Review Article

Monocytes as Regulators of Inflammation and HIV-Related Comorbidities during cART

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Received 6 March 2014; Accepted 15 May 2014; Published 12 June 2014

Academic Editor: Graham Ogg

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Combined antiretroviral therapy (cART) extends the lifespan and the quality of life for HIV-infected persons but does not completely eliminate chronic immune activation and inflammation. The low level of chronic immune activation persisting during cART-treated HIV infection is associated with the development of diseases which usually occur in the elderly. Although T-cell activation has been extensively examined in the context of cART-treated HIV infection, monocyte activation is only beginning to be recognized as an important source of inflammation in this context. Here we examine markers and sources of monocyte activation during cART-treated HIV infection and discuss the role of monocytes during cardiovascular disease, HIV-associated neurocognitive disorder, and innate immune aging.

1. Introduction

The introduction of combination antiretroviral therapy (cART) has dramatically increased survival of HIV-infected persons [1, 2]. Once only widely available in high-income countries, access to cART has steadily increased over the last decade in low- and middle-income countries where the majority of HIV-infected persons live. In 2011, for the first time cART became available to the majority (54%) of HIV-infected persons eligible for treatment in low- and middle-income countries, with the percentage of cover expected to continue to increase in the coming years [3].

Due to improved access and adherence to cART, it is predicted that most HIV-infected persons worldwide will live longer, healthier lives. However, recent observations have identified that effectively treated HIV-infected persons do not live as long as age-matched HIV-uninfected persons [4]. The cause of death for most HIV-infected persons has changed from AIDS-related opportunistic infections to chronic diseases with an inflammatory pathogenesis usually associated with the elderly [5]. The premature onset and increased risk of these inflammatory age-related diseases are associated with low levels of chronic immune activation that persist during cART treatment, a process that is believed to contribute to serious non-AIDS events (SNAEs). While most research examining chronic immune activation has focused on activation of T cells, the role of activated monocytes in promoting chronic inflammation during cART-treated HIV infection has been less thoroughly investigated.

Recent studies indicate that inflammatory mediators produced by monocytes, but not T-cell activation, predict SNAEs in virologically suppressed HIV-infected persons...
treated with cART [6, 7], demonstrating the important role of monocyte activation during cART-treated HIV infection. In these studies, the level of IL-6, a cytokine produced at high levels by monocytes that can also be produced at lower levels by other cell types in certain circumstances [8], was associated with increased odds of SNAE and death but not the percentage of activated CD4 and CD8 T cells (those expressing CD38 or CD38 and HLA-DR). These recent studies suggest that monocytes are a major source of inflammation in virologically suppressed persons treated with cART.

2. HIV Associated Comorbidities in the cART Era

Many of the diseases observed in cART-treated HIV-infected persons show similarities with chronic inflammatory disorders and diseases that predominantly occur in the elderly, such as cardiovascular disease (CVD), neurocognitive disorders, non-AIDS cancers, osteoporosis, and frailty. While the mechanisms defining these similarities have not been elucidated, it is believed that chronic inflammation, which remains a constant between these diseases, contributes to SNAEs caused by these diseases. Monocytes are chronically activated during HIV infection, and a large body of evidence now suggests that activated monocytes in the context of HIV infection are major mediators for the development of CVD, neurocognitive disorder, and aging of the innate immune system.

2.1. Cardiovascular Disease. CVD has emerged as one of the leading causes of death among HIV-infected persons in the cART era [5, 9]. HIV-infected persons are at an increased risk for developing CVD compared to HIV-uninfected controls, with HIV-infected cART-treated persons having a greater risk of developing CVD than treatment-naïve HIV-infected persons [10, 11]. The monocyte markers CD11b and CX3CR1 are associated with subclinical atherosclerosis in HIV-infected persons treated with cART [12], indicating an important role for monocytes in promoting CVD for these persons.

CVD-related deaths in the general population as well as in HIV-infected persons are attributed to underlying atherosclerosis, a disease in which monocytes play a central role. One of the earliest events in the development of atherosclerosis is mediated by activation of endothelial cells lining the wall of blood vessels [13], a process that is promoted by HIV infection [14]. Endothelial cell dysfunction leads to the recruitment and accumulation of circulating monocytes in the subendothelial lining. Once in the vessel wall, monocytes differentiate into macrophages that produce a number of proinflammatory mediators, some of which recruit additional monocytes to the lesion [15–19]. Macrophages in the vessel wall take up high levels of the cholesterol-rich particle low-density lipoprotein (LDL), causing cholesterol to accumulate under conditions of elevated LDL [20]. The accumulation of cholesterol in macrophages reduces their ability to emigrate out of atherosclerotic plaques [21] and can induce macrophage necrosis, resulting in a cholesterol-rich necrotic core that is prone to rupture and causes a deleterious clinical event [22, 23]. Elevated plasma LDL strongly predicts coronary artery disease and is the primary target for cholesterol-lowering therapies [24]. Treatment of HIV infection with cART may cause elevations in LDL-cholesterol [25–27] and can be associated with increased risk of cardiovascular disease compared to treatment-naïve and HIV-uninfected persons [10]. Certain protease inhibitors and nonnucleoside reverse transcription inhibitors are associated with elevated LDL-cholesterol, with some protease inhibitors associated with greater LDL-cholesterol elevations and risk of cardiovascular disease [10, 28, 29].

High-density lipoprotein (HDL) can remove cholesterol from macrophages using cell surface cholesterol transporters. However, during conditions of elevated LDL, as observed during cART-treated HIV infection [25–27], the rate of LDL-derived cholesterol accumulation in macrophages can be greater than cholesterol removal by HDL, resulting in net cholesterol accumulation in the vessel wall. Further favoring macrophage cholesterol accumulation, removal of macrophage cholesterol by HDL may be hampered during HIV infection, as cholesterol removal from HIV-infected human macrophages by HDL is impaired due to decreased levels and functionality of the cholesterol transporter ABCA1 [30]. Although HIV-infected macrophages within atherosclerotic plaques have been identified in HIV-infected individuals treated with cART [30], it is unclear if ABCA1-mediated cholesterol efflux from macrophages is also impaired in vivo. SIV-infected macaques fed an atherogenic diet have dysfunctional HDL that is likely mediated by nef downregulation of macrophage and liver ABCA1 [31], suggesting that inhibition of ABCA1-mediated cholesterol efflux from macrophages also occurs in vivo.

Most deaths attributable to atherosclerosis are due to thrombus formation. During cART-treated HIV infection, monocytes are chronically activated and can produce factors that stimulate thrombosis. When monocytes are activated in vitro with lipopolysaccharide (LPS), they produce microparticles that stimulate formation of the clotting factor fibrin [32]. Tissue factor is a clotting factor expressed on leukocytes that can also initiate thrombus formation. HIV-infected persons show an association between monocyte expression of tissue factor and the coagulopathy marker D-dimer [33, 34], providing evidence that monocytes may facilitate a prothrombotic environment. When peripheral blood monocyte subsets of HIV-uninfected and cART-treated HIV-infected patients with viral loads <400 copies/mL are compared, an increased percentage of nonclassical and intermediate monocytes expressing tissue factor are observed in HIV-infected patients [35]. In HIV-uninfected individuals with coronary heart disease, both nonclassical and intermediate monocyte subsets show increased platelet aggregation compared with healthy controls [36], demonstrating the prothrombotic role of these monocyte subsets.

Macrophages take up high levels of glucose in atherosclerotic plaques to facilitate the production of proinflammatory mediators [37]. In vivo plaque-resident macrophages take up the glucose imaging agent 18fluorodeoxyglucose, a process
used to identify atherosclerotic plaques with an inflammatory phenotype [37]. In HIV-infected patients treated with cART, \(^{18}\)fluorodeoxyglucose accumulates at higher levels in the ascending aorta and carotid arteries compared to HIV-uninfected controls [38, 39], with aortic uptake of \(^{18}\)fluorodeoxyglucose associated with the macrophage specific marker soluble CD163 [39]. These studies suggest that glucose uptake by macrophages may contribute to the increased cardiovascular disease risk associated with HIV-infected patients treated with cART. We recently identified intermediate (CD14++CD16+) monocytes expressing glucose transporter 1 (Glut1) as being significantly elevated in blood from HIV-infected individuals compared with HIV-uninfected individuals, regardless of cART treatment status [40]. These Glut1+ intermediate monocytes are activated [40], take up high levels of glucose [40], and retain Glut1 expression when differentiated into macrophages (Palmer CS and Crowe SM, unpublished observation). As Glut1 mRNA levels in atherosclerotic plaques predict accumulation of \(^{18}\)fluorodeoxyglucose [41], our results suggest that Glut1+ intermediate monocytes may be important mediators of cardiovascular disease.

2.2. HIV-Associated Neurocognitive Disorder. HIV-associated neurocognitive disorder (HAND) is a term that encompasses varying degrees of neurological impairment, from asymptomatic neurocognitive impairment to mild neurocognitive impairment and the most severe, HIV-associated dementia (HAD). Although cART has substantially reduced severe neurological impairment [42], milder forms of HAND continue to occur in up to fifty percent of HIV-infected persons in the cART era [42–46]. This neurological impairment persists despite virologically suppressive cART treatment and can lead to non-AIDS neuropsychiatric events even with CD4 counts >500 cells/mm\(^3\) [47].

The main HIV-infected cell type in the brain is macrophages [48, 49]. As the blood brain barrier is a highly selective barrier for solutes to traverse [50], it was initially proposed [51] and is now widely believed that HIV-infected monocytes traversing the blood brain barrier are a major source of HIV found in the brain [52]. Macrophages are in close proximity to the vasculature, and fluorescently labeled monocytes injected into acutely SIV-infected rhesus macaques accumulate in the brain and coincide with SIV detection in the brain [53].

Monocytes can remain productively infected with HIV during cART treatment [54–56] and are likely to represent a source of HIV found within the brain of HIV-infected persons treated with cART. HIV-infected monocytes that enter the brain are thought to give rise to perivascular macrophages which are commonly infected with HIV. Microglia are less commonly infected than perivascular macrophages and arise from different cell precursors [49, 57–59]. The level of HIV DNA in monocytes, but not plasma viral load or CD4 count, is associated with HAND for HIV-infected persons before and after cART treatment [60], with the association persisting at 3.5 years after cART initiation [61]. It is likely that some of these HIV-infected monocytes harboring HIV DNA could cross the blood brain barrier, contributing to the persistent presence of HIV-infected cells in the brain. As HIV-infected persons treated with cART show preferential HIV infection in CD16+ proinflammatory monocytes compared to CD16− monocytes [62], CD16+ monocytes could be a source of HIV-infected monocytes in the brain. In these experiments, T cells from PBMC were removed by magnetic beads prior to monocyte isolation, making it unlikely that T-cell contamination could explain the presence of HIV in monocytes. Although several studies suggest that HIV-infected monocytes can introduce HIV into the brain, this has not been conclusively demonstrated.

After HIV-infected persons are treated with cART, immune activation is decreased considerably but remains elevated compared with HIV-uninfected persons [63]. Activated macrophages produce the monocyte-derived immune activation marker neopterin, a molecule thought to participate in maintaining reactive oxygen and nitrogen products produced by macrophages [64, 65]. cART-treated HIV-infected persons with complete viral suppression for ≥3.5 years have elevated levels of cerebral spinal fluid neopterin compared with HIV-uninfected controls [66], indicating persistent low levels of macrophage activation in the central nervous system. Infection of monocytes with HIV or stimulation by gp120 causes monocytes to produce neurotoxic factors that interact with neuronal N-methyl-D-aspartate receptors [67, 68]. Neuronal stimulation of N-methyl-D-aspartate receptors can result in neuronal toxicity, as several HIV components can interact with neurons and cause toxicity [70–72].

2.3. Innate Immune Aging. Chronic immune activation causes monocytes to become dysfunctional and share characteristics of monocytes from the elderly. In a recent study by Martin and colleagues, proinflammatory cytokines produced by monocytes and markers of immune aging were shown to be elevated in age-matched HIV-infected women (87% of whom were receiving cART treatment) compared to HIV-infected women [73]. The levels of these cytokines and markers of immune aging were comparable to the levels seen in HIV-uninfected women 10.6–14.5 years older, demonstrating that HIV-infected persons display an aged phenotype [73].

In young HIV-infected women there are an increased proportion of CD16+ proinflammatory monocytes, similar to that observed in HIV-uninfected women 10.6 years older [73]. Young HIV-infected males, both treated and untreated, have increased plasma levels of the inflammatory biomarkers neopterin, sCD163, and CXCL10 when compared to age-matched HIV-uninfected males [74]. The levels of these inflammatory molecules in young treated and untreated HIV-infected males are comparable to the levels seen in older HIV-uninfected men, indicating that accelerated innate immune aging induced by HIV infection is not restored by cART [74]. Similar to what is seen in the elderly, monocytes in blood from young HIV-infected men have impaired phagocytosis and shortened telomeres implicating accelerated innate immune aging that might underlie the dysfunction of
monocytes in the setting of HIV infection [74]. The “aging” of monocytes during HIV infection, even during virologically suppressive cART treatment, is likely to contribute to the development of premature age-related diseases.

3. Monocyte Parameters of Systemic Inflammation

The detection of biological markers that identify cART-treated HIV-infected individuals with increased risk of comorbid disorders is useful for the management of these disorders. Recent work has identified biological markers associated with monocytes and/or macrophages that predict non-AIDS mortality.

3.1. Interleukin-6. Interleukin-6 (IL-6) is a proinflammatory cytokine produced by monocytes and macrophages during trauma, infection, and stress that instigate acute-phase protein production and inflammation [8]. Both untreated and cART-treated HIV-infected persons have elevated levels of IL-6 [63, 75], with elevated IL-6 levels associated with increased risk of all-cause mortality and death due to CVD in HIV-infected persons [34]. Monocytes from HIV-infected persons at risk for CVD produce higher levels of IL-6 compared with HIV-uninfected persons at risk for CVD [76], providing a potential explanation for the inflammatory pathogenesis and related increased CVD risk associated with HIV infection. The association of IL-6 with increased risk of CVD for HIV-infected persons is independent of other risk factors and higher levels of IL-6 are associated with a hazard ratio higher than for levels of other inflammatory markers such as hsCRP and D-dimer [77]. In addition to CVD, persons with HAND have elevated IL-6 levels in cerebral spinal fluid that remains elevated 12 weeks after initiation of cART [78]. The elevated levels of IL-6 observed during HIV infection are also observed in the elderly [79], suggesting that low levels of chronic inflammation and chronic production of IL-6 could lead to immunosenescence observed during normal aging as well as in chronic HIV infection. As lymphocytes are activated by IL-6 [80], it is possible that chronic stimulation with IL-6 could lead to immunosenescence. Consistent with this idea, elderly persons with elevated IL-6 levels have decreased responsiveness to vaccination compared to elderly persons with lower levels of IL-6 [81]. However, it is currently unresolved whether IL-6 is a cause or consequence of immunosenescence.

3.2. Soluble CD14. CD14 is a coreceptor expressed predominantly on monocytes and macrophages that together with TLR4 recognize LPS and other pathogen-associated molecular pattern molecules. After activation, monocytes produce soluble CD14 (sCD14) by enzymatic shedding of CD14 from the plasma membrane [82]. Plasma levels of sCD14 are significantly elevated in HIV-infected persons, regardless of cART treatment status, compared with healthy controls [83, 84]. The plasma level of sCD14 in HIV-infected persons is an independent predictor of mortality and correlates with levels of the inflammatory molecules IL-6, CRP, serum amyloid A, and D-dimer [85]. Plasma sCD14 levels in HIV-infected persons also correlate with carotid artery intima-media thickness (a measurement of atherosclerosis) independent of HIV infection and type of antiretroviral therapy [86]. In addition to cardiovascular disease, increased plasma levels of sCD14 have been shown to be associated with neurological impairment in HIV-infected individuals as assessed by formal neurological testing and evaluations [75]. Although sCD14 is produced by activated monocytes, hepatocytes also secrete sCD14 as an acute-phase protein [87]. Therefore, measurement of plasma sCD14 may not be an exclusive representation of the levels of monocyte activation, a factor that should be considered when utilizing this plasma marker.

3.3. Soluble CD163. CD163 is a hemoglobin scavenger receptor expressed exclusively on monocytes and macrophages. Activation of monocytes and macrophages with LPS and other stimuli causes CD163 to be shed from the cell surface in a soluble form, referred to as soluble CD163 (sCD163) [88]. As sCD163 is shed only from mononuclear phagocytes, it is a specific activation marker for these cells. Although sCD163 is associated with monocyte activation and inflammatory diseases, it has anti-inflammatory effects and is believed to be involved in resolving inflammation [88]. Compared with HIV-seronegative controls, plasma sCD163 is elevated in chronically HIV-infected persons before ART and is reduced 3 months after ART, but at levels that are elevated compared to controls [89]. Plasma sCD163 is also increased during acute HIV infection compared to HIV-seronegative controls though at lower levels than chronic infection [89]. In acutely infected patients treated with cART for three months, sCD163 levels are similar to those in HIV-seronegative controls [89], suggesting that early cART initiation can limit mononuclear phagocyte activation.

Elevated levels of sCD163 are observed in several comorbidities associated with cART-treated HIV infection. Plasma sCD163 is associated with an increased prevalence of atherosclerotic plaques in cART-treated HIV-infected persons with undetectable HIV RNA, a relationship that is not observed in HIV-negative controls matched for cardiovascular risk factors [90]. The authors suggest that activation of mononuclear phagocytes during HIV infection could cause a unique atherosclerotic plaque phenotype not observed in HIV-uninfected persons. In support of this, young (23–32 years old) HIV-infected persons show a unique atherosclerotic plaque phenotype that resembles a phenotype observed in patients that rejected cardiac transplant [91]. CART-treated HIV-infected patients with HAND have elevated levels of plasma sCD163 compared with HIV-infected controls without HAND [92], indicating an important role of activated mononuclear phagocytes during HAND. Finally, elevated levels of sCD163 occur at an earlier age in HIV-infected women than in uninfected women [73], suggesting that chronic mononuclear phagocyte activation is a mediator of immunosenescence.
4. Sources of Monocyte Activation

The source of chronic inflammation observed during cART-treated HIV infection has been an area of intense research in recent years, as it is believed to be the underlying cause for the increased risk of SNAEs that are progressively seen in clinics caring for HIV-infected persons treated with cART. Three major mechanisms have been proposed to explain the persistently high levels of inflammation in HIV-infected individual on antiretroviral treatment: (1) increased microbial translocation through the compromised intestinal mucosa, (2) residual HIV viremia, and (3) coinfection with human cytomegalovirus (HCMV) and other pathogens. Each of these mechanisms is associated with monocyte activation that is likely to contribute directly to SNAEs or indirectly by induction of innate immune aging (Figure 1). Microbial translocation, residual HIV viremia, and coinfection with pathogens may be codependent processes. For example, coinfecting pathogens and products from microbial translocation could activate HIV-infected cells to produce low levels of HIV that contribute to residual viremia present in HIV-infected persons treated with cART, and residual viremia and coinfecting pathogens could contribute to damage of the intestinal mucosa, enhancing microbial translocation.

4.1. Microbial Translocation. During acute HIV infection there is a dramatic depletion of gut CD4 T cells, resulting in increased permeability of the gut mucosal barrier that persists during chronic untreated HIV infection and also during cART treatment [93, 94]. This increased gut permeability allows bacterial components such as the Gram-negative bacterial cell wall component LPS to become elevated in the plasma of both untreated and cART-treated HIV-infected persons compared to HIV-uninfected controls [93]. Elevated plasma levels of LPS during HIV infection results in increased plasma sCD14, signifying that circulating monocytes are chronically activated by LPS [93]. This increase in sCD14 is positively correlated with LPS levels, suggesting that monocyte activation by LPS is likely responsible for sCD14 production [93]. Activation of monocytes by LPS also causes increased levels of sCD163 [88], a mononuclear phagocyte activation marker that is elevated in untreated and cART-treated HIV-infected persons compared to HIV-uninfected controls [89]. These observations indicate that microbial translocation is likely to be a key inducer of monocyte activation and chronic low level systemic inflammation observed in individuals infected with HIV.

Activation of monocytes by LPS may be exacerbated due to alterations in HDL levels that are associated with HIV infection. Plasma lipoproteins bind LPS, the majority of which is bound to HDL [95]. HDL binding of LPS neutralizes the stimulatory activity of LPS towards monocytes in vitro [96], and LPS treatment of persons with low HDL levels is associated with higher levels of inflammatory mediators compared to persons with higher HDL levels treated with LPS [97]. These data indicate that HDL can limit inflammation induced by LPS. As cART-treated HIV-infected men and certain cART-treated HIV-infected women have decreased HDL-cholesterol levels [26, 98], the level of neutralized plasma LPS may be limited in these persons.

In addition to the activation of circulating monocytes, microbial translocation induces the accumulation of proinflammatory, functionally impaired macrophages within the subepithelium of the gut in untreated HIV-infected individuals [99]. These macrophages show increased expression of proinflammatory cytokines and chemokines and are unable to phagocytose microbes or microbial products [99]. The inflammatory characteristics of these macrophages may exacerbate microbial translocation since the proinflammatory cytokines they produce can increase gut epithelial permeability and thereby allow microbes and microbial products to cross the mucosal barrier [99].
4.2. Residual HIV Viremia. The introduction of cART has resulted in frequent reduction of HIV viremia to undetectable levels as assessed by conventional techniques. The SMART study highlighted that intermittent cART resulted in elevated inflammation and higher mortality and morbidity among HIV-infected persons who ceased therapy when compared to those receiving continuous cART [34, 100]. This underscores the significance of suppressed viral replication and repression of inflammation in the management of persons infected with HIV [100].

Ultrasonic assays capable of detecting HIV in plasma at 1 copy/mL have demonstrated that low levels of HIV viremia continue to occur in individuals with virologic suppression (i.e., <50 copies/mL) during cART [101–103]. Raltegravir intensification, introduced in patients to suppress residual viremia, resulted in lower plasma levels of the inflammatory procoagulant marker D-dimer in some treated HIV-infected individuals compared to patients receiving placebo, illustrating a potential link between low level viral replication and inflammation [104]. However, residual viremia is unaffected by raltegravir intensification [105]. It therefore remains unclear if the residual viremia that occurs in virologically suppressed HIV-infected persons treated with cART is due to HIV replication or production (i.e., generation of new viruses without completion of the replication cycle) [106]. Regardless of the mechanism of residual HIV viremia, it is likely to be a chronic source of monocyte activation because many components of HIV induce monocytes to produce proinflammatory molecules [107–109].

4.3. Coinfections. Most HIV-infected persons are latently infected with HCMV and are able to effectively control this virus [2, 110, 111]. However, it is now clear that HIV-infected persons invest a considerable immune response to limit pathogenesis of HCMV even when HIV replication is controlled by cART. For example, the percentage of HCMV-specific CD8 T-cell clones in HIV-infected persons treated with cART is twice that of HIV-uninfected persons [112], indicating an important role of the cellular immune response in controlling HCMV replication. Although HCMV has a broad cell tropism, monocytes are believed to be important at disseminating HCMV to tissue as they migrate with latent virus and produce virus during differentiation [113, 114]. When infected with HCMV, monocytes become activated and proinflammatory genes are upregulated [115, 116].

HIV-infected persons treated with cART are also commonly infected with herpesviruses other than HCMV that can also establish latency. Epstein-Barr virus (EBV), human herpesvirus 8 (HHV-8), and herpes simplex virus type 1 are more commonly detected in the saliva of cART-treated HIV-infected persons compared to HIV-uninfected controls [117]. Monocytes can be infected with EBV which causes reduced phagocytic functionality [118, 119], and stimulation of monocyte TLR2 by EBV promotes induction of cytokine secretion [119]. HHV-8 can infect monocytes and macrophages and establish productive infection when stimulated with inflammatory cytokines [120–122], and HHV-8 infection induces upregulation of monocyte TLR3 and production of inflammatory cytokines [123]. HSV-1 can also infect monocytes and macrophages, which produce inflammatory cytokines when exposed to HSV-1 [124, 125]. Though not directly examined, herpesvirus coinfection is therefore likely to be a source of chronic monocyte activation in the context of cART-treated HIV infection.

5. Conclusion

With the majority of cART-eligible HIV-infected persons now receiving treatment, SNAEs have increased and are one of the greatest health concerns for HIV-infected persons. In HIV-infected persons treated with cART, monocytes are an important source of proinflammatory mediators associated with cardiovascular disease, HIV-associated neurocognitive development, and innate immune aging. It remains to be determined if monocytes are also mediators of other premature age-related diseases such as non-AIDS cancer and liver diseases that cART-treated HIV-infected persons are at an increased risk for developing. With sources of monocyte activation and identification of monocyte activation pathways emerging in recent years, therapeutically targeting sources and pathways of monocyte activation could be a useful strategy to limit immune activation associated with the premature development of age-related diseases for HIV-infected persons treated with cART.

Conflict of Interests

The authors declare that there is no conflict of interests.

Acknowledgments

The authors thank Mr. Wallace Wainhouse from NICE-Consultants.com for contribution to graphic designs. Clovis S. Palmer is funded by the Australian Centre for HIV and Hepatitis Virology Research (ACH2) and a 2010 Developmental Grant (CNHR) from the University of Washington Center for AIDS Research (CFAR), an NIH funded program under award no. AI027757, which is supported by the following NIH Institutes and Centers (NIAID, NCI, NIMH, NIDA, NICHD, NHLBI, and NIA). Clovis S. Palmer is a recipient of the CNHR and ACH2 Grant. Suzanne M. Crowe is a recipient of a National Health and Medical Research Council of Australia (NHMRC) Principal Research Fellowship. The authors gratefully acknowledge the contribution to this work by the Victorian Operational Infrastructure Support Program received from the Burnet Institute.

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