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NEURAL EFFECTS OF INFLAMMATION, CARDIOVASCULAR DISEASE, AND HIV: PARALLEL, PERPENDICULAR, OR PROGRESSIVE?

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Abstract

The pervasive reach of the inflammatory system is evidenced by its involvement in numerous disease states. Cardiovascular disease, marked by high levels of circulating inflammatory mediators, affects an estimated 83.6 million Americans. Similarly, human immunodeficiency virus (HIV) produces a paradoxical state of generalized immune activity despite widespread immunosuppression, and affects 35 million people worldwide. Patients living with HIV (PLWH) suffer from inflammatory conditions, including cardiovascular disease (CVD), at a rate exceeding the general population. In this combined disease state, immune mechanisms that are common to both CVD and HIV may interact to generate a progressive condition that contributes to the exacerbated pathogenesis of the other to the net effect of damage to the brain. In this review, we will outline inflammatory cell mediators that promote cardiovascular risk factors and disease initiation and detail how HIV-related proteins may accelerate this process. Finally, we examine the extent to which these comorbid conditions act as parallel, perpendicular, or progressive sequela of events to generate a neurodegenerative environment, and consider potential strategies that can be implemented to reduce the burden of CVD and inflammation in PLWH.

Keywords

inflammation; HIV; cardiovascular; cerebrovascular; AIDS; immune

INTRODUCTION

The reach of the inflammatory system into all other bodily processes is extraordinary, with evidence of inflammatory components in numerous disease states (Zhang et al., 2013), including marked detrimental effects to brain and behavior (Frank-Cannon et al., 2009; Shalev et al., 2009). Understanding the intricate overlap of inflammation within disease is critical as we have come to learn that inflammation can factor in disease initiation,

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maintenance, and progression. In a 2014 American Heart Association update, cardiovascular disease (CVD) was estimated to affect 83.6 million Americans and in 2010 it accounted for one of every three deaths (Go et al., 2014). The term ‘inflammation’ casts a long shadow in terms of CVD and contributes to disease initiation and progression from almost every angle (Libby, 2006; Zhang et al., 2013). Furthermore, the contribution of inflammation to the progression of atherosclerosis and cardiovascular events is slow and often silent leading to progressive damage that remains undetected until a subsequent event, such as stroke or heart attack, occurs (Lee et al., 2000; Bernick et al., 2001; Vermeer et al., 2007). This silent and long progression underscores the need for better disease recognition with careful consideration of inflammatory activity and highlights the potential for early intervention and therapeutic options.

The interplay of inflammation and CVD appear to be augmented in the context of human immunodeficiency virus (HIV) infection. Approximately 35 million people are infected with HIV worldwide (www.CDC.gov) and this population is increasing at a steady rate of nearly 50,000 new infections documented each year in the U.S. alone (CDC, 2012). Treatment advances have dramatically improved the prognosis for those infected with HIV. With adequate combination antiretroviral therapy (cART), people living with HIV (PLWH) have a life expectancy close to that of uninfected individuals (Samji et al., 2013), and the number of annual deaths due to acquired immune deficiency syndrome (AIDS) is beginning to decline (Murray et al., 2014). Despite these remarkable treatment advances, PLWH suffer from CVD and other inflammatory conditions more frequently than the general population (Ross et al., 2009; Gutierrez et al., 2013), leading to significant physical and economic burden (Foley et al., 2010). While some of these conditions may stem from side effects of chronic cART (Friis-Møller et al., 2003), HIV appears to generate excessive inflammation and cardiovascular complications independent of treatment (Barbaro et al., 2001; Kim et al., 2003; Singh et al., 2014). Some of the most common cardiovascular comorbidities seen in HIV – dilated cardiomyopathy, atherosclerosis, myocardial infarction, systemic and pulmonary hypertension, thrombosis and cerebrovascular damage (Barbaro et al., 2001) – are seen in both untreated patients and those receiving cART. In fact, elite controllers, defined as HIV infected patients who maintain CD4 counts and exhibit a comparatively slow progression toward AIDS without cART, have an “unexpectedly high degree” of atherosclerosis and an equally elevated degree of monocyte activation even when controlling for cART and CVD risk factors (Pereyra et al., 2012). Though low-grade viral replication may directly contribute to endothelial damage in elite controllers, data from this population illustrate a severe disconnect between CD4 count and coronary health.

In addition to these more serious cardiovascular events, PLWH might experience somatic symptoms including shortness of breath, chest pain, and fatigue as well as behavioral changes in mood and cognition including comorbid depression and anxiety (Foley et al., 2010; Schroeksnadel and Kurz, 2012) which may be linked to immune activity (see Fig. 1). The pathogenesis of CVD involves disruption of endothelial integrity, a process that both gives rise to, and is fueled further by, inflammatory cascades. This apparent enhancement of immune function is paradoxical in a disease that is known for the generation of immunosuppression (Barbaro et al., 2001); however, other disorders and diseases, such as stroke, also exhibit this shift in immune system function to a paradoxical state which causes

harm to the organism while failing to effectively ward off exogenous pathogens (Esmaeili et al., 2012; Nemeth et al., 2014). Although HIV progression leads to immunosuppression, the continuous replication of the virus also causes a state of generalized immune activation as reflected by viral load-dependent increases in the pro-inflammatory cytokines tumor necrosis factor (TNF) and interleukin (IL)-6, as well as inflammatory biomarkers such as neopterin and soluble tumor necrosis factor receptors (sTNF-R75) (Schroecksnadel and Kurz, 2012). Even when viral load is suppressed by cART, treated patients show residual levels of pro-inflammatory cytokines. Growing evidence suggests that this excessive inflammation is partially responsible for the elevated CVD risk seen in HIV.

Chronic inflammation and CVD, individually and in combination, catalyze neurodegenerative processes leading to significant impairments in neural function and behavior (Kipnis et al., 2008; Frank-Cannon et al., 2009). Inflammatory responses to an acute stress or injury are often short-lived and contained; however, chronic inflammation stemming from disease or a dysregulated system can lead to a perpetuated inflammatory response which contributes to increased transcription of inflammatory cytokines, accelerated neuronal death, and an unstable blood–brain barrier (BBB; Frank-Cannon et al., 2009; Slavich and Irwin, 2014). Similarly, the role of inflammation in almost all aspects of CVD paves the way for atherosclerosis, increased release of inflammatory markers (Libby, 2006), ischemic events (Blake and Ridker, 2002), depression (Kales et al., 2005; Nemeroff and Goldschmidt-Clermont, 2012), and dementia (Hakim, 2011; Wint, 2011). As discussed below, although initially independent, the effects of chronic inflammation and CVD likely synergistically accelerate the damaging consequences to brain functioning and behavior.

In this review, we discuss the intricate relationship of CVD and inflammation and how HIV pathology interacts with inflammation to influence CVD progression and presentation leading to neural impairment. Specifically, we outline inflammatory cell mediators that promote cardiovascular risk factors and disease initiation and detail how HIV-related proteins may accelerate this process. Finally, we examine the extent to which these comorbid conditions act as parallel, perpendicular, or progressive sequela of events to generate a neurodegenerative environment, and consider potential strategies that can be implemented to reduce the burden of CVD and inflammation in PLWH.

Before understanding the mechanisms by which inflammation, CVD, and HIV may all interact to generate a progressive condition, it is first necessary to establish a framework for consideration by reviewing each of these conditions independently.

PERIPHERAL VASCULAR DISEASE

As a disease fostered in blood vessels, it is important to acknowledge the pervasiveness of vasculature and the inflammatory markers that mediate pathology within. The peripheral vasculature is a dynamic organ system designed to deliver oxygen and nutrients to all systems while maintaining a homeostatic state. The formation of blood vessels begins early in embryonic development with vasculogenesis and angiogenesis promoting blood vessel expansion until vasculature innervates all areas of the body (Liu et al., 2011). Inflammatory cells interact with vasculature from development, aiding in the migration of angioblasts to

the sites of vasculogenesis (Schmidt et al., 2007). Once established, vessels of the body are quite ubiquitous, with an estimated length of 100,000 km, of which over 40,000 km are microvessels (Aird, 2005).

Blood vessels allow for trafficking of immune cells throughout the body and several disease states are characterized by flaws in cellular junctions that otherwise maintain a defense against pathogen leakage into the bloodstream. At these tight junctions, adherens, protein complexes that bridge the actin cytoskeletons of neighboring cells, maintain a tight linkage between endothelial cells that line the blood vessels. Within CVD, endothelial cell dysfunction precedes reductions in nitric oxide availability. Nitric oxide, a product of L-arginine and anti-atherosclerotic gas, prevents leukocyte adhesion, cellular migration, and adhesion molecule expression under normal, healthy conditions (Versari et al., 2009). In patients with HIV, systemic oxidative stress emanates from shed HIV-related proteins and contributes to increased activation of thromboxane-prostanoid receptor and endothelin 1 signaling (Wang et al., 2014). Independent of HIV, endothelial cell dysfunction within blood vessels begins the sequelae of events which provide a favorable environment for a pro-inflammatory cardiovascular state.

Several inflammatory cells are involved in the atherosclerotic process once the integrity of the endothelium has been compromised. Leukocytes begin by binding monocytes to the cellular wall. Monocytes, through the ingestion of lipids and lipoproteins, become macrophages which eventually comprise fat streaks and vessel plaques (Willerson and Ridker, 2004). In a feed-forward manner, other inflammatory cells including T cells and mast cells bind the endothelium and release factors which recruit additional inflammatory cells and initiate the migration of cytokines, chemokines, growth factors, and adhesion molecules to the site (Willerson and Ridker, 2004). Some of the most important contributing mediators of CVD initiation include monocytes, macrophages, and cellular adhesion molecules. These factors then release pro-inflammatory cytokines and chemokines, including C-reactive protein (CRP), TNF, IL-1, and IL-6 which aid in the maintenance and progression of CVD.

Monocytes are among the first inflammatory cells at the scene of a lesioned endothelium. Following monocyte differentiation to macrophages, these new cells release interferon- γ (IFN- γ), vascular cell adhesion molecules (VCAM-1), IL-8, IL-6 and matrix metalloproteinase 9 (MMP-9), among other inflammatory activators (Libby, 2006) that promote and participate in the progression of CVD. Illustrating the multi-faceted role of macrophages in the progression of CVD, these cells comprise the main component of ruptured plaques (Willerson and Ridker, 2004) and inflammatory cytokines maintain plaque instability by both preventing the formation of new collagen and promoting the destruction of existing collagen (Libby, 2006). Furthermore, the severity of CVD appears related more to the degree of inflammatory activation than the level of stenosis (Packard and Libby, 2008), suggesting that ongoing cellular activation, likely mediated by macrophages, may serve as a better predictor of CVD events than static disease state.

Intercellular Adhesion Molecule 1 (ICAM-1) and VCAM-1 proteins belong to the immunoglobulin superfamily and are expressed at low levels continually and upregulated by

in the periphery; however, in the cerebral compartment the consequences precipitate alterations in behavior and cognition.

CEREBROVASCULAR DISEASE

Cardiovascular processes are not unique to the periphery. Vascular disease in the brain is linked to a greater risk of silent strokes, focal ischemic stroke (Chen et al., 2010), an increased risk of depression (Kales et al., 2005; Santos et al., 2009) and increased incidence of mild-cognitive impairment (Grau-Olivares and Arboix, 2009), dementia (Knopman, 2007), and Alzheimer's disease (Farkas and Luiten, 2001; Purandare et al., 2012). Similar to peripheral arterial disease, cerebrovascular disease symptoms include thickening of arterial walls, microvascular lesions, and microembolic stroke (Farkas and Luiten, 2001; Vermeer et al., 2007; Chen et al., 2010). Reports of cerebrovascular disease are varied, ranging from 27% to 87% of the population over age 65 (Wong et al., 2002), underscoring the need to improve the understanding of the pathology and diagnosis of the disease.

According to the “Data collection on Adverse events of Anti-HIV Drugs” (D:A:D) study, a large prospective multi-cohort study, HIV positivity confers an increased risk for both cardiovascular and cerebrovascular disease (Friis-Møller et al., 2003). Furthermore, an additive effect of cerebrovascular disease and HIV in the brain contributes to cognitive decline, as both affect cognition as a common target. Although HIV does not readily infect neurons, it is capable of infiltrating through the BBB to cause a variety of neurotoxic consequences in the brain including excitotoxicity and excessive immune activation (Berman and Eugenin, 2012). Another such consequence is the establishment of reservoirs, or pools of latent HIV infectivity, in microglial cells, the brain's resident macrophage (Kumar et al., 2014; Le Douce et al., 2014). Microglia and macrophages play prominent roles in the advancement of HIV to the brain (Surdo et al., 2013); however, due to the relative resistance of microglia/macrophages to HIV-induced apoptosis, these reservoirs are extremely difficult to eradicate (Kumar et al., 2014). In addition, it has recently been established that HIV can infect astrocytes and although astrocytes do not support viral replication, infection impairs their function (Churchill et al., 2014). Furthermore, several proteins involved in the progression of both HIV in the brain and inflammation contributing to cardiac pathology are housed in these reservoir cells (Le Douce et al., 2014).

The clinical outcome due to viral and/or HIV protein presence in the central nervous system is a spectrum of disorders collectively known as HIV-1-associated neurocognitive disorders (HAND). While the most severe forms of HAND such as HIV-associated dementia are responsive to cART, its milder forms affecting behavior, cognition, and motor function continue to be prevalent among infected individuals. Importantly, within a cohort of PLWH, cerebrovascular risk correlated with slower processing speed, deficits in learning and memory, and impaired executive functioning, when compared to those without known cerebrovascular risk (Foley et al., 2010). Conversely, cerebrovascular risk markers associated with decreased cognitive function – including IMT and increased ophthalmic artery resistance index (OARI) – are more common in PLWH compared to seronegative controls (Butters et al., 2008; Grima et al., 2012). These data suggest that cerebrovascular disease

and HIV each exacerbate the pathogenesis of the other, to the net effect of worse cognitive outcome.

CEREBROVASCULAR IMMUNE MODULATORS

Mechanisms that underlie cerebrovascular processes mirror those of the periphery. Namely, higher levels of inflammation compounded by variations in blood flow promote the accumulation of vascular adhesion molecules, increased permeability of the BBB, cell extravasation into tissues, and the production of additional inflammatory factors. Throughout the body, blood flow and shear stress are driving factors in the localization and adherence of inflammatory cells (Turjman et al., 2014). Nowhere, however, is this more evident than in cases of aneurysm and stroke. Areas of the brain most prone to plaque or emboli formation are those at vessel bifurcations or areas of extreme curvature where blood flow is more frequently turbulent (Turjman et al., 2014). As a highly vascularized organ, the blood vessels of the brain are numerous and vary depending on the structure and metabolic needs of the tissue. Deep subcortical regions of the brain, characterized by terminal processes of microvessels, therefore, are exceedingly susceptible to rupture.

Peripheral inflammation is associated with increased inflammatory activity within the brain, and certain markers, including CRP, are associated with the future risk of stroke events and death (Blake and Ridker, 2002; Drake et al., 2011). Though little is known about how peripheral inflammatory activity contributes to neuropathology within the context of cardiovascular disease, animal models have shed light on the mediators of this relationship (Wohleb et al., 2012, 2013). Inhibition of the IL-1 receptor in a multiple sclerosis mouse model of inflammation markedly reduces overall cytokine activity including levels of VCAM-1, a significant contributor to cardiovascular disease progression (Denes et al., 2012). Similarly, in a ApoE^{-/-} rodent model, diet-induced vascular distress (atheroma) is reduced in both the periphery and the brain following IL-1r ablation (Denes et al., 2012). Finally, IL-1 knockdown in mice reduced stress-induced inflammation and the manifestation of anxiety-like behaviors, again demonstrating the influential role of inflammation within the brain (Wohleb et al., 2014). Within CVD, little evidence supports the direct correlation of central inflammatory markers and functional changes such as cognitive decline; however, cognitive decline in the context of HIV (HAND) is most closely correlated with activated microglia and infiltrating monocytes rather than with other variables such as CNS viral load (Singh et al., 2014).

COMBINED CONSEQUENCES OF CVD AND HIV: WHAT IS THE NATURE OF THE RELATIONSHIP?

Cardiac chambers are a common source of cerebral emboli and result in large vessel stroke (Ogata et al., 2011). Much research to date has focused on strokes on a grand scale; however, strokes affecting arterioles and smaller vessels that feed deep gray matter are more common than classic stroke episodes. For example, it is estimated that five silent (asymptomatic ischemic events of small vessels) occur for every one recognized clinical stroke (Dempsey et al., 2010). In such cases, patient levels of CRP are noted to be higher than patients without silent brain infarction (Hoshi et al., 2005), again implicating

inflammatory processes as a mechanism for the formation and likely rupture of microemboli. The downstream consequences of microembolic events are alarming, and much evidence to date supports the role of microvascular ischemia in changes of mood, cognition, and the severity of Alzheimer's and Parkinson's disease, to name a few (thoroughly reviewed by Taylor et al. (2013) and Nemeth et al. (2014)).

HIV can incur CVD-associated damages in the brain through several different mechanisms such as disruption of the BBB as well as direct disruption of the cerebrovascular endothelium. The former mechanism compromises BBB integrity through trafficking of infected and activated monocyte-macrophages, thus simultaneously promoting viral dissemination in the CNS (Kanmogne, 2012). Recent literature suggests additional mechanisms by which HIV can cross the BBB including more readily permeable complexes formed between activated platelets and monocytes (Singh et al., 2014). The resulting increase in permeability allows for infiltration of pro-inflammatory cytokines, thereby substantially elevating neuroinflammation. This process may become a feed-forward cycle because HIV likely acts through similar mechanisms as in the periphery to disrupt the endothelium of blood vessels in the brain. At a macro level, HIV can also cause dilatation of cerebral arteries by triggering an outward vascular remodeling of brain arteries (Gutierrez et al., 2013). Although not yet demonstrated in the context of HIV, arterial damage has been linked to changes in behavior, as evidenced from rodent models of both cardiac arrest (Neigh et al., 2009) and acute cerebral ischemia (Nemeth et al., 2012).

In addition to exerting direct effects on central blood vessels, HIV inflicts secondary damages to nearby brain tissue. White matter hyperintensities (WMHs) are lesions in the deep white matter appearing as hyperintensities on T2-weighted magnetic resonance imaging (MRI) scans, and depict areas of demyelination and mild gliosis. WMHs are thought to result from disruption of microvasculature in the brain and are predictive of an increased risk of stroke and other cerebrovascular events (Debette and Markus, 2009). Although WMHs are present in normal aging, an increase in WMHs was significantly more common among PLWH with lower CD4 count (Dooneief et al., 1996), thus suggesting that disease progression exacerbates this brain abnormality. Interestingly, a recent study by McMurtray et al. (2008) showed that among PLWH the presence of moderate WMHs was associated with decreased cortical volumes in the frontal lobes bilaterally, supporting previously determined links between WMHs and poorer performance on neuropsychological tests dependent on frontal lobe functions. Collectively, the research to date suggests that CVD and HIV bidirectionally interact to cause progressive amplification of both conditions to the ultimate deficit of cerebral health and behavior.

COMBINED CONSEQUENCES OF INFLAMMATION AND CVD: WHAT IS THE NATURE OF THE RELATIONSHIP?

The interaction of the immune system with cardiovascular processes is complex and often difficult to discern. Patients with elevated markers of inflammation are at an increased risk for both CVD and diabetes (Haffner, 2006), and cardiovascular events produce levels of circulating inflammatory cytokines elevated to a degree that resembles a “sepsis-like” state

(Adrie et al., 2002). Atherosclerotic processes stem from inflammatory activation of cellular adhesion molecules, chemokines, and cytokines. These inflammatory molecules trigger oxidative stress and the accumulation of immune cells in perivascular fat and contribute to blood pressure changes and hypertension (Schiffrin, 2014). While the inflammatory ‘activator’ of atherosclerosis remains unclear, many consider inflammation to be a response to injury. These injuries, per se, are triggered by cigarette smoking, hyperglycemia, and hypertension- and themselves comprise inflammatory processes seemingly forming a continuous loop of inflammatory activation and CVD progression (Pearson et al., 2003; Packard and Libby, 2008). Similarly, HIV presents an injury-like stimulus which triggers inflammatory sequelae (Schroeksnadel and Kurz, 2012).

Data available currently demonstrate that the influence of HIV infection on CVD and inflammation is twofold: first, HIV directly affects many of the key players involved in CVD pathogenesis at various stages, including endothelial integrity, lipid composition, coagulation, and monocyte trafficking, thus potentiating CVD-triggered inflammation. Second, the generalized state of inflammation caused by the presence of HIV and its gene products potentially perpetuates the CVD-inflammation loop by rendering some of the above-mentioned processes more likely. Even when viral load is suppressed and deleterious immune activation is reduced through the use of cART, both residual low-grade inflammation and toxic effects of cART continue to contribute to this loop. Furthermore, HIV-associated comorbidities such as drug abuse may also independently elevate inflammation and CVD risk. For example, morphine – a substance commonly abused by PLWH – accelerates neuroinflammation through enhancing vascular permeability in brain endothelial cells (Wen et al., 2011).

Research in model animal systems has helped to systematize many aspects of immune-cardiovascular process interactions. Work in a mouse model of cardiac arrest/ cardiopulmonary resuscitation (CA/CPR) demonstrates that immune challenge in the form of antigen presentation prior to CA/CPR decreased survival from the procedures and CA/CPR decreased the antibody response to subsequent exposure (Neigh et al., 2005). These findings demonstrate the bidirectional relationship under laboratory conditions: cardiovascular events lead to immune suppression and immune suppression decreases survival following cardiovascular events. Further, a rodent model of microvascular infarction demonstrates that the induction of microvascular damage, independent of classic cardiovascular risk factors, leads to increases in central and peripheral inflammation and deficits in affective behavior (Nemeth et al., 2012) underscoring that inflammatory consequences following a vascular event, alone, are sufficient to impair functionality. Due to limitations in rodent models of HIV (Brehm et al., 2013), comprehensive research on the relationship between inflammation and CVD in the context of HIV has not been completed to date; however, new rodent models are being developed and initial assessments of cardiovascular implications of HIV within rodent models have recently been published (Hansen et al., 2013). Future work should focus on the cerebral response to cerebrovascular challenges in well-accepted rodent models of HIV. Given the progressive interactions between CVD and HIV and the apparently mediating role of inflammation, understanding of the neural response to ischemia in the context of HIV will be of critical importance to adequate treatment of PLWH.

BREAKING THE REVERBERATING LOOPS

In summary, and to better illustrate the complex relationship of inflammation and CVD, inflammation can be thought of in one of two ways: first, inflammatory mechanisms may serve as the “risk factor” of atherosclerosis and progressive CVD, or alternatively, traditional cardiovascular risk factors may initially trigger the inflammatory response which then serves as a “risk marker” of CVD (Pearson et al., 2003). Though both models include inflammatory activation early in the progression of CVD, the true relationship is likely more entwined with inflammation serving as both a factor and marker of atherosclerotic processes. Once HIV is added into the equation (see Fig. 2), the virus serves as both an inflammatory and cardiovascular challenge leading to a progressive feed-forward relationship in response to the omnipresent virus which appears to have a pervasive influence even with adequate viral control. Left unchecked, this HIV-fueled undercurrent of inflammation and cardiovascular challenge catalyzes a neuroimmune response and potentially inflicts direct neural damage through cerebrovascular compromise. The initiation of neuroinflammation then likely promotes further cerebral viral entry which would lead to additional harboring of the virus and potentially increased replication establishing a third reverberating loop in this scenario. These ongoing interactions, which could each independently alter neural function and behavior, are likely to precipitate profound neural dysfunction and manifest as both affective disturbances and HIV-associated neurocognitive disorders. The progressive nature of these interactions strongly suggests that neural consequences of HIV should be prevented through early intervention focused on reducing chronic inflammation and CVD. The best practices to facilitate this intervention have not yet been established and is an area in critical need of study in order to improve the quality of life of PLWH and reduce co-morbid conditions.

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Abbreviations:

AIDS	acquired immune deficiency syndrome
BBB	blood-brain barrier
CA/CPR	cardiac arrest/cardiopulmonary resuscitation
cART	combination antiretroviral therapy
CRP	C-reactive protein
CVD	cardiovascular disease
EPCs	endothelial progenitor cells
HAND	HIV-1-associated neurocognitive disorders
HIV	human immunodeficiency virus

ICAM-1	intercellular adhesion molecule 1
IL	interleukin
IML	intima media thickness
PLWH	patients living with HIV
TNF	tumor necrosis factor
VCAM-1	vascular cell adhesion molecules
WMHs	white matter hyperintensities

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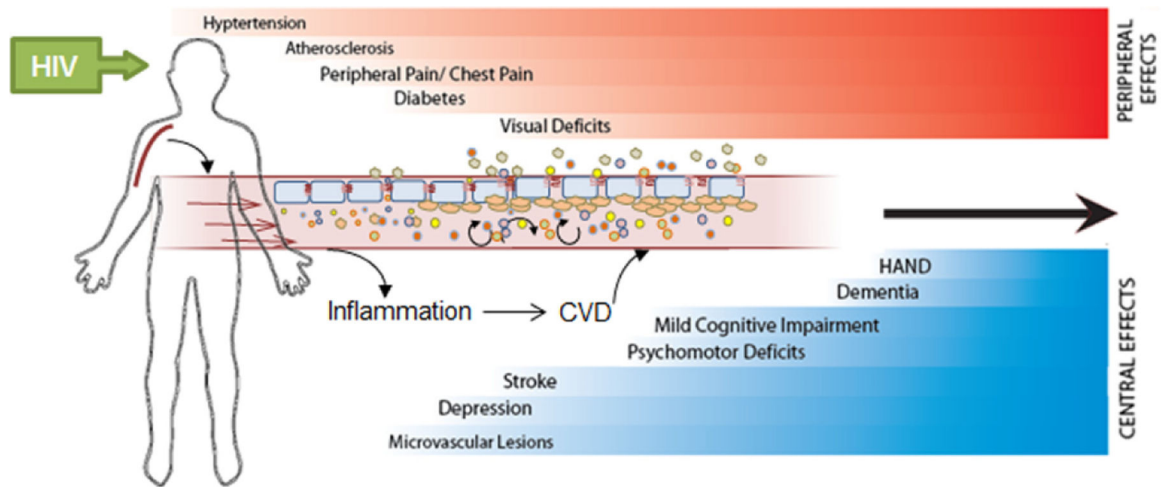


Fig. 1. Schematic depicts the timeline of somatic symptoms and cardiovascular events which occur as a result of increased inflammatory activation within peripheral and cerebral arteries. In people living with HIV (PLWH), these symptoms and events may be accelerated and exacerbated as a result of HIV-related immune activation. Together, cardiovascular disease (CVD) and HIV pathologies combine to form a progressive disease state with worsening consequences to overall health.

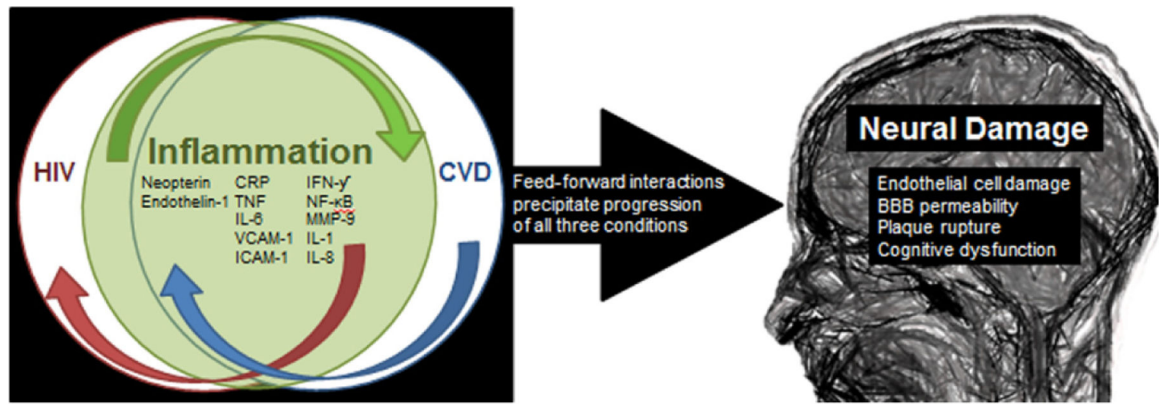


Fig. 2. The synergistic and feed-forward mechanisms of inflammatory activation within both CVD and HIV precipitate both conditions as well as the chronic inflammatory state. All three processes precipitate neural damage through endothelial cell damage, increased permeability of the blood-brain barrier, rupture of inflammatory plaques within the vessels and the development of cognitive impairment, including HIV-1-associated neurocognitive disorders (HAND).