

Human Immunodeficiency Virus and Cardiovascular Disease: Revisiting the Inflammation–Thrombosis Axis

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Introduction

There are more than 37 million people living with the human immunodeficiency virus (PLWH) worldwide with an estimated 2 million new infections occurring annually. Antiretroviral medication has dramatically prolonged the life expectancy of PLWH resulting in a growing population of older PLWH. Based on recent data from the Netherlands, by 2030, 73% of human immunodeficiency virus (HIV)-positive patients will be older than 50 years of age.¹ Despite this increasing life expectancy, there is a twofold increased risk of atherosclerotic cardiovascular disease (ASCVD) and a two- to 10-fold increased risk of venous thromboembolism (VTE). The reasons for the increased risk of cardiovascular disease among PLWH are complex and multifactorial. In addition to a high frequency of traditional risk factors in PLWH, persistent inflammation and coagulopathy appear to contribute to the increased risk of ASCVD and VTE.

HIV-1 infects CD4+ cells, mainly T helper cells, but also macrophages and dendritic cells, and directly or indirectly destroys these cells leading to immune dysfunction and deficiency.² HIV is able to activate pattern recognition receptors (PRRs) that promote inflammasome activation in circulating monocyte-derived dendritic cells, human monocytes, and monocyte-derived macrophages.³ Although combined antiretroviral therapy (cART) suppresses circulating viral counts, there is no complete elimination of viral latency, chronic inflammation, or immune activation. This chronic inflammation in PLWH, despite cART with viral suppression, is probably related to increased traditional risk factors and proinflammatory lipids, certain antiretroviral combinations, low levels of viral replication, coinfection with other pathogens such as cytomegalovirus, and microbial translocation (► Fig. 1).⁴

Contributing to the proinflammatory phenotype in PLWH is lipodystrophy and adipocyte tissue dysfunction.⁵ Lipodystrophy (abnormal fat redistribution) is associated with metabolic derangements, such as dyslipidemia and insulin

resistance, and is well described following cART initiation.^{5,6} It is not clear whether a particular antiretroviral therapy drug or class of drugs is responsible for the abnormal fat accumulation since lipodystrophy appears to occur to some degree with any combination, even in patients with no prior exposure to protease inhibitors.^{7,8} Adipocyte tissue dysfunction, which is caused by both the HIV infection and certain antiretroviral agents, promotes systemic inflammation through secretion of adipokines.⁹ In addition, due to chronic viral load suppression with effective cART among PLWH, there is an increasing frequency of obesity, which promotes insulin resistance and chronic inflammation through adipocyte dysfunction and lipotoxicity.¹⁰

Thromboinflammation in PLWH

There is a bidirectional relationship between thrombosis and inflammation. Circulating monocytes and tissue macrophages are able to initiate thrombosis through expression of tissue factor (TF),^{11,12} and coagulation intermediates, such as fibrinogen, can induce and accelerate inflammation.^{13,14} Furthermore, activated platelets are an important source of proinflammatory cytokines such as interleukin-1 β (IL-1 β), supporting their role in both coagulation and inflammation.¹⁵ Since the interaction between thrombosis and inflammation is bidirectional, chronic activation of these pathways is likely to contribute to cardiovascular morbidity and mortality in PLWH.^{13,16}

Evidence for Increased Inflammation and Thrombosis in HIV

Markers of inflammation and thrombosis are frequently raised in PLWH regardless of viral suppression status, and are independently associated with increased morbidity and mortality.¹⁶

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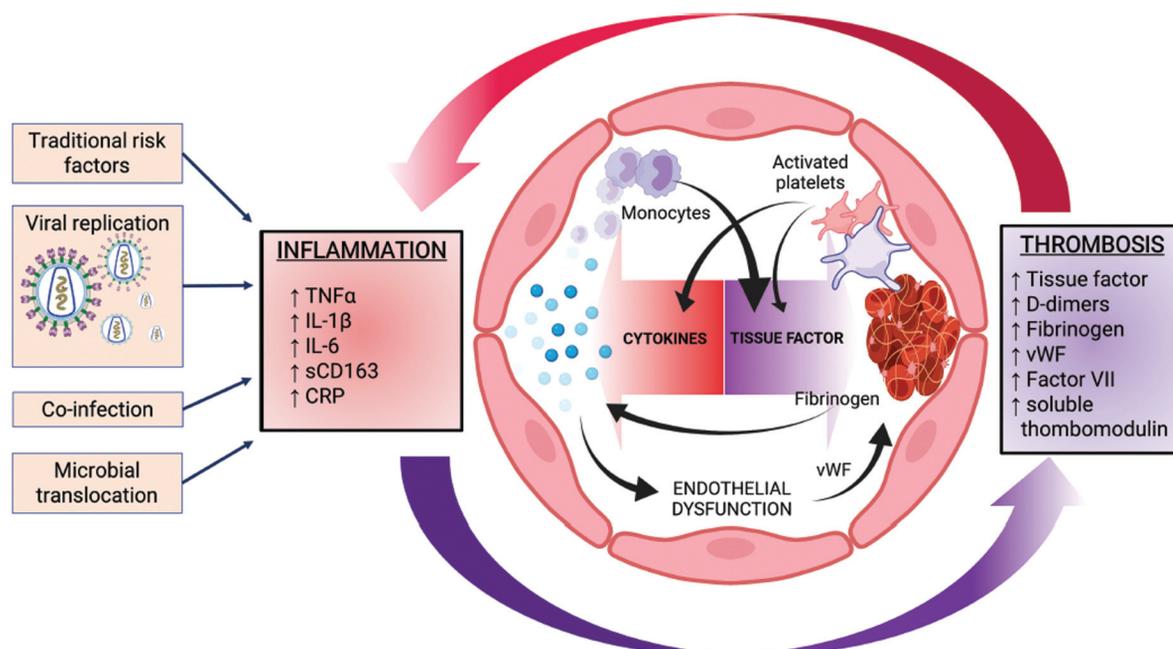


Fig. 1 Bidirectional relationship between inflammation and thrombosis in HIV-infected patients. CRP, C-reactive protein; IL-1 β , interleukin-1 β ; IL-6, interleukin 6; sCD163, soluble CD163; TNF- α , tumor necrosis factor- α ; vWF, von Willebrand factor.

Serum markers of inflammation such as IL-6, tumor necrosis factor- α 1 (TNF- α 1), and TNF- α 2, and positron emission tomography-computed tomography evidence for chronic inflammation are more prevalent in PLWH compared with HIV-negative individuals and have been shown to be associated with ASCVD.¹⁷ Soluble markers of inflammation such as sCD163 and sCXCL10, and CD14+ and CD16+ monocytes are also increased in PLWH and have been found to be independent predictors of the presence of coronary plaque.^{4,18}

These inflammatory factors increase circulating TF, which can activate the extrinsic pathway of the coagulation cascade. Expression of TF can be induced by exposure of pericytes and fibroblasts to proinflammatory cytokines and PRRs, such as toll-like receptors, and TF is also released by circulating monocytes. It has been demonstrated that the profile of monocyte activation and TF levels in uncontrolled HIV-1 infection is similar to that of non-HIV patients with acute coronary syndromes.¹⁹ This suggests that the inflammatory and thrombotic *milieu* seen in patients with an acute coronary syndrome is somewhat similar in PLWH. Abnormal elevation of D-dimers, fibrinogen, factor VII, von Willebrand factor (vWF), soluble thrombomodulin, and TF levels are common in PLWH,⁴ and are independently associated with the risk for ASCVD and VTE events.^{20,21}

Coagulopathy in PLWH

Thrombus formation requires activation of the extrinsic pathway through TF, which is expressed on all cells, or activation of the intrinsic pathway due to vessel-wall damage or endothelial dysfunction. TF expression is increased in monocytes, platelets, and plasma of PLWH,²² and is increased by several mechanisms including inflammatory cytokines

and PRRs, which are induced by HIV itself or an increase in microbial products such as lipopolysaccharide (LPS) due to microbial translocation. LPS also stimulates TF expression and increases plasminogen activator inhibitor-1, which inhibits fibrinolysis thus promoting coagulation.

Endothelial Dysfunction and Thromboinflammation in PLWH

The endothelium is the interface between circulating cells, circulating factors, and the vessel wall. Endothelial cells maintain vascular health by exerting antiplatelet, antithrombotic, and anti-inflammatory actions and therefore play a critical role in the regulation of thrombosis and inflammation.¹² Healthy endothelial cells secrete nitric oxide, which reduces adhesion molecule (P-selectin, E-selectin, vascular cell adhesion molecule-1 [VCAM-1], and intercellular adhesion molecule-1 [ICAM-1]) expression, thereby minimizing inflammatory cell attachment. In addition, the endothelium expresses many anticoagulant molecules such as thrombomodulin and TF pathway inhibitor.²³ Chronic endothelial damage reduces the anticoagulant properties of endothelial cells by reducing the bioavailability of nitric oxide amongst others.¹² The endothelium is also a major source of vWF, which mediates the initial adhesion and activation of platelets with subsequent activation of the coagulation system.¹²

PLWH are at increased risk of endothelial and coronary microvascular dysfunction, which is an independent risk factor for cardiovascular events.^{24,25} Evidence for endothelial dysfunction in PLWH has been described in several studies and is even present in young PLWH. In a prospective study of 431 youths living with perinatally acquired HIV, an increased risk of endothelial dysfunction was reported, compared with

age-matched controls, even after adjusting for physiologic differences.²⁶ In other studies in PLWH, elevated levels of markers of endothelial dysfunction including ICAM-1 and VCAM-1 have been described,^{27,28} and have been associated with thrombosis.¹⁵ The endothelial dysfunction in PLWH is likely a result of persistent inflammation, similar to other diseases associated with chronic inflammation, such as obesity, diabetes, and rheumatoid arthritis.²⁹

Platelet Activation in PLWH Contributes to Thromboinflammation

Activated platelets promote inflammation, endothelial dysfunction, and hypercoagulability, contributing to cardiovascular events.³⁰ In PLWH, platelets are activated by the HIV-1 virus itself, viral proteins or inflammatory molecules induced by HIV.¹⁵ Activated platelets in PLWH are able to form complexes with inflammatory T cells via adhesion molecules such as P-selectin.³¹ HIV-infected patients have high level of monocytes that express TF and P-selectin, increasing the risk for platelet-inflammatory cell complexes.¹⁹ Platelets are also responsible for the expression of TF, contributing to coagulation amplification. Ultimately, activation of the intrinsic and extrinsic pathways and amplification by platelet activation leads to fibrin deposition and thrombus formation, which is evidenced by an increase in plasma D-dimers.²⁰

Reducing the Risk of Inflammation and Thrombosis in PLWH

Although cART decreases markers of inflammation and coagulation, these indices often do not normalize.³² Platelet hyperactivation persists even when patients are on cART.¹⁵ Therefore, interventions to reduce inflammation and thrombosis are still being sought in this population since treatment of the persistent inflammation and immune activation may lead to a reduction in the risk of ASCVD in PLWH.³³

Drawing on the CANTOS (the Canakinumab Anti-inflammatory Thrombosis Outcomes Study) findings,³⁴ the monoclonal anti-IL-1B canakinumab reduced plasma IL-6, high-sensitivity C-reactive protein, and sCD163 after a single dose in 10 treated and suppressed HIV-infected patients.³⁵ But larger studies with longer follow-up will be required. In a phase 2 randomized, double-blind, multicenter trial in 176 PLWH at increased risk for ASCVD, low-dose methotrexate had no significant effect on endothelial function or inflammatory biomarkers, but was associated with a significant decrease in CD8+ T cells.³⁶ Several small trials are assessing the effect of antiplatelet agents on vascular surrogates, such as flow-mediated dilation. Clopidogrel has been shown to exhibit anti-inflammatory activity in addition to its antithrombotic effect in PLWH.³⁷ Other strategies such as aspirin, factor Xa antagonists, IL-6 antagonists, janus kinase inhibitors, and adenosine reuptake inhibitors have, thus far, not yielded robust data that support the use of these agents in reducing inflammation in PLWH.³³ Finally, sevelamer, a drug that lowers phosphate, has been shown to reduce factors

related to ASCVD, such as soluble TF, and low-density lipoprotein cholesterol, which may have cardiovascular benefits,³⁸ but further studies are warranted.

Conclusion

Despite viral suppression, people living with HIV on antiretroviral therapy have persistent inflammation related to several factors including traditional risk factors, adipocyte tissue dysfunction, low levels of viral replication, coinfection with other pathogens, and microbial translocation. These proinflammatory factors promote TF expression on platelets and monocytes, and promote endothelial dysfunction. This leads to a bidirectional thromboinflammatory amplification, which increases the risk of cardiovascular events such as myocardial infarction, stroke, and venous thromboembolic disease. Interventions to reduce inflammation and thrombosis in PLWH are still being actively investigated.

Conflict of Interest

None declared.

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