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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.

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Key words: 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, 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

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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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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; Schroecksnadel 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.

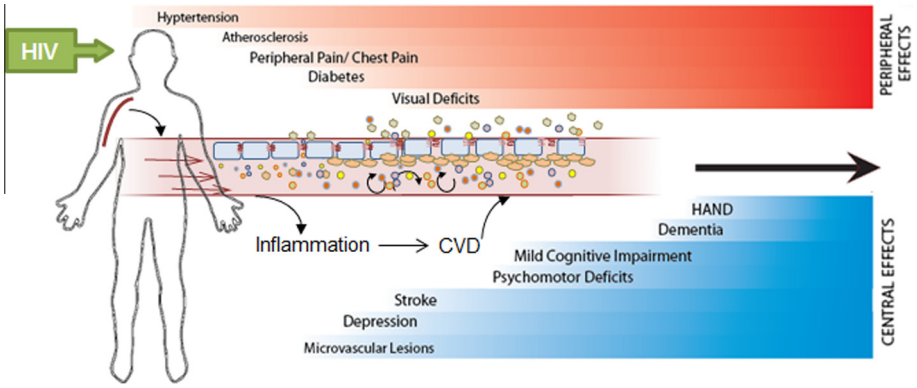

Fig. 1. Schematic depicts the timeline of somatic symptoms and cardiovascular events which occur as a result of increased inflammatory activation within peripheral and cerebral arteries. In people living with HIV (PLWH), these symptoms and events may be accelerated and exacerbated as a result of HIV-related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