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Contribution of Common Infections to Cardiovascular Risk in HIV-Positive Individuals

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Abstract

HIV-positive individuals are at increased risk for cardiovascular disease due to complex interactions between the increased incidence of traditional cardiovascular risk factors and HIV and antiretroviral-associated inflammation and dyslipidemia. Increasing evidence suggests that a number of important co-pathogens, including cytomegalovirus, hepatitis C virus, and periodontal disease, are likely to also be contributing. Mechanisms such as molecular mimicry and modification of lipids play a role; however, induction of systemic inflammation is the likely key pathogenic link by which this occurs. Treatments to reduce the presence of infection, such as antibiotics, antivirals, or dental hygiene, show potential as modifiers of cardiovascular risk in HIV-positive individuals. This review will discuss the evidence regarding the contribution of these key co-pathogens, **Chlamydia pneumoniae*****, cytomegalovirus, and hepatitis C virus, to cardiovascular risk in HIV-positive individuals. It will also review the roles that inflammation, microbial translocation, and periodontal infection play in promoting cardiovascular disease. The potential cardiovascular benefits of treating these infections with antimicrobials (such as valganciclovir) or improvements in dental hygiene (in the setting of periodontal disease) will be explored. As the life expectancy of HIV-positive individuals increases and the HIV-positive population thus ages, reducing the impact of age-related comorbidities, and particularly cardiovascular disease, will be of increasing importance at both an individual and population level.*** **(AIDS Rev. 2017;19:72-80)**

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Key words

HIV. Cardiovascular disease. CMV. Periodontitis. Hepatitis C virus. Inflammation. Coronary heart disease.

Introduction

Advances in the treatment of HIV have led to dramatic improvements in life expectancy and overall health[1].

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Yet these gains have been tempered by the discovery that HIV-positive individuals are at increased risk for non-AIDS related comorbidities, and in particular cardiovascular disease (CVD), which may occur at up to twice the rate of the general population[2]. Due to complex interactions between traditional cardiovascular risk factors, antiretroviral (ARV) side effects, and HIV-associated inflammation and immune activation, CVD is now one of the leading causes of morbidity and mortality amongst HIV-positive individuals on ARV therapy (ART)[3].

While HIV itself may be a key promoter of CVD in HIV-positive individuals, other bacterial and viral

pathogens may additionally contribute to cardiovascular risk through direct and indirect mechanisms, which increase inflammation and lead to endothelial damage.

This review will discuss the evidence regarding the contribution of key co-pathogens, *Chlamydia pneumoniae,* cytomegalovirus (CMV), and hepatitis C virus (HCV) to cardiovascular risk in HIV-positive individuals. It will also review the roles that inflammation, microbial translocation, and periodontal infection may play in promoting CVD. The potential cardiovascular benefits of treating these infections with antimicrobials (such as valganciclovir) or improvements in dental hygiene (in the setting of periodontal disease) will be explored.

Inflammation, atherosclerosis, and cardiovascular disease

Atherosclerosis is primarily a disease of inflammation, in which monocytes and T-cells interact with endothelial cells and plasma lipids to promote the formation of fatty streaks and subsequent progression to atherosclerotic disease[4]. HIV is associated with chronic inflammation, reflected in elevated levels of inflammatory biomarkers such as high-sensitivity C-reactive protein (hsCRP) and interleukin (IL)-6, both of which have been associated with cardiovascular events in the general population and HIV-positive individuals[5]. The proposed causal link between inflammation and CVD is strengthened by the finding that other chronic inflammatory conditions, such as rheumatoid arthritis, are also associated with elevated rates of CVD[6]. In patients with rheumatoid arthritis, the use of disease-modifying anti-rheumatic drugs lowers the risk of cardiovascular events, presumably by decreasing disease-related inflammation[7]. While cardiovascular risk does decrease with successful ART, in many settings it does not return to that of the general population[8]. This is partly explained by the finding that the inflammation and immune activation associated with HIV persists in the setting of viral suppression[9], but there is also increasing evidence that bacterial and viral coinfections are contributing significantly to systemic inflammation and subsequent cardiovascular risk.

Microbial translocation and inflammation

Acute HIV infection leads to a loss of mucosal integrity and CD4$^+$ T-cell depletion in the gut, allowing translocation of microbial products, such as lipopolysaccharide (LPS) derived from gram-negative bacterial cell walls, into the systemic circulation[10]. Lipopolysaccharide is a potent immunostimulatory product, which interacts with macrophages to promote oxidation of low-density lipoprotein (LDL) cholesterol and dendritic cells to promote production of tissue necrosis factor-α (TNF-α) along with IL-6, IL-8, and IL-12 (Fig. 1)[11].

HIV-positive individuals have higher levels of LPS than uninfected controls, and the degree of endotoxemia, as measured by LPS, correlates with cardiovascular risk[12]. Initiation of ART leads to decreased but not normalized LPS levels, supporting that ongoing microbial translocation may be responsible for some of the HIV-associated inflammation that persists despite suppressive ART[10]. Persisting elevations of LPS are seen even in those individuals with restored CD4$^+$ T-cell counts, but higher LPS levels may contribute to a lower degree of CD4$^+$ T-cell restoration overall[13].

This is an evolving field of research where there is new evidence that not only microbial translocation *per se* but alterations in the intestinal microbiome may contribute to CVD[14,15]. HIV infection has been associated with significant changes in the intestinal microbiome, and these HIV-associated alterations have also been shown to be associated with arterial plaque burden, with levels of bacterial by-product trimethylamine correlating with coronary calcium score and subclinical disease in HIV-positive individuals[16,17]. Work is ongoing to examine the additional effects that ART may be exerting on intestinal flora, which may shed further light on the coupling between HIV, ART, and chronic inflammation. The impact that antibiotics and probiotics could play in this delicate balance remains to be determined.

Contribution of bacterial and viral pathogens to cardiovascular risk

A large number of bacterial and viral infections have been implicated in the pathogenesis of CVD in the general population. These may additionally modulate cardiovascular risk in HIV-positive individuals by enhancing HIV-associated inflammation and immune responses or through direct effects on the endothelium. While some, such as CMV and the oral periodontal pathogen, *Porphyromonas gingivalis,* have consistently been linked with increased cardiovascular risk, the association of others, such as HCV and *C. pneumoniae,* is more contentious[18].

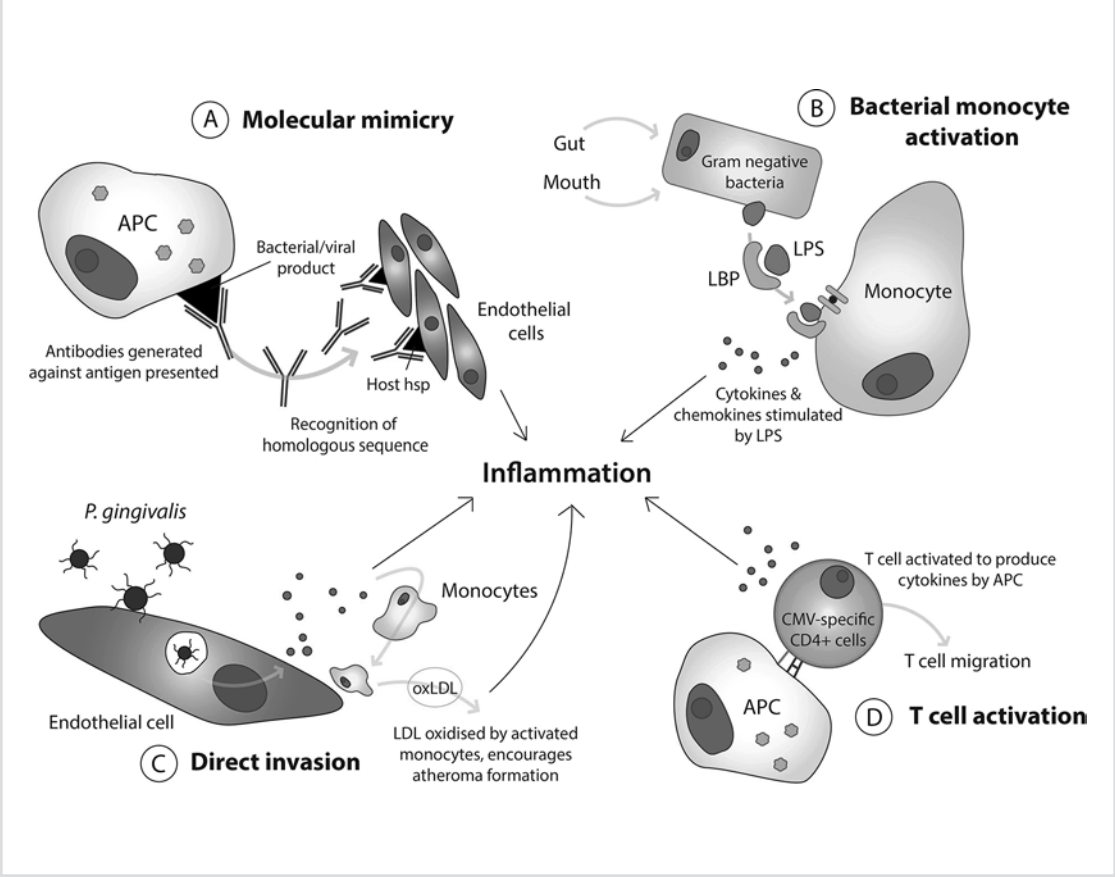

Figure 1. *Mechanisms by which bacterial and viral infections can contribute to the development and progression of cardiovascular disease.* **A:** Molecular mimicry occurs when antibodies are generated to sequences of infectious antigen, which are homologous to host cells, such as endothelial cells. These antibodies go on to bind to host cells and lead to apoptosis of cells, release of inflammatory cytokines and adhesion factors, as well as encouraging smooth muscle development. **B:** Gram-negative bacteria translocated to the bloodstream from sites such as the gut and mouth contain lipopolysaccharide in the cell wall, which activates monocytes, leading to the release of cytokines and, subsequently, inflammation. **C:** Infections such as *P. gingivalis* can directly invade host cells such as endothelial cells, activating transcription of cytokines and chemokines, causing inflammation, and attracting monocytes that can oxidize lipids and encourage atheroma formation. **D:** Infections can activate T-cells, leading to cytokine release and further trafficking of T-cells both towards and inside of atherosclerotic plaques. APC: antigen-presenting cell; CD: cluster of differentiation; CMV: cytomegalovirus; hsp: heat-shock protein; LBP: lipopolysaccharide binding protein; LPS: lipopolysaccharide; oxLDL: oxidized low-density lipoprotein; *P. gingivalis*: Porphyromonas gingivalis.

Exposure to multiple organisms appears to have a cumulative effect on the progression of atherosclerosis[19]. In comparison to individuals with antibodies to ≤ 2 pathogens, the prevalence of coronary artery disease in one study was 44% higher in those with antibodies to three or four pathogens ($p = 0.009$) and 77% higher in those with antibodies to five pathogens thought to be associated with CVD ($p < 0.0001$)[20]. These results remained significant following adjustment for traditional cardiovascular risk factors. While the effect of seropositivity to multiple pathogens has not been explicitly examined in HIV-positive individuals, this is an important area for future research, given the high rates of coinfection with CMV and HCV[21,22], among others, in HIV-positive individuals.

Cytomegalovirus

Cytomegalovirus has been causally related to accelerated atherosclerosis in transplant recipients and treatment of CMV in this setting with reduced atherosclerotic complications[23,24]. In the general population, CMV seropositivity is associated with increased all-cause mortality (HR: 1.19; 95% CI: 1.01-1.41)[25], and

in some studies has been associated with cardiovascular mortality and acute myocardial infarction[26]. However, in a number of large cohort analyses, this association with CVD was only true when accompanied by elevated inflammatory markers (such as hsCRP or IL-6)[25,27], supporting the hypothesis that the association between CMV and CVD is mediated by increased inflammation.

Cytomegalovirus DNA has been detected in the walls of atherosclerotic vessels and has been shown to induce antigen-specific T-cells, which are found in abundance within early atherosclerotic lesions[28]. These CMV-specific $CD4^+$ T-cells demonstrate increased expression of CX3CR1, a chemokine receptor that plays a prominent role in the tissue migration of T-cells. Expression of CX3CR1 by $CD4^+$ T-cells is associated with enhanced production of TNF-α and interferon-γ[29]. The CX3CR1+/CMV-specific $CD4^+$ T-cells have also been shown to promote production of CX3CL1 (the chemokine ligand of CX3XR1) by CMV-infected endothelial cells. The CX3CL1 plays a role both as a chemotactant for activated T-cells and also induces transendothelial migration of T-cells into the developing atheroma (Fig. 1). HIV infection is associated with expansion of such CMV-specific T-cells[30].

Endothelial cells activated in this way by CMV demonstrate increased uptake of oxidized LDL, expression of proinflammatory chemokines and cytokines, and affinity for platelet binding[31-33]. CMV may also promote endothelial damage without direct infection of the vessel as the result of molecular mimicry. Two CMV-derived proteins (UL122, a protein regulating viral activation, and US28, a cell surface receptor) are homologous in sequence to a portion of human heat shock protein 60 (hsp60) expressed by endothelial cells. Cross recognition of hsp60 by antibodies against UL122 and US28 leads to endothelial apoptosis, smooth muscle proliferation, and expression of adhesion factors, all key events in the pathogenesis of atherosclerosis (Fig. 1)[34].

In HIV-positive individuals, CMV infection is almost ubiquitous, with seropositivity rates of over 90% reported[22]. In HIV-positive individuals, CMV-specific T-cell responses correlate with carotid intimamedia thickness (a surrogate marker of atherosclerosis), and mean CMV IgG levels, with decreased arterial distensibility and increased prevalence of atherosclerotic lesions (Table 1)[35,36]. In a cohort of largely treated HIV-positive individuals, CMV IgG positivity was associated with serious non-AIDS events including cardio- and cerebrovascular diseases and deaths[22]. It has also been reported by one group that following adjustment for CMV-specific T-cell responses in addition to hsCRP and traditional risk factors, the association between HIV and intimamedia thickness was no longer statistically significant, lending further weight to the important contribution of CMV-specific immunity to the pathogenesis of HIV-associated CVD[35]. It is, however, important to note that traditional cardiovascular risk factors (such as cigarette smoking) may be confounding some of these findings.

Trials of the efficacy of anti-CMV medications to reduce non-AIDS diseases, including CVD, appear promising, but to date have been hampered by drug toxicities, drug-drug interactions, and the development of antiviral resistance[37]. In HIV-positive individuals, treatment of asymptomatic CMV with valganciclovir leads to reductions in hsCRP and activated T-cell numbers[38], which, for the reasons described above, may lead to reductions in atherosclerosis; however, this theoretical benefit has yet to be proven in human trials. While still in development, an effective CMV vaccine provided at an early age and at a population level has the potential to dramatically impact overall morbidity and mortality both within the HIV-positive as well as the general population[39].

Hepatitis C virus

The association between HCV and CVD (with or without coinfection with HIV) has been the focus of considerable debate, with conflicting results from a number of studies[40,41]. Given that HCV infection is present in 16-33% of HIV-positive individuals, any increase in risk attributable to HCV is likely to have significant impacts in HIV-positive individuals who are already at increased risk for CVD compared with the general population[42].

Analyses from the Veterans Ageing Cohort Study have found that HIV/HCV-coinfected patients are at increased risk for CVD compared with those infected with HIV alone (adjusted HR for CAD: 1.93; 95% CI: 1.02-3.62)[43]; however, the most recent systematic review of data from the general population found no association between HCV and CVD[44]. Supporting this, alternate analyses also based on data from American veterans demonstrated that the association between HCV and CVD was no longer significant once the impact of diabetes, hypertension, and age were controlled for (adjusted HR [HIV/HCV vs. HIV]: 1.25; 95% CI: 0.98-1.61; $p = 0.072$)[45]. The Data Collection of Adverse Events of Anti-HIV Drugs (D:A:D) study group

Table 1. Impact of coinfections on cardiovascular endpoints in HIV-positive individuals

	Author	Year	Population	(n)	CVD endpoint	Marker of infection	Association with CVD
CMV	Lichtner, et al.[18]	2015	HIV+ without CMV disease	6,111	Composite CVD endpoint*	CMV IgG seropositivity	Adjusted HR 2.27 (95% CI: 0.97-5.32; p = 0.058)
	Goulenok, et al.[73]	2015	HIV+ men, without CVD or HCV	59	cIMT	CD8+ CMV T-cell response	Adjusted partial-r 0.09; p = 0.5
	Parrinello, et al.[32]	2012	HIV+ women	644	cIMT	CMV IgG titer	-0.7 change in cIMT with every 10 IU/ml rise in IgG; p = 0.88
					Carotid artery stiffness†	CMV IgG titer	0.5 increase in stiffness with every 10 IU/ml rise (95% CI: 0.1-0.9; p = 0.02)
					Carotid distensibility	CMV IgG titer	–1.0 decrease in distensibility with every 10 IU/ml rise (95% CI: –1.7 to –0.4; p ≤ 0.01)
HCV	Zhang, et al.[74]	2015	HIV+ not on ART	12,800	Composite CVD endpoint‡	HCV RNA	RR 1.59 (95% CI: 0.39-6.57)
	Tripathi, et al.[75]	2014	HIV+	6,816	Composite CVD endpoint§	History of HCV	RR 0.55 (95% CI: 0.31-0.97; p ≤ 0.01)
	Gillis, et al.[76]	2014	HIV+ on ART without CVD	4,152	Composite CVD endpoint¶	History of hepatitis C infection‖	HR 1.44 (95% CI: 0.97-2.13; p = 0.07)
	Bedimo, et al.[41]	2010	HIV+	19,424	MI	HCV antibody	HR 1.25 (95% CI 0.98 – 1.61; p=0.072)
					Composite CVD endpoint#	HCV antibody	HR 1.20 (95% CI: 1.04-1.38; p = 0.013)
	Weber, et al.[42]	2010	HIV+	33,347	MI	HCV serology or viral load	Rate ratio 0.86 (95% CI. 0.62-1.19; p = 0.36)
	Freiberg, et al.[77]	2007	HIV+ with alcohol disorder	395	MI	HCV RNA	OR 4.65 (95% CI: 1.70-12.71)
					Composite CVD endpoint#		OR 12.86 (95% CI: 1.63-100.33)
	Tedaldi, et al.[78]	2003	HIV+	823	Composite CVD endpoint††	History of HCV infection	RR 1.15 (95% CI: 0.88-1.51; p = 0.713)
	Masia, et al.[79]	2011	HIV+ with no cardiovascular risk factor therapy	201	cIMT	HCV RNA	Difference in cIMT between coinfected and monoinfected: 0.61 mm (0.55-0.65) vs. 0.60 mm (0.53-0.72), respectively (p = 0.39)
P. gingivalis	Vernon, et al.[70]	2011	HIV+ no CVD	43	cIMT	PCR quantification from dental samples	1 $\log_{10}$ increase in *P. gingivalis* associated with 0.013 mm increase in cIMT (95% CI: 0.0006-0.0262; p = 0.04)
					FMD	PCR quantification from dental samples	FMD: 1 $\log_{10}$ increase in *P. gingivalis* not associated with change (p = 0.55)
C. pneumoniae	Maggi, et al.[56]	2006	HIV+	59	Carotid plaque on ultrasound	Antibody titer IgG, IgM, IgA	IgM not detected No association with IgG; p = 0.535 No association with IgA; p = 0.935

*Cerebrovascular disease, MI, non-MI CAD, coronary intervention, peripheral vascular disease, pulmonary hypertension; †Measured by Young's modulus; ‡Cerebrovascular disease, MI, coronary intervention, cardiac death; §Cerebrovascular disease, MI, non-MI CAD (angina), coronary intervention; ¶Cerebrovascular disease, MI, non-MI CAD, coronary intervention, cardiac death; ‖HCV antibody, viral load, genotype positivity; #Cerebrovascular disease, MI, non-MI CAD; ††MI, non-MI CAD, peripheral vascular disease, hypertension, congestive heart failure.

cIMT: carotid intimamedia thickness; CAD: coronary artery disease; CD: carotid distensibility; CVD: cardiovascular disease; FMD: flow-mediated dilation; HCV: hepatitis C virus; HR: hazard ratio: MI: myocardial infarction; OR: odds ratio; PCR: polymerase chain reaction; RR: relative risk.

have also reported no association between HCV seropositivity and acute myocardial infarction (RR: 0.86; 95% CI: 0.62-1.19) in HIV-positive individuals (Table 1)[46].

Some of the discordance in findings may be the result of unmeasured confounding due to socioeconomic and behavioral risk factors such as smoking and intravenous drug use. All such studies are limited by the use of HCV IgG positivity to indicate HCV infection, when in truth many of these patients will have cleared HCV, either spontaneously or as the consequence of successful treatment, and thus presumably are at lower risk than those with ongoing active viral replication.

Despite the conflicting clinical results, it is physiologically plausible that HCV could contribute to cardiovascular pathogenesis through potentiation of inflammation, alterations in monocyte function, or upregulation of vascular adhesion pathways.

Chronic HCV infection leads to increased monocyte responsiveness to inflammatory stimuli[47]. Monocytes from patients with HCV produce significantly higher levels of TNF-α in response to LPS and HCV core protein than do those from uninfected controls[48]. This effect is magnified by the presence of HIV coinfection, with higher IL-2 and IFN-γ produced in response to stimulatory antigens in HIV/HCV-coinfected patients when compared with patients infected with HCV alone[48]. This may partly explain why the association between HCV and CVD is most reliably detected in those with HIV coinfection. In line with this, HIV/HCV-coinfected patients have higher levels of key atherogenic biomarkers, including IL-8 and chemokine ligand-5, compared with HIV or HCV monoinfected patients[49].

HCV/HIV coinfection is also associated with increases in plasma levels of vascular adhesion molecules (soluble intercellular adhesion molecule-1 [sICAM-1] and soluble vascular adhesion molecule-1 [sVCAM-1]), which are released from damaged endothelium and have been associated with cardiovascular mortality[50,51]. Successful treatment of HCV leads to decreases in both sICAM-1 and sVCAM-1, indicating the potential for HCV treatment to reduce CVD risk[51]. Treatment of HCV has also been shown to decrease sCD163 levels, which have independently been associated with unstable coronary plaque in HIV-positive individuals[52,53].

Given the markedly improved efficacy of new direct-acting antiviral agents against HCV infection, including in the setting of HIV coinfection, it may be that any potential HCV-associated increase in cardiovascular risk will soon be a thing of the past[54].

Chlamydia pneumoniae

Chlamydia pneumoniae was one of the earliest pathogens studied in relation to CVD, with a 1988 study showing a higher prevalence of *C. pneumoniae* antibodies in patients with coronary artery disease[55]. Individuals with *C. pneumoniae* DNA detectable within plasma have been reported to have an odds ratio for CVD of 2.03 (95% CI; 1.34-3.08; $p < 0.001$)[56], although this has not been found in other trials. As described with CMV, molecular mimicry exists between chlamydial hsp and human hsp60 on endothelial cells. This could plausibly promote endothelial damage, as chlamydial hsp has been shown to localize within macrophages in atherosclerotic plaques and induce TNF production[57,58].

However, mounting evidence suggests that the impact of *C. pneumoniae* on CVD is likely minimal if present at all. While HIV-positive individuals do have a higher *C. pneumoniae* seroprevalence than population controls[59], multiple small studies show no connection between *C. pneumoniae* seropositivity and atherosclerosis in HIV-positive individuals[60]. A meta-analysis of prospective studies within the general population supports this, finding no association between *C. pneumoniae* specific IgG titer and coronary artery events (OR: 1.15; 95% CI: 0.97-1.36)[61].

Long-term treatment of chlamydia with azithromycin or gatifloxacin in patients with a first diagnosis of coronary artery disease has been shown to have no effect on secondary cardiovascular events[62,63]. It therefore appears probable that the results of earlier trials which did demonstrate an association between *C. pneumoniae* infection and CVD were affected by confounders, such as the seasonal change in myocardial infarction rates and association between cigarette smoking and respiratory infections[64], and are not reflective of a true relationship between *C. pneumoniae* infection and CVD.

Periodontal disease

Dental and cardiac infections have long been linked, with bacteremia due to oral pathogens known to be a leading cause of infective endocarditis. However, there is increasing evidence that the presence and severity of periodontal disease (a continuum of conditions that begin with dental plaque accumulation) is also associated with atherosclerotic cardiac disease[65]. While research in the field has been hampered by a lack of consensus on the most accurate means to define and

measure the condition, clinically assessed severe periodontal disease is reliably associated with an increase in cardiovascular risk[65]. It is important to note, however, that studies in the field may be limited by significant confounding effects due to the common risk factors, including cigarette smoking, diabetes, and socioeconomic status, which periodontal disease and CVD share[66].

In the setting of periodontal disease, the usual aerobic gram-positive organisms that make up the microbiome of a healthy mouth are replaced with anaerobic gram-negative organisms such as *P. gingivalis, Tannerella forsythia* and *Aggregatibacter actinomycetemcomitans*[67]. Periodontal inflammation resulting from replication of these organisms is associated with increased systemic inflammatory markers including TNF-α, hsCRP, and IL-6 and IL-8[68], and subsequent pro-atherogenic upregulation of monocyte and platelet function. *P. gingivalis*-derived LPS can cross into the systemic circulation and, as with LPS derived from lower gastrointestinal tract flora, activate macrophages and promote the release of inflammatory cytokines and oxidation of LDL cholesterol[69]. *P. gingivalis* may also contribute to CVD via direct invasion and subsequent damage of endothelial cells, which may result from transient bacteremia associated with activities such as dental trauma or tooth brushing (Fig. 1)[70,71]. As with other infections linked to CVD, molecular mimicry also plays a role in periodontal-associated cardiovascular risk, with hsp antibodies cross-reactive to both *P. gingivalis* and human hsp60 detected in patients with comorbid periodontal disease and CVD[72].

Periodontal disease is more common in HIV-positive individuals than the general population, with up to 90% of middle-aged individuals on ART experiencing moderate-to-severe disease[73]. Despite this, very little research into the impact of periodontal disease on CVD in HIV-positive individuals has been reported. A European single-center study found that the severity of clinically assessed periodontal disease, following adjustment for traditional CVD risk factors, correlated with carotid intimamedia thickness, a validated surrogate marker of atherosclerosis in HIV-positive individuals[74].

Given the strong association between gingivitis and CVD, treatment of periodontal disease by mechanical debridement of root surfaces and antibiotics as appropriate is a promising possible therapeutic approach with the potential to reduce cardiovascular risk. Cohort studies in the general population have found improvements in endothelial function and markers of inflammation (modest reductions in hsCRP) with periodontal treatment, although the degree to which this may affect incident cardiovascular events remains to be determined[75,76]. Given the high prevalence of periodontal disease in HIV-positive individuals, access to timely and appropriate periodontal treatment may be an important strategy as part of a multimodal approach to cardiovascular risk management and warrants further investigation.

Conclusion

HIV-positive individuals are at increased risk for CVD and a number of important co-pathogens, including CMV, HCV, and periodontal disease, are likely to be contributing. Mechanisms such as molecular mimicry and modification of lipids play a role, but induction of systemic inflammation is the key pathogenic link by which this occurs. Treatments to reduce the presence of infection, such as antibiotics, antivirals, or dental hygiene, show potential as modifiers of cardiovascular risk in HIV-positive individuals. Given the ageing HIV-positive population, reducing the inequity in rates of CVD between HIV-positive individuals and the general population is of increasing importance.

Declaration of interest

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