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REVIEW ARTICLE

Oral infectious diseases: a potential risk factor for HIV virus recrudescence?

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As the highly active antiretroviral therapy (HAART) has transitioned human immunodeficiency virus (HIV) infection into a 'chronic disease' management strategy, there is growing evidence that infection with non-HIV pathogens in HIV+ patients may have important public health implications in undermining HAART success and acquired immunodeficiency syndrome progression. Several bacterial and host cell products during infections with non-HIV pathogens have shown the capacity to regulate HIV replication in latently infected cells. A high prevalence of oral infections caused by bacteria, viruses and fungi has been described in HIV+ patients, including periodontal disease. The oral cavity appears to be a site of HIV pathogenesis and potential reservoir for the disease as HIV RNA and DNA forms are present in saliva as well as in gingival crevicular fluid, and oral epithelial cells are susceptible to either cell free or cell-associated HIV infection. The clinical and biological bases of potential associations between chronic oral inflammatory disorders, such as periodontal disease, and exacerbation of HIV viraemia have received little attention. This review attempts to evaluate the current understanding of HIV reactivation as a result of co-infection and/or inflammation induced by non-HIV pathogens in HIV-infected patients, and presents a hypothetic model about the potential role of periodontitis as a global oral infection that potentially contributes to HIV recrudescence.

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Introduction

According to the last report of the Joint United Nations Program on HIV/AIDS (UNAIDS), about 33 million people globally are living with acquired immunodeficiency syndrome (AIDS) (UNIAIDS. 2007 report on the global AIDS epidemic. http://www.unaids.org/en). Acquired immunodeficiency syndrome is a disease caused by infection with the human immunodeficiency virus (HIV) and it is typically characterized by severe immune alterations, particularly targeting lymphocyte subpopulations (e.g. $CD4^+$ T-cells) with consequent immunosuppression and appearance of a variety of potentially fatal opportunistic infections (Chermann *et al*, 1983). The continually expanding HIV-infected population remains a worldwide issue, with estimates that HIV/AIDS will be the 3rd leading cause of death in the US within the next decade. It has been about 25 years since HIV was identified as the primary aetiologic agent leading to AIDS (Broder and Gallo, 1984). However, while the available treatments cannot completely eliminate AIDS, HIV infections have changed from a progressing fatal condition to a more manageable chronic illness resulting from the continued development of antiretroviral therapeutics (Ho *et al*, 1995).

The combination of nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors, or highly active antiretroviral therapy (HAART), not only has significantly decreased the morbidity and mortality of HIV disease, but also is directly related to a significant diminution of opportunistic infections (Smith, 2006). Despite these crucial improvements in controlling the disease progression in patients receiving HAART, a complete eradication of HIV infection is not yet possible, specifically related to the ability of HIV to integrate and produce a latent infection in long-lived host cells, e.g. T cells, macrophages and dendritic cells (Sungkanuparph *et al*, 2003). The ability of HIV to hide and evade the immune system by integrating into the host genome has become an important target of HIV research, with a goal of elucidating molecular mechanisms that control HIV latency and reactivation, as well as examining a range of new molecules, which target this portion of the HIV life cycle of infection and disease (Stevens *et al*, 2006).

Chronic immune activation associated with co-infections by non-HIV pathogens (e.g. *Pneumocystis carinii*, *Mycobacterium tuberculosis* and *Herpesviruses*) (Koziel *et al*, 1999; Goletti *et al*, 1996; Caselli *et al*, 2005) has

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been suggested as a critical factor that influences the severity and progression of AIDS and HAART success/failure, as well as the reduction in survival rate and increase in the risk of HIV transmission in HIV^+ patients (Whalen *et al*, 1995; Blanchard *et al*, 1997; Ott, 2002). In addition, some pro-inflammatory cytokines/chemokines and mediators produced by immune and non-immune host cells have also been shown to act as inhibitors or stimulators in regulating HIV recrudescence (Collman *et al*, 2003; Oguariri *et al*, 2007). Therefore, understanding the role of immune activation associated with non-HIV co-infections in HIV replication may have important clinical significance for the development of novel therapeutic strategies to control AIDS progression during opportunistic infections. There is a growing body of evidence supporting an increased prevalence and severity of a variety of oral diseases associated with immunosuppression coincident with HIV infection that appears early after viral infection. Thus, 40–50% of HIV+ patients exhibit an oral fungal, bacterial or viral infection (Reznik, 2005). Additionally, clinical evidence reveals a positive correlation between HIV viral load and oral infectious diseases, such as periodontal disease, hairy leukoplakia and candidiasis (Alpagot *et al*, 2004, 2007; Patton, 2000; Ramirez-Amador *et al*, 2005; Black *et al*, 2000). However, the potential for oral pathogens to impact HIV cell reservoirs and induce HIV reactivation has not been delineated. The main goal of this review was to describe general concepts about HIV infection, latency and reactivation as well as to consider the evidence of HIV reactivation associated with non-oral opportunistic infections. Finally, based on these considerations, we present periodontal disease as an example of oral chronic infections that may have the ability to induce HIV exacerbation in HIV+ patients. Future studies could explore such a relationship the understanding of which may impact on the management of HIV+ patients and create opportunities to develop new long-term strategies to eradicate HIV.

Biological basis of HIV reactivation

HIV is a ribonucleic acid (RNA) virus that belongs to the retrovirus family and lentivirus sub-group. This group of viruses generally must make a deoxyribonucleic acid (DNA) copy (cDNA) of their RNA to replicate inside the host cell, taking advantage of an enzymatic machinery that includes reverse transcriptase (Freed and Mouland, 2006).

Infection is initiated by the encounter of a HIV virion with a cell expressing the CD4, cluster determinant receptor. The interaction between the CD4 molecule and the viral surface glycoprotein, gp120, induces a conformational change of gp120, allowing it to interact with chemokine receptors, CCR5 or CXCR4. This binding leads to fusion of the virus and the cell membrane, which further enables the virus to enter into the host cell. The viral glycoprotein, gp41, also appears critical for the viral fusion process. In the cytoplasm of the host cell, the HIV reverse transcriptase converts viral RNA into DNA, and this new DNA associated with viral and host proteins (pre-integration complex) then translocates into the nucleus, where it is spliced into the host's DNA via the activity of another viral enzyme integrase. The viral DNA that becomes integrated into the host genome is known as a provirus. At this point of the viral cycle, HIV can remain latently infecting some host cells. Although $CD4^+$ T cells appear to be the primary targets of HIV, other immune and non-immune cells with or without CD4 molecules on their surfaces can also be infected. Thus, macrophages, dendritic cells, $CD8^+$ T cells, endothelial cells, epithelial cells and fibroblasts also can harbour HIV proviruses in their genome (Freed and Mouland, 2006).

Viral latency

Viral latency is defined as a reversible state in which the viral genome is present in the host cell without production of infectious virus particles, a scenario that has accompanied the success of HAART therapy. However, the molecular, cellular and immunological features that are involved in latency are diverse and depend on the specific biology of specific viruses, but in all cases, latency consists of an infection cycle that can be separated in three phases: (I) establishment, (II) maintenance and (III) reactivation (Redpath *et al*, 2001).

At the cellular level, during the establishment of latency, there is an inhibition of viral gene expression at an early stage following entry into the host cell, with most productive viral cycle genes being quiescent. At the establishment phase, host cell factors seem to be the determinant for suppressing viral gene expression and replication. During the maintenance phase, while virus expression is not required, some viral transcripts may play an important role, such that viral gene transcription is not necessarily completely silenced in latency. The reactivation phase transits from a state with no replicating virus to the production of new virions (Redpath *et al*, 2001).

Two major forms of HIV latency have been described, pre- and post-integration latency (Lassen *et al*, 2004). HIV post-integrated latency has been shown in numerous cell types, including $CD4^+$ T cells, macrophages, dendritic cells, NK cells, B cells, endothelial cells, glial cells and epithelial cells (Blankson *et al*, 2002). Apparently, the most stable reservoirs in the post-integration state of latency are $CD4^+$ T cells, with a predicted half-life of 43 months (Finzi *et al*, 1999), although a low level of transcription has been identified. Thus, down-regulation of viral transcriptional activity after integration into the host genome seems to be related to several mechanisms, including inaccessibility of the integrated provirus to the cellular transcriptional machinery, the absence in resting cells of transcription factors necessary for HIV reactivation, the presence of transcriptional repressors and the premature termination of HIV transcription elongation due to the absence of the viral Tat protein and its cofactors (He *et al*, 2002).

The population of latently infected cells in HIV+ patients seems to be refractory to HAART, and even in patients receiving antiretroviral therapy, HIV

replication has been shown, which could account for the persistence of infection and resulting AIDS (Blankson *et al*, 2002). Importantly, emerging evidence shows that the high mutation rate of HIV in the presence of HAART is associated with drug resistance and diminished efficacy, which tend to increase in both treatment-naïve and treated patients (Little *et al*, 2002; Kuritzkes, 2007). Therefore, the study of mechanisms that modulate HIV replication during the latent stage is important to understand the pathogenesis of this infection as a chronic disease and to develop new therapies for eradicating latently infected cells or preventing the activation of HIV replication from these cell reservoirs.

Mechanisms involved in HIV reactivation

As a critical part of HIV life cycle, reactivation of the provirus results in the transcription of new viral RNA (genomic and mRNA) and synthesis of new viral proteins, which further leads to assembly and production of new virions during which the viral proteases play an important role. These particular events are regulated by both viral (e.g. Tat) and cellular transcription factors (e.g. NFκB, C/EBP, Sp1, CREB and AP-1) with binding sites present in the HIV promoter, as shown in Figure 1 (Garcia and Gaynor, 1994; Pereira *et al*, 2000). Two different phases could be regulating HIV transcription and controlling reactivation: (I) the early phase or initiation of transcription that is mainly activated by cellular transcription factors and only few transcripts elongate throughout the viral genome, resulting in transcription of the viral transactivator Tat. (II) The late phase of transcription occurs when enough Tat protein has accumulated, which then binds to the transactivation response element or TAR (an RNA hairpin loop formed at the 5′ end of all nascent HIV transcripts) and recruits the cellular protein kinase complex termed TAK/P-TEFb complex (Tat-associated kinase/positive transcriptional elongation factor b). Further, this complex causes the hyperphosphorylation of the RNA polymerase II and dramatically increases its ability to elongate (Freed, 2004). This set of molecular events clearly shows that HIV is able to adapt transcription of its integrated proviral genome by exploiting the specific cellular environment. In fact, the molecular mechanisms of HIV reactivation seem to differ depending upon the cell type, degree of cell activation and micro environmental factors, including cytokines and other soluble factors (Rohr *et al*, 2003). Interestingly, it also has been suggested that HIV-1 reactivation from latently infected cells can be a Tat-independent mechanism, where only activated cellular transcription factors such as NFκB and interferon regulatory factor-1 (IRF-1) will promote proviral transcription irrespective of the presence of Tat (Sgarbanti *et al*, 2008).

Among all HIV latently infected cells, macrophages have received particular attention because unlike CD4$^+$ T cells, which are depleted by apoptosis during AIDS, these antigen presenting cells appear to be resistant to virus-mediated apoptotic death, promoting a long-term persistence of the HIV infection and potential contribution to developing of immunodeficiency. In addition to being a substantial viral reservoir, infected

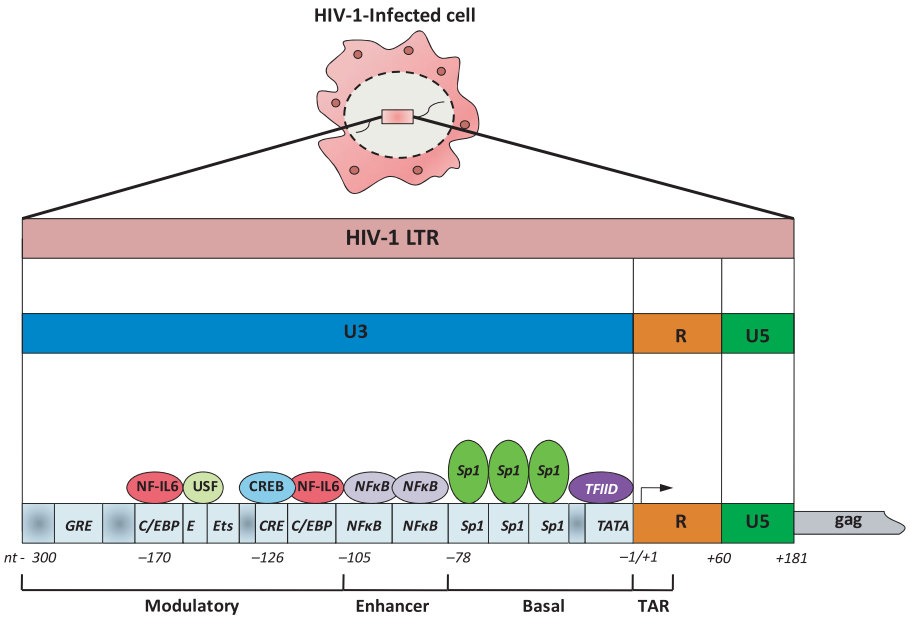

Figure 1 Structure of human immunodeficiency virus 1-long terminal repeat (HIV-1 LTR) promoter. Transcription of HIV-1 provirus is regulated by both viral and cellular transcription factors with binding sites in the HIV-1 LTR that contains a number of *cis*-regulatory regions: (i) transactivation response element (TAR), encodes an mRNA that binds the viral transactivator Tat; (ii) core or basal region, which contains the initiator, the TATA box and three Sp1-binding sites; (iii) enhancer region which binds NFκB and (iv) modulatory region that has several target sequences for a variety of cellular transcription factors, such as NF-interleukin 6 (NF-IL6), cyclic AMP response element protein (CREB), etc. In the absence of the viral Tat protein, transcription of HIV-1 LTR is initiated but elongation is not successful, with production of few non-functional transcripts. Tat protein stimulates transcriptional elongation by interacting with mRNA TAR and promoting the formation of a transcriptional complex composed of Tat, cyclin T1 and CDK9, which then recruit RNA polymerase II to the initiation site

macrophages may also transfer HIV to uninfected T cells (Wahl *et al*, 2003). Unlike T cells, the mechanisms for HIV reactivation in macrophages involve the loss of the C/EBP family of transcriptional repressors which bind three different sites of the HIVLTR and may be mediated by T cell-macrophage interactions (Tesmer *et al*, 1993). However, the activity of NFκB transcription factor is critical to HIV reactivation in both T cells and macrophages (Henderson *et al*, 1995; Zhang *et al*, 1995).

Co-infections and HIV reactivation

Previous studies analysing the impact of vaccination for influenza and tetanus in HIV-infected patients found a temporal increase in the RNA viral load that returned to pre-vaccination levels in 3–4 weeks (Staprans *et al*, 1995; Stanley *et al*, 1996; O'Brien *et al*, 1995). These unexpected observations led to the hypothesis that co-infections in HIV+ patients may contribute to disease progression; a concept supported by a relationship between microbial infections and the clinical evolution of AIDS. Most of these studies have examined mycobacterial infections, which are associated with the production of large amounts of pro-inflammatory cytokines, such as TNF-α, IL-1β and IL-6, each of which has also been identified to elicit HIV reactivation in monocytes/macrophages (Poli *et al*, 1994). Thus, immunosuppression in HIV-1+ patients enables opportunistic infections to lead to significant increase in the abundance of HIV virions. These findings suggested that HIV-associated immunodeficiency increases susceptibility to opportunistic infections, and opportunistic infections promote HIV reactivation that may enhance AIDS progression (Wahl *et al*, 2003). *Mycobacterium tuberculosis* is the most common opportunistic infection resulting in AIDS-related fatalities, and seems to be specifically associated with an increased viral mutation as well as accelerated course of HIV infection (Condos *et al*, 2000). Coincidently, in patients with successful tuberculosis therapy, a reduction in the viral load has been demonstrated (Whalen *et al*, 1995; Pape *et al*, 1993).

Basically, two general cellular responses have been described in monocytes/macrophages obtained from HIV+ patients with tuberculosis when exposed to *M. tuberculosis*: (i) increased transcriptional activity of HIV genes and virus production (Zhang *et al*, 1995; Goletti *et al*, 1996); and (ii) increased susceptibility of additional cells to infection with HIV (Toossi *et al*, 1993). Similar findings have been reported for infection with *Streptococcus pneumoniae* (Bush *et al*, 1996), *Neisseria gonorrhea* and *Chlamydia trachomatis* (Rotchford *et al*, 2000). These results have contributed to the inclusion of prophylactic antibiotics as part of AIDS treatment, with noted benefit for these immunocompromised patients in industrialized countries (Blanchard *et al*, 1997).

The HIV reactivation induced by other pathogens commonly found in HIV+ patients has also been studied. Thus, herpes simplex virus-1 (HSV-1) appears to use the same NFκB pathway to up-regulate transcriptional activity of HIVLTR in latently infected cells (Amici *et al*, 2004). Measles virus inhibits the *in vitro* production of HIV protein, p24, in peripheral blood mononuclear cells (PBMCs) latently infected cells; a finding that was also observed in HIV+ children with measles. The reduction of HIV RNA levels was correlated with a reduction in T cell proliferation during measles infection, potentially related to the $CD4^+$ cells that where crucial for HIV replication (Garcia *et al*, 2005). Whether the measles virus is involved in inhibition of HIVLTR promoter activation remains unknown. Additionally, controversial results have been found using antigens of the parasite *Plasmodium falciparum*. *In vitro* studies suggest increased HIV replication in T $CD4^+$ cells, whereas epidemiological studies have not detected a more rapid clinical progression of HIV disease. Recently, it was found that *P. falciparum* antigens can reduce the HIV infectivity in $CD4^+$ T cells apparently through production of IFNγ and down-regulation of the CCR5 receptor, which could explain the clinical outcomes (Moriuchi *et al*, 2002). Using rhesus monkeys, it was also shown that the parasite *Schistosoma mansoni* exhibited the ability to reactivate HIV replication (Ayash-Rashkovsky *et al*, 2007). Finally, *Trichomonas vaginalis*, one of the most common non-viral sexually transmitted pathogens worldwide, exhibited the ability to not only disrupt epithelial monolayer but also enhance HIV replication in newly infected peripheral blood mononuclear cells (Guenthner *et al*, 2005).

Although the cellular and molecular mechanisms by which opportunistic pathogens could be stimulating HIV reactivation in latently infected cells remain somewhat unclear, a growing body of evidence suggests an important role for Toll-like receptors (TLRs), and signalling molecules involved in TLR-induced cell activation (Figure 2). To date, HIVLTR transactivation and HIV replication associated with TLR2, TLR4 and TLR9 has been shown (Equils *et al*, 2003, 2004). Treatment of HIV-infected cells with enterobacterial lipopolyssacharide (LPS) exhibited substantial NFκB activation and HIVLTR transactivation, which appears to involve the IL-1R-associated signalling molecules MyD88, IRAK, TRAF-6, as well as p38 MAPK and PI3 kinase in macrophages (Equils *et al*, 2001, 2004). However, in a recent study, Nordone *et al* (2007) found that TLR4 stimulation did not induce HIV production in different cell lines, by using an ultra-purified LPS from *Escherichia coli*, and suggested that up-regulation of NFκB alone is not sufficient to activate HIV promoter. These results suggest a potential failure or impairment of TLR-4 signalling pathways during HIV infection. It is important to consider whether HIV reactivation is being evaluated in a model of acute or chronic infection, which may elicit different results associated with the same TLR (Nordone *et al*, 2007). It has been shown that re-stimulation of monocytes/macrophages previously exposed to various TLR ligands, LPS (TLR4 ligand), CpG (TLR9 ligand) and lipoteichoic acid (TLR2 ligand), fails to elicit pro-inflammatory cytokines such as TNFα, IL-1, IL-6,

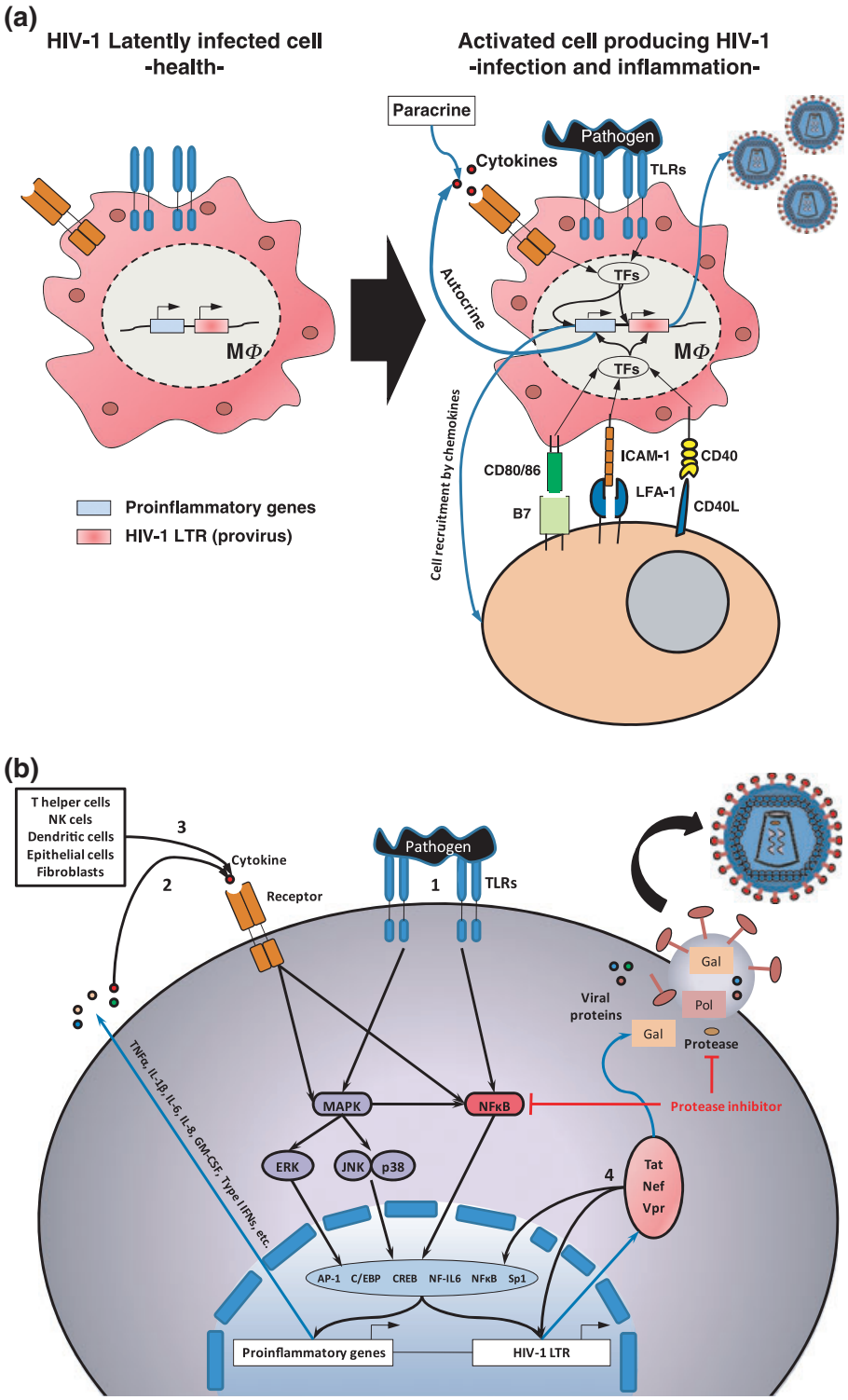

Figure 2 Model of human immunodeficiency virus 1 (HIV-1) reactivation during co-infections (**a**) HIV-1 latently infected cells in the absence of infection and inflammation remain undistinguishable from non-HIV-1 infected cells without production of new virions. During co-infections, activation of the HIV-1-infected cell by different membrane receptors [Toll-like receptors (TLRs), cytokine receptors, integrins, co-stimulatory molecules, etc.] induces activation of human immunodeficiency virus 1-long terminal repeat (HIV-1 LTR) provirus with the consequent production of new virions. (**b**) Activation of cell membrane receptors in HIV-1-infected cells turns on downstream signalling pathways that lead to activation of transcription factors with the ability for regulating not only proinflammatory genes but also HIV-1 LTR transcription and production of new virions. TLR activation leads to the production of pro-inflammatory cytokines as well as production of new HIV-1 virions (1). Pro-inflammatory cytokines produced by the HIV-1-infected cell itself in response to bacterial challenge (2), as well as cytokines from other cellular sources (e.g. T helper cells, natural killer (NK) cells, dendritic cells (DCs), epithelial cells, fibroblasts, etc.) (3), induce a synergistic HIV-1 viral production. Some viral proteins as Tat, Nef and Vpr also have the ability to induce HIV-1 LTR reactivation and cytokine production (4). A potential for some protease inhibitors used in highly active antiretroviral therapy to inhibit TLR-4 signalling through blocking NFκB has been suggested

Table 1 Soluble factors produced by oral host cells with potential to modulate HIV reactivation

	Epithelial cells		*Gingival fibroblasts*	
	Protein	*mRNA*	*Protein*	*mRNA*
Stimulators				
TNF-alpha	Yes	Yes	-	Yes
TNF-beta	-	-	-	-
IL-1 beta	Yes	Yes	-	Yes
IL-6	Yes	Yes	Yes	Yes
IL-7	Yes	Yes	-	-
IL-2	-	-	-	-
IL-18	Yes	Yes	-	-
M-CSF	Yes	Yes	-	-
Monocyte chemotactic protein-1 (MCP-1)	Yes	Yes	Yes	Yes
Prostaglandin E2	Yes	Yes	Yes	Yes
Inhibitors				
Alpha and beta defensins 1,2,3	Yes	Yes	No	No
Alpha-1 antitrypsin	-	-	-	-
CD8-positive cell product anti-thrombin III	-	-	-	-
Interferon alpha and beta	-	-	-	-
IL-10	Yes	Yes	-	-
IL-13	-	-	-	-
IL-16	-	-	-	-
IL-27	-	-	-	-
TGF-beta	-	Yes	Yes	Yes
RANTES (in the presence of TNF-alpha)	Yes	Yes	Yes	Yes
Macrophage inflammatory protein-1 α (MIP-1 alpha)	Yes	Yes	Yes	Yes
Macrophage inflammatory protein beta (MIP-1 beta)	Yes	Yes	-	-
Monocyte chemotactic protein-2 (MCP-2)	-	-	-	-
Stromal-derived factor 1 (SDF-1)	Yes	Yes	Yes	Yes
Leukaemia inhibitory factor (LIF) (Placenta component)	-	-	-	-
Macrophage-derived chemokine (MDC)	-	-	-	-
Rnase	-	-	-	-
Secretory leucocyte protease inhibitor (SLPI)	-	-	-	-
Prostaglandin A	-	-	-	-
Pivotal role				
IFN-gamma	Yes	Yes	Yes	Yes
IL-4	-	-	-	-
GM-CSF	Yes	Yes	Yes	Yes
IL-8	Yes	Yes	Yes	Yes

HIV, human immunodeficiency virus; TNF, tumour necrosis factor; IL, interleukin; M-CSF, macrophage-colony stimulating factor; TGF, transforming growth factor; RANTES, regulated on activation, normal T-cell expressed and secreted; IFN, interferon; GM-CSF, granulocyte/macrophage-colony stimulating factor.
-, Neither mRNA nor protein has been detected or evaluated.

IL-12, as part of the tolerance mechanisms of the immune system to control inflammatory responses, particularly at mucosal surfaces highly colonized by commensals microorganisms (Dobrovolskaia and Vogel, 2002). Surprisingly, this 'tolerogenic response' does not affect the HIV gene and protein expression after re-stimulation *in vitro* despite a dramatic reduction in pro-inflammatory cytokine production. These results suggest that HIV could be escaping normal mechanisms of host infection control, such as microbe-induced tolerance (Bafica *et al*, 2004). Most recently, it has been elegantly shown by Brenchley *et al* that microbial translocation mainly of Gram-negative bacteria from the gut to systemic circulation is a cause of systemic activation in chronic HIV infection and AIDS progression *in vivo*. Importantly, effective antiretroviral therapy appeared to reduce microbial translocation only partially, which suggests that persistence of abnormalities of gastrointestinal mucosal surface with a limited reconstitution of gastrointestinal $CD4^+$ T cells as well as impaired B-cell function could be accompanying HAART (Brenchley *et al*, 2006).

Although most studies evaluating HIV reactivation induced directly by microorganisms have been focused on monocytes/macrophages, some findings have revealed that bacterial stimulation also has the capacity to enhance HIV replication in $CD4^+$ T cells (Moriuchi *et al*, 2000). Most recently the demonstration that T cells also express TLRs (Gelman *et al*, 2004, 2006) suggests the possibility that co-infecting non-HIV pathogens can directly reactivate HIV proviral forms in $CD4^+$ T cells, the most important viral reservoir. In addition to TLR-associated viral reactivation, it has also been recently demonstrated that different TLR agonists

induce activation in CD8+ T cells and death in CD4+ T cells, events that positively correlate with the immunological changes typically observed during AIDS progression (Funderburg *et al*, 2008).

Cytokines/chemokines and soluble mediators associated with HIV reactivation

Immune activation during the host response to HIV infection itself or the presence of exogenous stimuli has an important effect on the HIV life cycle. Thus, the constant immune activation during chronic infections characterized by the constant release of pro-inflammatory cytokines can result in increased HIV replication and also lead to phenotypical and genotypical changes in the virus (Figure 2) (Devadas *et al*, 2004). A group of cytokines/chemokines and soluble mediators have been found to have the capacity to either stimulate or inhibit HIV replication, or in certain cases do both (Table 1). Thus, pro-inflammatory cytokines, such as TNFα, TNF-β, IL-1β and IL-6, are associated with an increased HIV replication in T cells and monocytes-derived macrophages (MDM) (Poli *et al*, 1990; Devadas *et al*, 2004), IL-2 and IL-7 up-regulate HIV activation in T cells (Wang *et al*, 2005) and macrophage-colony stimulating factor stimulates HIV in MDM. On the other hand, IL-10, TGFβ, IL-13, IL-16 and IL-27 inhibit HIV in MDM (Wang and Rice, 2006; Montaner *et al*, 1997; Truong *et al*, 1999; Imamichi *et al*, 2008), and IFNγ, IL-4 and granulocyte/macrophage-colony stimulating factor appear to have a pivotal role being activators or inhibitors under selected conditions for HIV reactivation (Biswas *et al*, 1992; Naif *et al*, 1994; Kedzierska *et al*, 2000; Osiecki *et al*, 2005). Although IL-10 plays a critical role down-regulating the cellular immune response to HIV-1, it appears to be involved in TNFα-mediated activation of HIV in monocytes/macrophages (Rabbi *et al*, 1998). IL-18 is a pro-inflammatory cytokine that acts on Th1 cells to produce IFNγ in the presence of IL-12, whereas in the absence of IL-12, it promotes the differentiation of Th2 cells (Nakanishi *et al*, 2001). It has been shown that IL-18 stimulates the replication of HIV in chronically infected promonocytic cells (Pugliese *et al*, 2002). Most recently, a significant increase in IL-17 production by $CD4^+$ and $CD4^-$ T cells has been associated with HIV infection; however, its role in HIV reactivation remains unknown (Maek *et al*, 2007).

As was mentioned earlier in this review, some chemokine receptors are important co-receptors for fusion between HIV envelope and target cell membrane during the first events of viral infection. These receptors belong to the superfamily of seven transmembrane G-protein coupled receptors, and have become a tempting target for the development of new anti retroviral drugs (viral fusion inhibitors). For instance, the C-C chemokines, macrophage inflammatory protein (MIP)-1alpha, MIP-1beta and regulated on activation, normal T-cell expressed and secreted are important inhibitors of macrophage-tropic strains of HIV, whereas the alpha chemokine stromal-derived factor-1 down-regulates infection of T-tropic strains of HIV (Demonte *et al*, 2004; Kedzierska and Crowe, 2001). In contrast, Monocyte chemotactic protein-1 has been shown to be capable of stimulating HIV replication (Borghi *et al*, 2000). On the other hand, the role of IL-8 (CXC chemokine) in HIV reactivation is still controversial; however, little evidence shows that it could have a pivotal role depending upon the state of infection. Thus, HIV acutely infected cells exposed to IL-8 seem to increase viral replication (Lane *et al*, 2001), and in contrast chronically infected cells treated with IL-8 fail to exhibit HIV exacerbation (Tiemessen *et al*, 2000). Apparently, cell signalling triggered by IL-8 receptor CXCR1 but not CXCR2 could be inducing internalization of CCR5, which would reduce the extent of HIV infection (Richardson *et al*, 2003).

Among a growing group of soluble factors with the ability to modulate HIV replication, inflammatory mediators associated to the innate immune response, such as antimicrobial peptides, α-defensins and β-defensins 1, 2 and 3 produced by epithelial cells, RNases, prostaglandin A (PGA) and the secretory leucocyte protease inhibitor (SLPI), also can inhibit HIV reactivation (Quinones-Mateu *et al*, 2003; Dumais *et al*, 1998; Ankel *et al*, 1991; McNeely *et al*, 1997). In contrast, the inflammatory mediator prostaglandin E2 (PGE_2) seems to be able to increase viral replication in T-cells (Dumais *et al*, 1998). Evidence suggests that some cytokines such as IL-1 and TNFα are able to activate the transcription factor NFκB, which in turn can further induce viral gene expression through interaction with the long terminal repeat (LTR) of HIV provirus (Folks *et al*, 1989); however, not all cytokines involve the same pathway, and thus IFNγ, IL-6 and TNFα also up-regulate IFN regulatory factor-1 (IRF-1) which leads to cell activation and drives HIV-1 replication (Fauci, 1996; Fujita *et al*, 1989). Interestingly, IRF-1 can bind the HIV transactivator protein Tat and NFκB, which allows further induction of HIV promoter activation and virus replication in an amplified transcriptional activity. In addition to HIV gene reactivation, other IRF members such as IRF-8 can negatively regulate this process, a potential molecular mechanism that could be associated with latency stages (Sgarbanti *et al*, 2008, 2002). Type-1 IFNs have also been proposed as part of the negative transcriptional regulatory mechanisms that alveolar macrophages use during resting stages without an identified infection (Khan *et al*, 1989). Thus, IFNs appear to alter the expression of C/EBPβ, producing a dominant negative transcription factor and repressing the HIV promoter. In fact, resting alveolar macrophages obtained from non-inflamed lung behave like IFNβ-treated macrophages, expressing the inhibitory 16-kDa C/ EBPβ and inhibiting HIV replication, likely contributing to viral latency in a non-inflamed lung (Honda *et al*, 1998). In addition to the IFN-response as a negative regulator of HIVLTR transcription, the anti-inflammatory cytokine IL-10 also induces the C/EBPβ repressor in macrophages but not in monocytes through a pathway mediated by STAT3 (Tanaka *et al*, 2005). It

has been hypothesized that the inclusion of C/EBP sites in the HIVLTR may be another example of HIV usurping normal immune regulation for its own advantage to develop viral latency. Thus, pathways that inhibit cytokine production may also promote viral latency, protecting provirally infected macrophages from immune surveillance (Weiden *et al*, 2000).

More recently, it was shown that interactions between activated $CD4^+$ and $CD8^+$ lymphocytes and macrophages are critical for HIVLTR transcription and viral replication, which resemble the clinical features observed during tuberculosis in HIV+ patients (Figure 2). Such cell interactions lead to the loss of inhibitory C/EBPβ and an activation of NF-κB, with a consequent increase in HIV-1 replication in a process that seems to be developed in two steps: (i) The contact leads to a loss of inhibitory C/EBPβ that de-represses the HIVLTR; and (ii) soluble lymphocyte factors (e.g. IL-1β, IL-6 and TNFβ) elicit NF-κB activation that enhances HIVLTR transcription (Hoshino *et al*, 2002). The same type of responses following cell–cell contact has been reported for neutrophils. Thus, the interaction of macrophages and polymorphonuclear neutrophils (PMNs) abolished the inhibitory C/EBPβ which led to de-repression of the HIVLTR in macrophages. The contact-mediated activation was dependent on cross-linking of 3 co-stimulatory receptors (CD40, CD80/86 and ICAM-1) by their respective ligands (CD40L, CD28 and LFA-1), all of which are expressed in lipid raft fractions of PMNs (Hoshino *et al*, 2007). The presence of repressors and de-repressors seems to influence a large group of inflammatory genes containing promoters with C/EBP sites. Therefore, as proposed by Tanaka *et al*, the interplay between repressors and de-repressors is pivotal in determining if a given stimulus leads to up or down-regulation of inflammation and HIV replication (Tanaka *et al*, 2005).

Like many pro-inflammatory cytokine genes, the long tandem repeats (LTR) promoter sequence of the HIV provirus that is integrated in the genome of latently infected host cells contains binding sites not only for NFκB but also for other transcription factors such as Sp1, CRE and CCAAT/Enhancer Binding Protein (C/EBPβ) (Figure 1). As mentioned earlier, alveolar macrophages strongly express C/EBPβ that correlates with very low levels of HIV levels in un-inflamed lung (Nakata *et al*, 1995). In contrast, pro-inflammatory cytokines induced during tuberculosis directly increased the HIVLTR activity and HIV replication. One outcome was that TNFα increased HIV production in mononuclear phagocytes through transcriptional activation of the LTR promoter by NFκB (Bernstein *et al*, 1991; Goletti *et al*, 1996). It has been hypothesized that tuberculosis switches the pulmonary microenvironment from one that suppresses HIV replication to one that stimulates it (Zhang *et al*, 1995). Interestingly, when monocytes are differentiated into macrophages *in vitro*, several stimuli, such as LPS, *M. tuberculosis* or other pro-inflammatory stimuli, suppress HIV replication, an effect mediated by type-1 IFNs (Weiden *et al*, 2000).

Different cellular transcription factors with the ability to bind HIV promoter are normally activated through cytokine and chemokine receptors as well as TLRs. This suggests that HIV replication induced by cytokines/chemokines could be a net result of complex interactions between several transcription factors during inflammation (Figures 1 and 2). To understand the molecular mechanisms of HIV reactivation or inhibition associated to TLR agonists is currently a focus of intense research, as potential modulation of particular signalling pathways associated to these factors could be helpful for the development of new anti-HIV therapeutic strategies based on targeting HIV transcription.

Interestingly enough, most of the described cellular and molecular factors of the innate immune system associated with HIV reactivation in monocytes/macrophages have also been broadly described as critical players in oral infectious diseases, such as periodontal disease (e.g. macrophages, neutrophils, CD4+ and CD8+ T cells, etc.). Therefore, particular microbial and immune events associated with the oral environment, such as polymicrobial infections and tolerance, may be relevant for understanding a potential HIV reactivation during oral co-infections.

Hypothesis: oral co-infections as a risk factor for HIV recrudescence

Historically, a high prevalence of oral infectious diseases has been strongly associated with HIV infection, including pseudo-membranous candidiasis (OC), oral hairy leukoplakia (OHL), HIV gingivitis and periodontitis and Kaposi's sarcoma (Coogan *et al*, 2005). The advent of HAART appears to reduce the frequency of HIV-associated oral pathology (i.e. OHL and OC), particularly in industrialized countries; however, the available evidence only supports a significant reduction for OC in patients under antiretroviral therapy (Patton *et al*, 2000; Greenspan *et al*, 2004). In addition, new oral clinical manifestations associated with HAART therapy have been described, such as an increased prevalence of oral warts associated with human papiloma virus (HPV), which appears to represent a form of immune reconstitution syndrome (King *et al*, 2002). Whether oral infectious diseases in HIV+ patients have an impact in HIV exacerbation remains unclear. However, results obtained from cross-sectional studies have shown a positive correlation between OC or OHL and HIV-1 viral load (Patton, 2000; Chattopadhyay *et al*, 2005; Greenspan *et al*, 2000; Black *et al*, 2000). Interestingly, Alpagot *et al* in a prospective study have recently shown a positive correlation between HIV viral load and periodontal disease as well as increased presence of PGE2, metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 in gingival crevicular fluid (Alpagot *et al*, 2007, 2006). In addition, a significant increase in the levels of *Fusobacterium nucleatum*, *Prevotella intermedia*, as well as IFNγ and TGFβ in gingival crevicular fluid has also been shown, which may be risk factors for rapid progression of periodontitis in HIV+ patients (Alpagot *et al*, 2003, 2004, 2007, 2008).

A biological explanation for this association remains undetermined.

On the other hand, it has been shown that normal oral mucosa tissues display infiltrating immune cells, such as Langerhans dendritic cells, macrophages and $CD4^+$ T cells, as part of the immune response elicited against oral bacteria (Juhl *et al*, 1988; Jotwani and Cutler, 2003; Schroeder and Listgarten, 1997). These cells are an important target for HIV infection and replication, as well as for providing a long-lived host cell population to act as a reservoir for latent HIV (Chou *et al*, 2000). The oral cavity seems to be a site of HIV pathogenesis and potential reservoir for the disease in HIV^+ patients, as both HIV RNA and DNA proviral forms are present in saliva as well as in gingival crevicular fluid (Maticic *et al*, 2000; Shugars *et al*, 2001). Nevertheless, substances that inactivate HIV (e.g. SLPI), lower viral loads and specific anti-HIV antibodies that mediate antibody-dependent cell-mediated cytotoxicity appear to reduce the infectivity of virions in saliva (McNeely *et al*, 1995; Shugars *et al*, 1999; Kim *et al*, 2006).

Interestingly enough, the possibility for HIV to infect oral epithelial cells has been demonstrated *in vitro*. Thus, oral epithelial cells are susceptible to either cell free or cell-associated HIV-1 infection through the glycosphingolipid galactosylceramide (GalCer) receptor and CXCR4 co-receptor (Liu *et al*, 2003; Moore *et al*, 2003). In addition, CCR5-tropic virus infecting oral epithelial cells can be transferred to circulating $CD4^+$ T lymphocytes and macrophages (Liu *et al*, 2003). These results are consistent with a positive expression of all HIV receptors and co-receptors found in healthy gingiva, i.e. Langerin, DC-SIGN, macrophage mannose receptor (MMR), GalCer, CCR5 and CXCR4, which suggests that these tissues are susceptible to infection by HIV. Among these receptors, DC-SIGN, MMR, CXCR4 and CCR5 show increased expression in periodontitis, where $CCR5^+$ cells were mostly T cells, macrophages and dermal dendritic cells (Jotwani *et al*, 2004). Most recently, the ability of HIV to infect and replicate in oral mucosa epithelial cells *in vivo* has also been demonstrated (Rodriguez-Inigo *et al*, 2005). Thus, immune and oral epithelial cells latently infected with HIV in gingival tissues may be an important source for HIV reactivation during chronic inflammatory events triggered by oral pathogens. There remains an incomplete understanding concerning the origin of latently infected immune cells in the oral mucosa. These cells could potentially involve a direct HIV infection of oral mucosal immune cells by viruses crossing the oral epithelial barrier, or may also be recruited from the systemic circulation of HIV-infected patients. The individual or combined contribution to the local infected cells in the gingival tissue has not been demonstrated; thus, additional investigations are required as these regional latently infected cells probably may have a significant impact on the potential for HIV replication, transmission, as well as AIDS progression.

Table 2 Microorganisms detected in supra- and sub-gingival plaque of HIV+ patients

Microorganism	*Reference*
Porphyromonas gingivalis, *P. intermedia*, *Fusobacterium nucleatum*, *Actinobacillus actinomycetemcomitans*	Murray *et al*, 1989
A. actinomycetemcomitans, *Campylobacter rectus*, *Micromonas micros*, *P.intermedia*, spirochetes	Rams *et al*, 1991
P. intermedia, *P. buccale*, *P. oralis*, spirochetes	Piluso *et al*, 1993
CMV, EBV type 1, HSV, HHV-6	Contreras *et al*, 1997, 2001
P. gingivalis, *A. actinomycetemcomitans*, *Candida albicans*, mycoplasma spp.	Chattin *et al*, 1999
HHV-6, -7, -8	Mardirossian *et al*, 2000
C. dubliniensis, *C. glabrata*, *C. parpsilosis*	Jabra-Rizk *et al*, 2001
Capnocytophaga spp., *P. loescheii*, *Streptococcus sanguis*, *Lactobacillus* spp., *Fusobacterium* spp.	Tsang and Samaranayake, 2001
Bulleidia extructa, *Dialister* spp., *Fusobaterium* spp., *Selenomonas* spp., *Peptostreptococcus* spp., *Veillonella* spp.	Paster *et al*, 2002
Spirochetes, yeasts	Cobb *et al*, 2003
Combinations of *P. nigrescens*/*C. rectus*, *P. nigrescens*/*P. gingivalis*, *P. nigrescens*/ *Treponema denticola*	Patel *et al*, 2003
F. nucleatum, *P. intermedia*, *A. actinomycetemcomitans*	Alpagot *et al*, 2004
Gemella spp., *Dialister* spp., *Streptococcus* spp., *Veillonella* spp., *S. cerevisae*, *C. albicans*	Aas *et al*, 2007
Pseudomonas aeruginosa, *Enterobacter cloacae*, *Klebsiella pneumoniae*	Botero *et al*, 2007

HIV, human immunodeficiency virus; CMV, cytomegalovirus; EBV, Epstein–Barr virus; HSV, herpes simplex virus; HHV, human herpes virus.

The oral cavity is colonized by an enormous variety and number of microorganisms that interact with each other in complex biofilms, including commensal, opportunistic and pathogenic species. Some of these microorganisms, particularly Gram-negative bacteria have been proposed as periodontopathogens, due to their greater capacity to elicit an inflammatory response with a consequent destruction of supportive tissues of the teeth (Feng and Weinberg, 2006). Most of the bacteriological studies in $HIV\text{-}1^+$ patients (Table 2) have demonstrated that the prevalence of periodontal pathogens appears to be similar between HIV-infected and HIV-uninfected subjects (Goncalves Lde *et al*, 2004; Gornitsky *et al*, 1991; Patel *et al*, 2003; Tsang and Samaranayake, 2001; Rams *et al*, 1991; Piluso *et al*, 1993). However, recent findings suggest that other opportunistic bacterial species, rather than the classical periodontal pathogens, may also be involved in HIV-1-associated periodontal disease (Paster *et al*, 2002; Aas *et al*, 2007; Goncalves Lde *et al*, 2007; Cobb *et al*, 2003; Botero *et al*, 2007). During the last decade, the potential association between periodontal disease and systemic disorders has generated substantial interest, and available data supports that the infectious/chronic responses in periodontal disease may have a role as risk modifiers of systemic conditions, including diabetes (Southerland *et al*, 2006), low-weight birth and preterm delivery (Bobetsis *et al*, 2006), atherosclerosis/heart failure

(Hujoel *et al*, 2000), osteoporosis (Jeffcoat, 2005) and chronic obstructive pulmonary disease (Azarpazhooh and Leake, 2006). Periodontitis also has been studied in HIV-infected populations including those with AIDS, as an altered immune response would be predicted to modify the course of this oral inflammatory disease. In fact, recent and growing evidence shows significant immunological changes at oral level in HIV-1$^+$ patients compared with healthy controls, which appear to be risk factors for more rapid progression of aggressive forms of periodontal disease in HIV-1-infected population (Alpagot *et al*, 2008, 2007). Importantly, severe forms of oral disease, including necrotizing ulcerative periodontitis, do appear to relate to the immunodeficiency of HIV infection, and correlate with a downhill progression of the viral infection and mortal opportunistic infections (Glick *et al*, 1994).

The immunosuppressive condition resulting from HIV infection has been associated with the appearance of varied opportunistic infections, e.g. tuberculosis, pneumonia and candidiasis. The oral cavity of HIV$^+$ patients can also provide a great environment for seeding such infections by, for example, various fungi, including several strains of *Candida*, such as *C. dubliniensis*, *C. glabrata* and *C. parapsilosis* (Murray *et al*, 1989; Chattin *et al*, 1999; Jabra-Rizk *et al*, 2001), as well as *Cryptococcus neoformans*, *Histoplasma capsulatum* (McKinsey, 1998; Stansell, 1993), and viruses (HSV, herpes zoster virus and HPV). In addition to bacteria and fungi, higher detection frequency of viruses has been reported in the oral cavity of HIV$^+$ patients, including human cytomegalovirus, human herpes viruses 6, 7, and Epstein–Barr virus, when compared with that in healthy controls (Contreras *et al*, 1997; Mardirossian *et al*, 2000; Contreras *et al*, 2001).

Several studies exploring the immunological characteristics of HIV-1$^+$ patients have shown that the potential T-helper polarization in leucocytes from gingival tissues showed a trend towards a Th2 response, characterized by IL-4 synthesis (Gomez *et al*, 1997). It was hypothesized that this Th2 response may be correlated with a reduction in PMNs recruitment to crevicular fluid and enhances the potential colonization of *Candida* spp. in the subgingival sulcus, which would act in concert with certain periodontopathogens to increase inflammation and destruction in HIV$^+$ patients

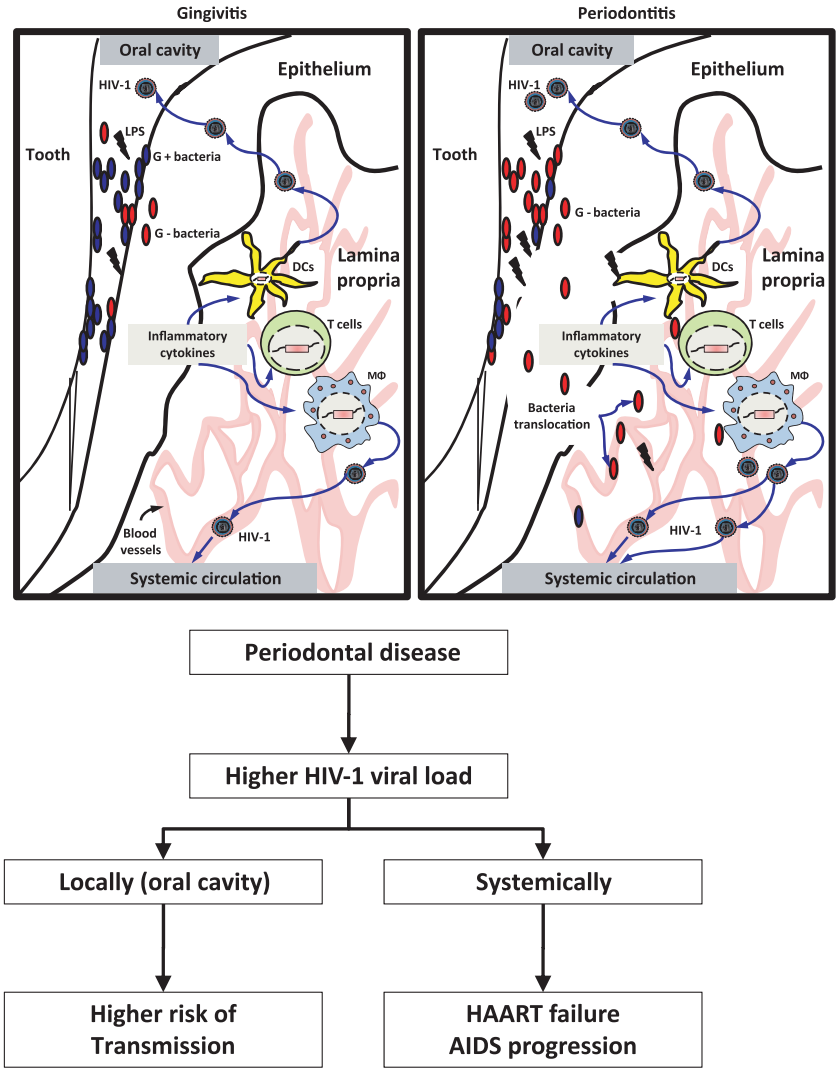

Figure 3 Schematic of the concepts underlying the potential role of periodontal disease in human immunodeficiency virus (HIV) reactivation. Both gingivitis and periodontitis, like other mucosal infections, represent a chronic infection and inflammation that can provide host cell stimulation. HIV-infected patients demonstrating low viral loads following highly active antiretroviral (HAART) therapy contain long-life cells [e.g. macrophages, T cells and dendritic cells (DCs)] with provirus integrated into their genome. Interaction of these cells directly with oral bacteria and/or indirectly with soluble factors (e.g. cytokines/chemokines) from gingival resident cells would activate HIV production, which results in viral recrudescence. An increased reactivation of virus may have an impact both at local level in the oral cavity or systemically, which may be a risk modifier for HIV transmission as well as HAART failure and acquired immunodeficiency syndrome progression respectively

(Lamster *et al*, 1998). Nevertheless, additional studies have reported a significant increase of Th1 inflammatory cytokines in crevicular fluid and saliva, such as IL-1β, IL-6, TNFα and IFNγ (Black *et al*, 2000; Spear *et al*, 2005). Among these cytokines, only IL-1β was correlated with high viral loads (Baqui *et al*, 2000b). The prevalence of pro-inflammatory cytokines in crevicular fluid is in agreement with the significant increased synthesis of the same cytokines by monocytes from HIV^+ patients compared with that in healthy individuals following challenge of these cells with periodontopathogens and LPS (Baqui *et al*, 2000a). In addition, an altered apoptosis of mononuclear cells in gingival tissue from HIV^+ patients correlates well with the Th1 gingival response in periodontal disease of these patients, because their prolonged presence at the periodontitis sites would guarantee a constant production of inflammatory Th1 cytokines that promotes more aggressive tissue destructions (Vieira *et al*, 2003).

An important consideration in this review is that the biological underpinnings of the pathogenesis of periodontitis have been described with other infectious diseases that can reactivate HIV in latently infected cell reservoirs. This suggests that the inflammatory and infectious components of periodontal disease in HIV-1^+ patients might have the capacity to induce viral reactivation. Based on these observations, it is tempting to hypothesize that latently infected cells either locally at gingival tissues or systemically, including $CD4^+$ T lymphocytes, macrophages and dendritic cells, could be targeted either directly by oral common and/or opportunistic pathogens as well as their activating components (e.g. LPS), or indirectly by soluble mediators and cytokines/chemokines produced by immune and non-immune cells (fibroblasts and oral epithelial cells). The net result of this local chronic stimulation would contribute to HIV reactivation and potentially exacerbate local and/or systemic increases of viral load with undesirable clinical consequences for HIV^+ patients (Figure 3). Attempting to develop biological evidence for a potential impact of oral infectious diseases and HIV reactivation, we have been able to demonstrate that oral bacteria associated with periodontal disease have the ability to trigger HIV-1 promoter reactivation in monocytes/macrophages, dendritic cells and T cells, using *in vitro* models (Huang CB, Emerson KA, Gonzalez OA and Ebersole JL unpublished data). Further *in vitro* and *in vivo* studies will be needed to provide a sufficient weight of evidence to better understand the magnitude of this contribution.

As the advent of HAART therapy in HIV infection has transitioned into a 'chronic disease' management strategy, there is growing evidence that co-infection and inflammation in HIV^+ patients may have important public health implications in undermining HAART success. Therefore, the study of a potential role of periodontitis as a global co-infection contributing to HIV recrudescence as well as other oral infectious diseases is necessary. Thus, the adequate and efficient control of oral infections, including HIV-associated periodontal disease in HIV-1^+ patients, would be expected to contribute to minimizing viral reactivation, which would marginalize the effect of HAART therapy and enabling opportunistic infections on this population.

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Author contributions

O. Gonzalez analyzed the data, wrote the manuscript draft and developed the schematics. J. Ebersole advised the authors on data analysis, interpretation and manuscript preparation. C. Huang directed the study, finalized the manuscript and served as the corresponding author.

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