of preexisting periodontal disease (Winkler and Robertson, 1992; EC-Clearinghouse, 1993; Robinson, 2002). Periodontal diseases strongly associated with HIV infection are classified as linear gingivitis erythema (LGE), necrotizing ulcerative gingivitis (NUG) and necrotizing ulcerative periodontitis (NUP) and are included among the seven cardinal oral lesions, which have been identified and recognized internationally, as follows: oral candidiasis, oral hairy leukoplakia Kaposi sarcoma, LGE, NUG, NUP and non-Hodgkin lymphoma (EC-Clearinghouse, 1993; Armitage, 1999; Coogan *et al*, 2005).

The criteria for diagnosis of HIV-related oral lesions are not well defined in children. Orofacial manifestations have been categorized into three groups: those less commonly, commonly and strongly but rarely associated with pediatric HIV infection. LGE has been reported between those commonly associated (Ramos-Gomez *et al*, 1999; Coogan *et al*, 2005).

Together with other oral infections, HIV-associated periodontal diseases are regarded as serious complications of HIV infection and have an important diagnostic and prognostic value (EC-Clearinghouse, 1993; Glick *et al*, 1994a; Shangase *et al*, 2004; Coogan *et al*, 2005). They belong among the earliest clinical features of the infection and could predict progression of HIV disease to AIDS (Robinson, 2002; Coogan *et al*, 2005). It should also be mentioned that for patients on antiretroviral therapy, HIV-related oral lesions in general, may suggest possible treatment failure as will be further discussed in the present review (Margiotta *et al*, 1999; Eyeson *et al*, 2002; Gaitán-Cepeda *et al*, 2005; Flint *et al*, 2006; Ramírez-Amador *et al*, 2007). However, HIV-associated periodontal infections are less common than oral candidiasis and oral hairy leukoplakia and thus not included as criteria in the Centers for Disease Control (CDC) classification (CDC, 1992). HIV-associated periodontal infections have characteristic clinical appearance which has been well described (Winkler and Robertson, 1992; Murray, 1994; Reznik, 2006; Greenspan and Greenspan, 2008).

Linear gingival erythema (LGE) is a form of gingivitis characterized by a distinct fiery red band along the margin of the gingiva (EC-Clearinghouse, 1994). It is usually associated with anterior teeth, commonly extended to the posterior teeth, accompanied in some cases by bleeding and discomfort (Reznik, 2006). In other cases it presents as petechia-like patches on attached or free gingiva. Currently, *Candida* species have been implicated to the aetiopathology of LGE as well as other HIV-associated periodontal pathology.

Necrotizing ulcerative gingivitis (NUG) is characterized by rapid onset and acute painful inflammation of gingiva with rapid destruction of soft tissues, while necrotizing ulcerative periodontitis (NUP) is escorted by bleeding, sharp pain, ulcerated gingival papillae, rapid and extensive soft tissue necrosis and advanced loss of periodontal attachment, frequently leading to bone exposure (Murray, 1994; Reznik, 2006; Greenspan and Greenspan, 2008).

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

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

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

Regarding periodontal disease, there is little and unclear data, especially during the HAART era. In 1994, Glick *et al* have reported an association between NUP and CD4 + count below 200 cells mm^{-3} in HIV-infected patients and suggested that NUP may be a good marker of immune deterioration. The same authors reported in another 1994 study a positive predictive value (95.1%) for periodontal diseases, which was higher than the values reported for oral hairy leukopla-

kia (70.1%) and oral candidiasis (69.9%) (Glick *et al*, 1994a). High positive predictive values have also been reported for necrotizing ulcerative periodontitis (80%) and a moderate (54.5%) one for LGE (Begg *et al*, 1996; Patton, 2000). In agreement with the previous studies, Margiotta *et al* (1999) reported that NUP and NUG were significantly associated with CD4 + counts lower than 200 cells mm^{-3} in a cohort of Italian subjects infected with HIV. In contrast to these reports, Schuman *et al*, in a study conducted in a US population, after the introduction of HAART, reported that LGE and NUG were not related to HIV serostatus or CD4 + lymphocyte count (Schuman *et al*, 1998).

Contradictory results have also been reported in a 2000 study by Patton. The author reported that the viral load was significantly related to the presence of strongly HIV-associated oral lesions (Patton, 2000) but that among periodontal lesions, only LGE has a significant predictive value (70%) for immune suppression when measured by CD4 cell counts below 200 cells mm^{-3}. In the same study, the predictive value for necrotizing ulcerative diseases was lower (47.4%) compared to the values reported previously, a finding which could be attributed to the improved antiretroviral management of HIV disease of the population under investigation. A significant correlation between necrotizing ulcerative diseases and CD4 + T cells number below 200 mm^{-3} was also reported in a study from South Africa, with a positive predictive value of 69.6% for HIV infection in otherwise asymptomatic subjects (Shangase *et al*, 2004).

As HIV infection gradually becomes a chronic disease, the features and course of chronic periodontal disease in HIV infected patients require more extensive investigation. The 'conventional' periodontal diseases in the HAART era have been mentioned in very few studies (Alpagot *et al*, 2004; Kroidl *et al*, 2005). Conventional periodontitis progresses gradually, causing no or minimal pain or discomfort, being thus undiagnosed, until considerable tissue loss occurs (Alpagot *et al*, 2004). Generally, periodontal inflammation seems to be more severe in cases where CD4 + counts are low (Kroidl *et al*, 2005) and research nowadays is focused on the accelerated rate with which chronic adult periodontitis presents in seropositive patients (Lamster *et al*, 1997).

Overall, findings from the above mentioned studies suggest the value of the identification of periodontal disease, even in patients on HAART therapy, in screening the immune suppression, both in diagnosed and undiagnosed HIV infection in adults.

The relation between oral lesions in general and immune and virologic status is still not well established in children. No association was found between the prevalence of oral lesions and immunological status or viral load in children, while there are no data for periodontal diseases (Gaitán-Cepeda *et al*, 2002).

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 adjuctive 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 (Palella *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 (Patton *et al*, 2000; Schmidt-Westhausen *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 and 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.

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

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. Data from representative studies in developed and developing countries concerning adult and paediatric populations are shown in Table 1. The effect of HAART on prevalence of HIV-associated periodontal disease is shown in Table 2. It appears that HAART is associated with a lower prevalence of HIV-associated periodontal disease in adults. The difference between pre- and post-HAART in most of the studies was found to be statistically significant.

On the contrary, HAART does not appear to significantly affect the prevalence of periodontal disease

Table 1 Prevalence of HIV-associated and conventional periodontal disease in the HAART era

			HIV-associated periodontal disease			*Conventional*	
Authors	*Country*	*Subject sample*	*LGE*	*NUG*	*NUP*	*GING*	*PERIO*
Adults							
Schuman *et al* (1998)	USA	867 HIV+35% on ART	13.6%	11.6%			
Patton *et al* (2000)	USA	606 HIV+30% on HAART/PI	3.3%	NUG/NUP = 3.1%			
Ceballos-Salobreña *et al* (2000)	Spain	154 HIV+100% on HAART	0.6%	0.6%			
Eyeson *et al* (2002)	UK	203 HIV+69% on HAART	6%	8%	3%		
Reichart *et al* (2003)	Thailand, Cambodia	87HIV+63HIV+none on HAART	Thai – 8% Cambodian – 12%	Thai 0% Cambodian – 27.7%			
Pinheiro *et al* (2004)	Brazil	161 HIV+70.8% on ART	Periodontal disease = 4.4%				
Kroidl *et al* (2005)	Germany	139 HIV/AIDS 100% on HAART	9%	NUG/NUP = 3.6%		28%	30%
Bravo *et al* (2006)	Venezouela	75 HIV+63% on ART 52% on HAART	8%				
Ranganathan *et al* (2004)	India	774 HIV+11% on ART				72%	33%
Gaitan Cepeda *et al* (2008)	Spain	86 HIV/AIDS 100% on HAART	0%	0%	0%	0%	0%
Brady *et al* (1996)	USA	25 HIV/AIDS				84%	52%
Ceballos-Salobreña *et al* (1996)	Spain	396 HIV+				Periodontal disease 78.3%	
Alpagot *et al* (2004)	USA	152 HIV+ patients 63% on HAART				19%	73%
Children							
Santos *et al* (2001)	Brazil	80 HIV+				17.5%	
Khongkunthian *et al* (2001)	Thailand	45 HIV+ 33.3% on ART		2.2%			
Gaitán-Cepeda *et al* (2002)	Mexico	48 HIV+	Periodontal/gingival disease 4.2%				
Reichart *et al* (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 *et al* (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-Westhausen *et al* (2000)	Germany	103 HIV+ patients 1 month on HAART	1.9%.		2.9%	After 6 months of therapy, from 61 re-examined patients only one had NUP
Patton *et al* (2000)	USA	Pre-HAART, 271 HIV+ 8% on HAART Post-HAART, 299 HIV+ 42% on HAART.			4.8% 1.7%	Significant decrease of NUP ($P = 0.03$)
Ceballos-Salobreña *et al* (2000)	Spain	154 HIV/AIDS on HAART/PI for atleast 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
Ramírez-Amador *et al* (2003)	Brazil	Study of 12 years before HAART (1989–1995) after HAART (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 *et al* (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-Galitis *et al* (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-accociated periodontal disease: LGE: linear gingival erythema; NUG: necrotizing ulcerative gingivitis; NUP: necrotizing ulcerative periodontitis.

in children (Flanagan *et al*, 2000; Khongkunthian *et al*, 2001; Parveen *et al*, 2007).

Bacteria associated with periodontal disease in HIV-infected patients

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

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

Several authors agree that certain microbial species such as *Candida* spp. (Jabra-Rizk *et al*, 2001), *Enterobacter faecalis* (Zambon *et al*, 1990; Nakou *et al*, 1997; Gonçalves de Souza *et al*, 2004, 2007), *Clostridium clostridiiforme* (Zambon *et al*, 1990) *Clostridium difficile* (Zambon *et al*, 1990; Nakou *et al*, 1997; Gonçalves Lde *et al*, 2007), *Klebsiella pneumoniae* (Zambon *et al*, 1990; Nakou *et al*, 1997; Botero *et al*, 2007; Gonçalves de Souza *et al*, 2007), *Mycoplasma salivarium* (Zambon *et al*, 1990; Moore *et al*, 1993; Nakou *et al*, 1997; Gonçalves de Souza *et al*, 2007), *Pseudomonas aeruginosa* (Nakou *et al*, 1997; Botero *et al*, 2007; Gonçalves de Souza *et al*, 2007), *Acinetobacter baumanii* (Nakou *et al*, 1997; Gonçalves de Souza *et al*, 2007), *Enterobacter cloacae* (Nakou *et al*, 1997; Botero *et al*, 2007), which are frequently found in the periodontal environment of HIV-positive patients, are uncommon in other individuals. The role of these 'uncommon' species in the pathogenesis of periodontal disease in HIV-infected individuals is not yet fully understood, while it is suggested that the higher prevalence of such opportunistic micro-organisms is due to the immune status of those patients as colonization and overgrowth of atypical pathogenic species is facilitated by severe immunosuppression (Gonçalves de Souza *et al*, 2004).

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.

As shown in Table 3, bacteria that are not usually linked with periodontal disease, such as *Enterococcus faecalis, Acinetobacter baumanii, Pseudomonas aeruginosa* and *Campylobacter pylori*, were frequently detected in HIV-infected patients, in most of the studies (Gonçalves de Souza *et al*, 2004, 2007; Gonçalves de Souza *et al*, 2009; Aas *et al*, 2007). Putative periodontopathogenic bacteria, such as *T. forsythia, P. gingivalis, P. intermedia*, were associated with periodontitis (Alpagot *et al*, 2004; Gonçalves de Souza *et al*, 2004) in HIV-positive patients and were considered as risk factors (Gonçalves de Souza *et al*, 2004), whereas in many studies the prevalence of these classical periodontopathogenic bacteria was found smaller in HIV-positive than in HIV- negative subjects (Paster *et al*, 2002; Patel *et al*, 2003; Aas *et al*, 2007; Gonçalves de Souza *et al*, 2007; Gonçalves de Souza *et al*, 2009). Possibly, pathogens such as *P. gingivalis*, that are commonly associated with periodontal disease, do not consist the principle pathogenic factor, while both atypical oral organisms and typical periodontopathogenic bacteria influenced the pathogenesis of periodontitis in HIV-infected patients.

Moreover the recognition of different microbial profiles in the subgingival area of these patients may be significant. More complex microbial profiles were demonstrated in diseased sites than in healthy periodontium in HIV-infected patients (Paster *et al*, 2002), while certain combinations of microbes were detected exclusively in HIV-infected individuals. These specific 'complexes' may be responsible for chronic periodontitis in this group of patients (Patel *et al*, 2003) since it is known that changes in the humoral and cellular immunity can affect the establishment and growth of pathogens and the resultant combination of microbes in the subgingival pockets of HIV-positive subjects.

HIV–host interaction in the periodontal environment

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

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

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

Authors	*Subject sample*	*Methodology*	*Principal findings*
Paster *et al* (2002)	8 HIV+/NUP HAART: data not available	Checkerboard DNA hybridization assay Over 200 probes	108 species identified (65 uncultivable) Most frequent: *Bulleidia extructa, Dialister, Fusobacterium, Selenomonas, Phylum TM7 Peptostreptococcus, Veillonella,* Classical periodontal pathogens not detected Different and more complex microbial profiles in periodontitis than in healthy periodontium
Patel *et al* (2003)	20 HIV+/CP HAART: data not available	PCR for *P nigrescens, C.rectus, P.intermedia,P gingivalis, T.denticola, E.corrodens, A.actinomycetemcomitans*	*T. denticola and P .gingivalis* less prevalent in HIV+ subjects Three microbial profiles exclusively in HIV+ *P. nigrescens/C.rectus* *P. nigrescens/P. gigivalis* *P. nigrescens/T.denticola*
Alpagot *et al* (2004)	152 HIV+/CP 63% HAART	Fluorescent assay for selective Gram-negative species	*F.nucleatum, P. intermedia, A. actinomycetemcomitans, P. gingivalis:* risk factors for periodontitis in HIV+
Gonçalves de Souza *et al* (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: *E. faecalis, F. nucleatum* more prevalent in patients with lower T CD4 + cells
Gonçalves de Souza *et al* (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 (*T. forsythia, S. gordonii. P.gingivalis, S. intermedius*,) Unusual for CP species more commonly in HIV+ (*A.baumannii, E. faecalis*)
Aas *et al* (2007)	14 HIV+/CP, gingivitis, LGE HAART: data not available	16S and 18S rRNA- cloning and sequencing	109 species (42% uncultivable) were identified *Gemella, Dialister, Streptococcus, Veilonella* were predominant Classical periodontal pathogens not detected (*T.denticola, P.gingivalis, T. forsythia*) Unsual for CP microbes (*Pseudomonas, Neisseria*) more commonly in HIV+ and severe immunosupression
Gonçalves de Souza *et al* (2009)	13 HIV+/CP 10 HIV+/HP 100% HAART	PCR for *H. pylori, E. faecalis, P. aeruginosa*	Unusual for CP microbes more frequent in CP than in healthy periodontium (*E. faecalis, E. pylori, P. aeruginosa*) *E. pylori* 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.

most of the tissue damage is caused by host response (Lamster and Novak, 1992; Van Dyke and 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 periodonditis (Dutzan *et al*, 2009). High levels of significant mediators of inflammation involved in the pathogenesis of periodontal disease such as prostaglandin E_2 (PGE_2) (Leibur *et al*, 1999), transforming growth factor-beta (TGF-b1), matrix metalloproteinase -1 (MMP-1) were also found in gingival cervicular 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.

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 Williams and Greene, 2007; Mok and Lever, 2008; Colin and Van Lint, 2009; Dahl *et al*, 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 reservoirs have been identified in the reproductive tract, breast, lung, brain and gastrointestinal tract (Schrager and D'Souza, 1998)

Therefore, 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, should be investigated.

The oral cavity has rarely been reported as a site of HIV transmission (Klein *et al*, 1988; Cohen *et al*, 2000; Jotwani *et al*, 2004; Cutler and Jotwani, 2006). In saliva, HIV is present at very low levels (Spear *et al*, 2005) possibly due to low levels of macrophages and lymphocytes and to inhibitory factors in the saliva of HIV-infected patients. A number of host defence factors are present in the saliva including, the hypotonic nature of saliva (Baron *et al*, 1999), endogenous inhibitors of HIV, particularly secretory leucocyte protease inhibitor (SLPI) that blocks HIV infection in several cell-culture systems (Shugars *et al*, 1999), salivary mucins MUC5B and MUC7 which trap and aggregate the virus and can inhibit it by 100% (Habte *et al*, 2006), sIgA antibodies which neutralize HIV, antimicrobial peptides such as a- and b-defensins (Nakashima *et al*, 1993; Zhang *et al*, 2002; Mackewicz *et al*, 2003; Quiñones-Mateu *et al*, 2003; Jotwani *et al*, 2004), histatins (Groot *et al*, 2006) and lactoferrin. It seems that the inhibitory factors may act synergistically (Bolscher *et al*, 2002).

Recently, HIV-specific antibody dependent cell-mediated cytotoxicity (ADCC) activity, an important part of cell mediated immunity, was demonstrated in saliva. (Kim *et al*, 2006). Moreover, studying the possible effect of microbial components on HIV, inhibition of virus entry by a binding domain (HGP44) of *P. gingivalis* was demonstrated (Xie *et al*, 2006).

HAART appears not to adversely affect inherent salivary oral host defence in HIV-patients with mild to moderate immune dysfunction (Lin *et al*, 2006).

In many studies RNA (Shugars *et al*, 2001; Spear *et al*, 2005) and DNA of HIV have been detected in saliva (Levy and Greenspan, 1988; Goto *et al*, 1991; Yeung *et al*, 1993b). Possible sources of infectious virions and proviral HIV-1 DNA in saliva include serum and HIV-containing macrophages and lymphocytes from GCF, which is increased during periodontal infection. In most studies, HIV is present in patients' saliva at very low levels, lower than blood. However, Shugars *et al* (2001) reported that five out of 67 HIV-positive subjects expressed higher levels in saliva than blood and also had more advanced HIV-associated periodontal disease, suggesting that HIV can be produced locally in the oral cavity and may be influenced by oral tissue inflammation.

Although, relatively little and contradictory information on HIV excretion patterns in GCF is available in the literature, however the presence of periodontitis may be a contributing factor. Proviral HIV-1 DNA, viral RNA and p24 antigen has been detected in up to 50% of GCF samples from HIV-infected subjects with periodontitis (Sanz *et al*, 1996; Chebbi *et al*,1997; Maticic *et al*, 2000) while in some reports the virus or the p24 antigen have not been detected in GCF samples (O'Shea *et al*, 1990; Chebbi *et al*, 1997). These results suggest that infected mononuclear cells present in GCF could be a potential source of HIV-1.

More over it has been demonstrated that HIV-1 infects and replicates *in vitro* in keratinocytes isolated from normal oral mucosa (Moore *et al*, 2003) as well as *in vivo* in oral mucosal epithelial cells (Rodríguez-Iñigo *et al*, 2005), which could represent a reservoir for the virus, although this is not a universal finding (Quiñones-Mateu *et al*, 2003).

Regarding gingival tissues, studies have shown that dendritic cells (DCs) and macrophages in gingiva express C-type lectin receptors DC-SIGN (Dendritic-cell-specific ICAM-3-grabbing non-integrins, CD209), MR (mannose receptors, CD206) and Langerin (CD 207), which are targets for HIV and other microbes (Van Kooyk *et al*, 2004). Using these receptors HIV could advance by down-regulating intracellular signalling and effective immune response and cause chronic infections that persist for life. However, recent studies showed that, during health, in lamina propria cells usually express the DC-SIGN receptors and mannose receptors, but very few of the cells present the CCR5 on their surface and none present the CXCR4 HIV co-receptors (Jotwani *et al*, 2004). In the epithelium, cells do not express CD4 but instead glycospingolipid-galactosylceramide (GalCer) and Langerin receptors (Jotwani *et al*, 2004; Challacombe and Naglik, 2006). HIV co-receptors CCR5 and/or CXCR4 were found closer to the basal layer far from the surface-associated layers

(Jotwani *et al*, 2004). So, in health, low expression of CCR5, and restricted expression of CXCR4 in oral mucosa suggest an unfavourable environment for the virus and this may play a significant role in the resistance of gingiva to infection with HIV-1 (Jameson *et al*, 2002; Jotwani *et al*, 2004).

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 (Challacombe and Naglik, 2006). Moreover, in patients with chronic periodontitis there is a significant increase in the number of dermal dendritic cells (DDCs) expressing DC-SIGN receptors and a trend for increased mannose receptors identified in the inflamed gingival lamina propria (Jotwani *et al*, 2004). It is suggested that HIV uses both the above C-type lectin receptors to attach to different dentritic cells subsets (Turville *et al*, 2001). It has been shown that dentritic cells, DDCs and LCs, form immune conjugates with CD4 + T cells in the lamina propria (Jotwani and Cutler, 2003) and under these conditions it is possible for dendritic cells to transfer HIV in the T-lymphocytes in the inflammed gingival lamina propria.

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

According to the above mentioned findings, inflammation is considered as a risk factor for HIV infection, although defensive mechanisms. However, during chronic periodontitis there is a 10-fold increase in α-defensin-1 (Jotwani *et al*, 2004), known to have potent anti-HIV activity, while HBD2 and HBD3 are also upregulated during inflammation (Dale, 2002; Quiñones-Mateu *et al*, 2003).

Notably, co-infection with the endogenous pathogen *P.gingivalis in vitro*, revealed an upregulation of CCR5 receptors of oral keratinocytes, which are not usually expressed in health, through LPS stimulating the toll-like receptors (TLRs) and gingipains. The R5-type HIV-1 co-receptors CCR5, is the target of R5-type HIV-1 associated with most primary systemic infections. Thus infection with *P. gingivalis* could increase transmission of HIV infection through the oral cavity (Giacaman *et al*, 2007).

In addition, periodontal diseases and other oral opportunistic infections in HIV-infected patients could influence HIV reactivation. They represent chronic infections and associated inflammation, with a possibility of latently infected host cell stimulation. Transcription of the HIV-provirus is dependent on the interaction between cellular and viral transcription factors (reviewed in Williams and Greene, 2007; Mok and Lever, 2008). The mechanisms involved in the reactivation of latency remain to be elucidated, however a number of factors such as different cellular environments and long terminal repeat (LTR) variations in different HIV-1 isolates have been proposed that may play a role (Rohr *et al*, 2003).

In vitro exposure of latently infected resting CD4 + cells to a number of cytokines, bacterial antigens, mitogens or monoclonal antibodies directed to T-cell receptors CD3 can induce viral replication, but these findings have not been reproduced *in vivo*. It is also suggested that in the progress of an opportunistic infection micro-organisms or their components, such as LPS, stimulate and activate TLRs and subsequently NFκB and other transcription factors. In addition, transcription factors can be activated indirectly by the large amounts of pro-inflammatory cytokines and chemokines which are produced during infection (reviewed in González *et al*, 2009). Regarding periodontal pathogens, it has recently been shown that *P. gingivalis* produces high concentrations of butyric acids causing histone acetylation which is involved in repressing HIV transcription and results in virus persistency (Imai *et al*, 2009). The results of the study and the above mentioned possible mechanism of reactivation of HIV, suggest that periodontal disease could act as a risk factor for HIV reactivation in infected individuals and might contribute to the systemic dissemination of the virus.

This hypothesis could be the biological basis linking a chronic infection such as periodontitis to the 'immune reconstitution inflammatory syndrome' (IRIS) (Gaitan Cepeda *et al*, 2008) a situation in which, pre-existing asymptomatic or mildly symptomatic infections or inflammatory conditions paradoxically worsen with a substantial increase in inflammation during the initial months of host immune reconstitution, as a result of HAART (Feller *et al*, 2007; Murdoch *et al*, 2007).

Opportunistic oral infections have not yet been characterized as IRIS, but Nicolatou-Galitis *et al* (2004) and Greenspan *et al* (2004) have reported a lack of reduction of oral lesions despite a higher mean CD4 + count and a lower mean viral load, with HAART treatment. Recently, Gaitan Cepeda *et al* (2008) found that HIV + /AIDS patients under HAART who present CD4 + lymphocyte counts of > 500 cells ml^{-1} and undetectable viral loads can suffer opportunistic oral HIV-associated infections. IRIS may lead to increased frequency of periodontal disease as the presence of latent infection(s) has been considered as a risk factor for the syndrome (Crum-Cianflone, 2006; Murdoch *et al*, 2007). However, it is not known if the appearance of these lesions is the consequence of a qualitative failure of immune cell response or examples of *de novo* infections.

Conclusions

The introduction of HAART 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. Oral lesions are among the clinical manifestations whose prevalence, severity and course have been affected by this treatment. 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. 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.

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