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Authors
Hsue, Priscilla Y
Deeks, Steven G
Hunt, Peter W

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Immunologic Basis of Cardiovascular Disease in HIV-Infected Adults

Priscilla Y. Hsue,[1] Steven G. Deeks,[2] and Peter W. Hunt[2]

[1]Division of Cardiology and [2]Positive Health Program, Department of Medicine, San Francisco General Hospital, University of California

Cardiovascular complications are more common in human immunodeficiency virus–infected individuals than in age-matched uninfected individuals. Antiretroviral therapy reduces the risk of cardiovascular complications, suggesting that viral replication directly or indirectly causes vascular disease. Long-term effective antiretroviral therapy does not fully restore vascular health, and treated adults continue to have higher-than-expected rates of disease progression. Although this excess risk during therapy is likely due to multiple factors, a growing body of evidence suggests that chronic inflammation, which persists during effective antiretroviral therapy, is directly and causally associated with vascular dysfunction and the accelerated development of atherosclerosis.

Most motivated adults with access to modern treatment regimens are able to achieve and maintain plasma levels of human immunodeficiency virus (HIV) RNA that are undetectable by conventional assays. Treatment-mediated suppression of HIV replication results in immune reconstitution, less morbidity, and a prolonged life span. Despite these unquestioned successes of therapy, HIV-infected adults treated with antiretrovirals have excess risk of morbidity and, perhaps, mortality [1, 2]. These complications include cancer, liver disease, renal disease, neurocognitive decline, and osteoporosis [3, 4]. Another important cause of premature morbidity and mortality appears to be cardiovascular complications [5–7]. For reasons that have not yet been fully defined, long-term–treated patients have a greater prevalence of atherosclerosis and vascular dysfunction than age-matched uninfected adults. They also have increased risk of myocardial infarction, heart failure, and other vascular diseases [8–10]. While the underlying mechanism causing the increased risk of non-AIDS complications is most likely multifactorial and includes comorbid conditions and toxicity from antiretroviral therapy [6, 11], chronic HIV-associated inflammation and immune dysfunction have emerged as key factors that are strongly linked to non-AIDS complications [12]. In this review, we focus specifically on the potential role of HIV-associated immune perturbation as a cause of premature cardiovascular disease in HIV-infected individuals.

INFLAMMATION AND CARDIOVASCULAR DISEASE

As reviewed extensively by Lo et al in this supplement of *The Journal of Infectious Diseases*, inflammation is thought to be critical in atherosclerosis at all stages of the disease process [13]. Inflammation leading to atherosclerosis can be triggered by a number of factors. For example, proatherogenic lipid particles infiltrate the arterial intima and activate endothelial cells. This in turn results in increased expression of adhesion and inflammatory molecules, which attracts inflammatory cells [14]. Lipids are then taken up by macrophages to form foam cells, which accumulate and contribute to the development of atheromas. A variety of T-cell populations migrate to these areas, leading eventually to an unstable, chronically inflamed atherosclerotic plaque. The chronic inflammatory process in the arterial wall also leads to collagen deposition, fibrosis, and wall thickening.

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Correspondence: Steven G. Deeks, MD, Division of Cardiology, San Francisco General Hospital, University of California, San Francisco, Ward 84, Bldg 80, 995 Potrero Ave, San Francisco, CA 94110 (sdeeks@php.ucsf.edu).

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A strong body of evidence from multiple cohort studies involving a wide range of patient populations without HIV infection demonstrates that markers of inflammation, particularly high-sensitivity C-reactive protein (hsCRP), are strongly predictive of cardiovascular disease events and mortality [15–19]. Targeting inflammation as a means of reducing cardiovascular disease risk was partly addressed in the JUPITER trial, which showed that treatment with rosuvastatin among healthy individuals with normal low-density lipoprotein (LDL) cholesterol and elevated hsCRP levels reduced myocardial infarction, stroke, and all-cause mortality by 44% [20]. This clinical benefit was proportional to the magnitude of hsCRP reduction, suggesting that rosuvastatin was acting partly through an anti-inflammatory mechanism [21]. Since the beneficial effect of rosuvastatin may have been mediated by changes in lipid metabolism, there is as yet no definitive evidence that reduction in inflammation leads to reduced risk of cardiovascular disease in the general population.

That inflammation may be causally associated with cardiovascular disease is also supported by consistent observation that myocardial infarctions and other vascular complications are common in patients who suffer from diseases of chronic inflammation, including rheumatoid arthritis [22].

INFLAMMATORY PLASMA BIOMARKERS PREDICT CARDIOVASCULAR EVENTS IN HIV-INFECTED ADULTS

An important step in linking HIV-associated immunologic perturbations to cardiovascular disease is demonstrating that specific markers of these pathways predict subsequent cardiovascular disease events. As might be expected, hsCRP (a nonspecific acute-phase reactant) has generally been associated with cardiovascular disease in HIV-infected adults [23], although whether the prognostic role of hsCRP in HIV-infected adults differs from that in uninfected adults is not clear [24, 25].

A unique role of inflammation in HIV disease first became evident in the SMART study. As reviewed by Triant et al in this supplement, SMART was a study comparing individuals who were randomly assigned to receive continuous antiretroviral therapy with those who were randomized to receive intermittent therapy that was based on a strategy of maintaining CD4+ T-cell counts >250 cells/mm^3. Those who received continuous treatment had a lower risk of developing cardiovascular disease [26]. Across the entire study population, elevated levels of interleukin 6 (IL-6) and D-dimers at baseline were strongly associated with a higher risk of mortality [25]. These trends were observed in the antiretroviral-treated subset. Although the number of deaths attributed to cardiovascular disease was low and hence not fully analyzed, the findings were similar to those for all-cause mortality, suggesting a potential role of these biomarkers in predicting HIV-associated cardiovascular events. Importantly, while plasma IL-6 and D-dimer levels in treated HIV-infected individuals are only marginally higher than those in HIV-uninfected individuals [27], their impact on the subsequent risk of mortality and cardiovascular disease appears to be much greater in the HIV-infected population [25]. This observation may suggest that inflammation plays a greater role in the pathogenesis of cardiovascular disease in the HIV-infected population than in the general population. Other observational studies in HIV-infected individuals have reported similar findings. For example, in the FRAM study, elevations in hsCRP and fibrinogen levels were associated with all-cause mortality (this effect was evident even in those with high CD4+ T-cell counts) [28]. A case-control study from the National Institute of Allergy and Infectious Diseases (NIAID) cohort demonstrated an association between D-dimers and vascular cell adhesion molecule 1 levels to cardiovascular disease events, but the low prevalence of cardiovascular events and heterogeneity in the study population prevented a definitive assessment of all pathways, particularly in the antiretroviral-treated population [29]. Collectively, these studies indicate that a number of inflammatory plasma biomarkers known to predict cardiovascular events in the uninfected population are elevated in treated HIV disease and also predict cardiovascular events in this setting.

To determine whether HIV infection is associated with disease independent of high-level viremia, advanced immunodeficiency, and treatment toxicity, we compared carotid intima-media thickness (IMT) in HIV-infected individuals who were able to control viral load in the absence of therapy (ie, ''elite controllers'') with that in HIV-uninfected controls. Surprisingly, the elite controllers in our cohort had a higher median carotid IMT than that observed in HIV-uninfected subjects, even after adjustment for traditional cardiovascular risk factors [30]. Interestingly, we previously found in this cohort that certain measures of inflammation and immune dysfunction, including T-cell activation and hsCRP levels, were higher in elite controllers, compared with uninfected individuals [31]. These data provide additional evidence for some HIV-associated factor (which we hypothesize to be chronic inflammation) as a causal factor in early heart disease, although it is certainly possible that some unmeasured risk factors may have explained the differences in carotid IMT.

SPECIFIC HIV-ASSOCIATED MECHANISMS MEDIATING CARDIOVASCULAR DISEASE RISK

HIV may increase cardiovascular risk through several parallel pathways, as outlined in Figure 1. We review the evidence and knowledge gaps for each of these pathways below.

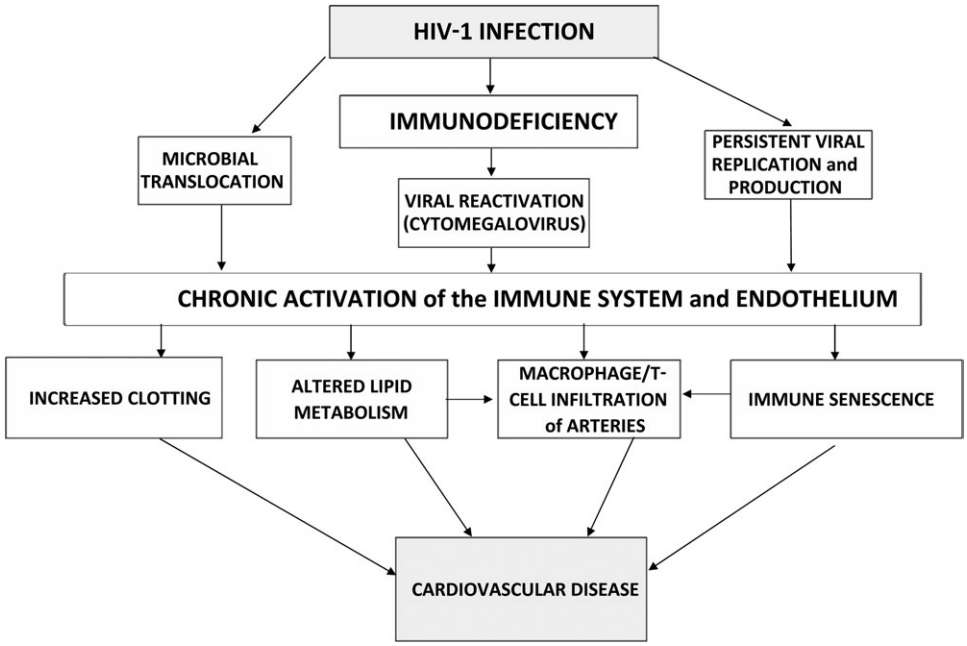

Figure 1. Human immunodeficiency virus (HIV) disease is associated with persistent inflammation. As shown in the figure, this effect is mediated via multiple pathways, including direct effect of viral replication, expanded burden of other copathogens as a consequence of immunodeficiency, loss of mucosal integrity, and chronic translocation of gut microbial products. These data, plus an emerging consensus regarding the central role of inflammation as a cause of cardiovascular disease in the general population, suggest that HIV-associated inflammation may be an important cause of the excess cardiovascular disease that has been consistently observed in HIV-infected adults. Abbreviation: HIV-1, HIV type 1.

HIV Replication

Among chronically infected individuals with early HIV disease in the SMART trial, continuous antiretroviral therapy was associated with reduced risk of cardiovascular disease as compared with delayed or intermittent therapy, suggesting that HIV replication may increase the risk for heart disease [26, 32]. The effect of HIV replication on cardiovascular disease and mortality appeared to be at least partially mediated via chronic inflammatory processes [25], although effects on lipid metabolism and other pathways are also likely [33]. Uncontrolled viral replication has also been strongly associated with vascular dysfunction in other studies [34, 35]. Collectively, these studies highlight the value of suppressive antiretroviral therapy in reducing cardiovascular risk.

If high-level HIV replication in the absence of antiretroviral therapy causes cardiovascular disease, then it is at least theoretically possible that low-level replication during effective therapy may prove to be harmful. The degree to which HIV replicates during antiretroviral therapy is controversial. The lack of HIV evolution during therapy and the inability of additional drugs to reduce residual viremia (ie, ''intensification'') argue against evolution [36–40]. However, emerging data from tissue-based studies [41] and theoretical considerations [42] argue that virus replication may persist in lymphoid tissues. The role of HIV replication and/or production as a cause of residual immune activation and cardiovascular disease will require careful investigation in the future.

CD4+ T-Cell Depletion

Perhaps the strongest evidence that immune perturbations related to HIV infection cause cardiovascular disease is the consistent association between peripheral CD4+ T-cell count and risk of an event. Since HIV disease causes CD4+ T-cell depletion, confirmation of a direct causal link between a low CD4+ T-cell count and risk of cardiovascular disease strongly suggests a central role of the immune system in this process. For example, in the FIRST study, after adjustment for risk factors, higher recent CD4+ T-cell counts were associated with lower rates of non-AIDS diseases [43]. A link between peripheral proximal CD4+ T-cell count during therapy was independently associated with incident cardiovascular disease among subjects in the HIV Outpatient Study [44] and was also associated with acute myocardial infarction among HIV-infected individuals in Boston, Massachusetts [45].

These clinical outcomes studies have been supported by studies that used surrogate markers of cardiovascular disease. In the WIHS and MACS cohorts, a recent CD4+ T-cell count <200 cells/mm^3 was associated with carotid plaque (defined as a carotid IMT >1.5 mm) [46]. Among mostly antiretroviral-treated individuals followed in earlier San Francisco–based

studies, a nadir CD4+ T-cell count ≤200 cells/mm^3 was also independently associated with carotid IMT [47]. A low peripheral CD4+ T-cell count has also been observed in some but not all studies of vascular function. For example, in a recent study performed by our group, a nadir CD4+ T-cell count <350 cells/mm^3 was strongly associated with worsened arterial stiffness [48].

Although many studies have observed a link between nadir CD4+ T-cell count and disease, exceptions to this trend exist [49], and some have argued that immune reconstitution may indeed be harmful in some clinical situations. Also, CD4+ T-cell lymphopenia may simply be a surrogate marker for some other mechanism (eg, HIV or cytomegalovirus [CMV] replication) rather than the specific immunologic mechanism driving cardiovascular disease. Indeed, increasing CD4+ T-cell counts with interleukin-2 had no effect on morbidity in mortality in the ESPRIT and SILCAAT trials [50]. Many of the persistent immunologic abnormalities in treated HIV disease are associated with lower CD4+ T-cell counts and may be more-direct mediators of cardiovascular disease in this setting, as detailed below.

T-Cell Activation

Among untreated patients, T-cell activation predicts HIV disease progression independently of viral load [51, 52]. Effective antiretroviral therapy reduces T-cell activation, but levels almost invariably remain higher than those observed in uninfected persons (particularly for the CD8+ T-cell subset) [53–55]. Emerging data suggest that the frequency of circulating activated (CD38+HLA-CR+) T cells during effective antiretroviral therapy predicts the degree of CD4+ T-cell recovery and the risk of mortality [56–58]. Whether T-cell activation is a direct mediator of or represents a marker for some other immunologic perturbation that causes morbidity and mortality in this setting is the focus of several large ongoing studies.

The impact of T-cell activation on cardiovascular disease remains undefined. In our own studies, we have found no consistent relationship cross-sectionally between frequency of activated T cells (defined on the basis of expression of HLA-DR and CD38) and either carotid IMT or endothelial function [59]. Similarly, no evidence for an association between T-cell activation and subsequent cardiovascular events was observed in a recent case-control study from the NIAID cohort [29]. In contrast to these largely negative findings, Kaplan and colleagues found that, among women in the WIHS cohort, the frequency of activated CD38+HLA-DR+ CD4+ T cells but not CD8+ T cells was associated with ultrasonographic measures of increased risk of carotid plaques and carotid artery stiffness, including decreased distensibility and increased Young's elastic modulus [60, 61]. Additional studies will be needed to confirm or refute these findings, given the divergent results from studies evaluating the role of T-cell activation and cardiovascular disease.

T-Cell Senescence

The increased risk of certain age-associated conditions among HIV-infected adults has led to a growing concern that HIV infection or its treatment might affect the aging process in a complex manner. This potential link between HIV disease and aging is controversial and limited by a lack of a consensus on how to define aging. Heart, bone, kidney, liver, and neurologic function decline with age, and the overall burden of this decline contributes to the onset of frailty and a number of other geriatric syndromes. Since organ dysfunction is more common in HIV-infected adults than in age-matched uninfected individuals, and since such organ dysfunction in some theoretical models contributes to aging [62], it is reasonable to assume that the clinical phenotypes associated with the aging process will likely emerge earlier among individuals with HIV infection than among those without infection.

Aging in HIV-uninfected individuals has been associated with several immunologic changes, including (1) increased levels of certain inflammatory biomarkers, such as IL-6; (2) reduction in the ratio of CD4+ to CD8+ T-cells; (3) decreased frequency of naive T cells; (4) decreased levels of T-cell proliferation; (5) reduced T-cell repertoire; and (6) increased frequency of oligoclonal, terminally differentiated CD8+ T cells, many of which lack CD28 and/or express CD57 (these cells are often described as being ''senescent'' and are thought to be poorly functional). This process is generally referred to as immunosenescence. Among very old individuals, many of these changes have been associated with subsequent risk of morbidity, vaccine unresponsiveness, and death. Since all of the common immunologic perturbations associated with aging can be caused by HIV infection, it is not surprising that HIV appears to cause accelerated immunologic aging [63].

Among the various markers associated with immunosenescence, the frequency of CD28− and/or CD57+ T cells has received the most attention. A high frequency of CD28− CD4+ T cells has been linked to both higher carotid IMT and worsened flow-mediated dilatation in individuals with rheumatoid arthritis [64]. The mechanism for this association is not known.

Unpublished data from our group and from others suggest that senescent T cells (defined as CD28− and/or CD57+) remain elevated in long-term–treated disease [63, 65], and most immunosenescence phenotypes tend to be highest in patients with persistently low CD4+ T-cell counts despite receipt of suppressive antiretroviral therapy [66]. In the WIHS cohort, having a higher frequency of CD28− CD57+ CD4+ and CD8+ T cells was associated with decreased carotid

distensibility [61], while a higher frequency of senescent CD8+ T cells was associated with increased prevalence of carotid artery lesions [60]. However, it is unclear whether T-cell senescence is a truly independent mediator of cardiovascular disease or whether it is simply a surrogate marker for another inflammatory mediator.

CMV Coinfection

Given the central role that chronic inflammation apparently plays in the development of atherosclerosis, there has been a long interest in the potential role of chronic proinflammatory infections in these diseases. *Chlamydia pneumoniae*, for example, was once thought to be causal, but interest in this hypothesis has waned because of negative outcomes of treatment studies [67–71]. Other than chronic HIV infection, the most well-studied proinflammatory chronic infection is that due to CMV. CMV infection elicits high levels of CMV-specific T-cell responses. In young, otherwise healthy CMV-seropositive adults, approximately 10% of CD8+ T cells are specific for this single virus [72]. The frequency of these cells increases dramatically with age and in conditions characterized by poor thymic output [73]. These cells are often CD28− and may potentially exhibit negative characteristics of "senescent cells." For reasons that are unclear, the frequency of CMV-specific T cells in untreated and treated HIV infection is dramatically increased (relative to that observed in age-matched uninfected individuals). Furthermore, treatment of CMV with short-term valganciclovir significantly reduces the excess T-cell activation associated with antiretroviral-treated HIV disease [74].

Observations in HIV-uninfected adults support the concept that CMV may also contribute to cardiovascular disease [75–78]. The effect of CMV may be more evident among individuals with immunologic disease. For example, CMV infection after transplantation is strongly associated with cardiac allograft vasculopathy [79]. Indeed, anti-CMV therapy has been proposed as a therapy to prevent adverse cardiovascular outcomes in this setting [80]. Given these observations, we hypothesized that heightened CMV-specific T-cell responses, particularly those producing the inflammatory cytokine interferon γ, may contribute to atherosclerosis in HIV-infected individuals. Indeed, higher CMV-specific T-cell responses—but not hsCRP or T-cell activation—were independently associated with greater carotid IMT ($P = .001$) [59]. This effect remained significant even after adjustment for traditional cardiac risk factors. In a well-characterized cohort in Boston, the CMV antibody levels were independently associated with the number of coronary segments with plaque [81]. More recently, investigators affiliated with the WIHS cohort found that HIV-infected women had higher CMV immunoglobulin G (IgG) antibody levels than uninfected women and that, among women with HIV infection, a higher CMV IgG antibody titer was associated with decreased carotid artery distensibility. Among women in the WIHS cohort who had undetectable HIV loads and were receiving therapy, a higher CMV IgG titer was associated with a higher risk of having subclinical carotid artery lesion [82]. These data support the intriguing possibility that an interaction between HIV-associated inflammation or immune dysfunction and chronic CMV infection drives excess inflammation and inflammation-associated disease. If this proves to be true, then the treatment of CMV might represent a therapeutic modality for decreasing cardiovascular risk, assuming that benign therapies for this infection become available.

Other common coinfections in HIV-infected individuals, including hepatitis C virus infection, have also been associated with cardiovascular disease risk in some studies [83, 84] but not others [85, 86], but whether these other infections are causally associated with cardiovascular disease or are simply surrogate markers for other cardiovascular risk factors (ie, injection drug use) remains controversial. Still, a broad consideration of all coinfections is warranted, as a higher pathogen burden (defined as the number of infectious pathogens that an individuals has been exposed to) has been independently associated with atherosclerosis [87], as well as with the risk of myocardial infarction or death [76].

Microbial Translocation

Another likely mechanism by which HIV infection causes persistent immune activation is microbial translocation. During acute HIV infection, substantial and possibly irreversible harm occurs in the mucosal barriers of the gut. HIV-mediated killing of CD4+ T cells and, perhaps, epithelial cells results in loss of mucosal integrity and persistent systemic exposure to gut luminal microbial products (the "leaky gut" syndrome) [88]. This includes lipopolysaccharide (LPS), which is known to have potent proinflammatory effects. In the context of HIV disease, LPS increases tissue factor on monocytes, which in turn may cause a procoagulant effect and increases the risk of thrombosis (D-dimer levels are elevated in HIV disease and strongly associated with morbidity and mortality) [89]. Plasma LPS levels and/or biomarkers related to LPS, such as soluble CD14, are also strong predictors of morbidity and mortality in HIV disease [90, 91].

Among individuals without HIV, exposure to LPS has harmful effects on endothelial function. Administration of endotoxin in healthy volunteers causes rapid and profound impairment of endothelium-dependent relaxation [92]; this effect is reproduced by the administration of proinflammatory cytokines commonly released by endotoxin [93]. Similarly, in a recent study of treated individuals, higher soluble CD14 was associated with a carotid IMT ≥1 mm, although there was no difference in plasma LPS level [94]. Taken together, these data suggest that, in patients with HIV infection, higher

levels of LPS may result in chronic inflammation, potentially leading to endothelial dysfunction and accelerated atherosclerosis [95]. Several planned and ongoing clinical trials are assessing interventions (ie, probiotics, bovine colostrum, hydroxychloroquine, rifaximin, and sevelamer) to reduce microbial translocation. With an effective and targeted intervention, one could begin to assess in surrogate end point trials whether microbial translocation is a cause or simply a marker of cardiovascular disease.

Immune Activation and Lipid Abnormalities

LDL cholesterol accumulates in the intima of the artery and starts the vascular inflammatory process [96]. Oxidized LDL cholesterol and turbulent blood flow occurring at vascular branch points cause expression of adhesion molecules on the endothelial surface of the artery [14, 97]; the expression of these adhesion molecules enables activated macrophages and T cells to infiltrate the arterial walls [98]. Monocytes differentiate into macrophages, which take up oxidized LDL cholesterol, forming foam cells, which is a critical step in the ultimate formation of atheromas. Proinflammatory lipids that accumulate in arterial walls can also ligate Toll-like receptors, triggering an inflammatory response [99] and eliciting both humoral and cellular immune reactions. Lipoproteins that are rich in triglycerides are associated with vascular inflammation via signaling of Toll-like receptor 2 [100]. The impact of HIV infection and HIV-associated inflammation on lipid metabolism is complex and beyond the focus of this review. It is clear, however, that HIV infection results in an altered lipid profile [101, 102], that treatment has complex direct effects on lipid levels [103, 104], and that proinflammatory and potentially harmful lipids persist during untreated and treated HIV infection [105, 106].

Monocyte Activation

Monocytes are the precursors of macrophages present in atherosclerotic lesions and produce inflammatory cytokines [107]. Monocyte turnover in HIV-infected individuals is associated with progression to AIDS [108]. Given the central role of these cells in atherosclerosis, a number of recent studies have focused on this cell population in HIV-associated cardiovascular disease. Polymorphisms in monocyte chemoattractant protein 1 were associated with higher carotid IMT among HIV-infected individuals and were associated with more-rapid carotid IMT progression [109]. Monocyte activation, as defined by plasma levels of soluble CD163 (which is a scavenger receptor released into plasma by activated macrophages), is chronically elevated in untreated and treated disease, and an elevated level of soluble CD163 is associated with noncalcified coronary plaque by computed tomography angiography among HIV-infected men [110]. In a series of ex vivo experiments, LPS was shown to activate monocytes, causing these cells to produce tissue factor, which might accelerate the formation of an acute thrombus. This conceptual model is supported by the in vivo correlations between tissue factor and D-dimers [89] and by the consistent observation that D-dimers strongly predict mortality in treated HIV disease. While the association between monocytes is likely to play a key role in HIV-associated atherosclerosis [111], the extent to which monocyte activation causes cardiovascular disease in HIV infection, independently of other inflammatory pathways, remains to be defined.

TREATMENT OF HIV-ASSOCIATED INFLAMMATION

Given the evidence linking inflammation to cardiovascular disease in HIV infection, specific anti-inflammatory therapies beyond antiretroviral therapy alone have emerged as a major treatment goal. However, as outlined above, there are several parallel immune activation and senescence pathways potentially mediating the risk of cardiovascular disease in HIV infection. A key first step in the path toward an effective intervention is to prioritize the various potential immunologic targets. This is best done in nested case-control studies assessing the relative prognostic usefulness of all the measures outlined above in predicting subsequent cardiovascular events. To date, there have been 2 such prognostic studies published [25, 29], but neither comprehensively assessed all the pathways outlined above. Both identified the coagulation marker D-dimer as a predictor of cardiovascular disease and/or death, but it remains unclear whether hypercoagulability is causally associated with cardiovascular disease or whether D-dimer is simply a surrogate marker of inflammation.

Given the low incidence of cardiovascular disease events in the HIV-infected population, these pilot clinical trials will likely need to use surrogate markers of endothelial function (eg, flow-mediated vasodilation of the brachial artery) and/or atherosclerosis (eg, carotid IMT) as primary outcome measures. Should an anti-inflammatory intervention hold promise for reducing other morbidities associated with aging, it is conceivable that these pilot clinical trials could be followed with clinical end point studies with composite end points that include events such as cancer, serious infections, bone fractures, and diabetes. It is unlikely that a clinical end point trial powered to reduce cardiovascular events alone can be conducted in the HIV-infected population in the near future.

In addition to the therapies targeting microbial translocation mentioned above, consideration should also be given to therapies used in other chronic inflammatory states, such as rheumatoid arthritis, that have been shown to reduce inflammatory markers and improve cardiovascular risk. Low-

dose methotrexate exposure is associated with a reduced risk of cardiovascular disease events and mortality among individuals with rheumatoid arthritis and psoriatic arthritis [112–117], and the CIRT study [118] will study the effect of low-dose methotrexate among high-risk individuals after myocardial infarction who have a high hsCRP level. While infectious complications are always a concern when treating HIV-infected individuals with immunosuppressive therapy, low-dose methotrexate does not appear to appreciably increase the risk of serious infectious complications in patients with rheumatoid arthritis, so this may be a reasonable intervention to pursue in carefully designed and monitored trials involving HIV-infected individuals. Last, statins should be given consideration in clinical trials of HIV-infected individuals who do not currently qualify for statin therapy on the basis of National Cholesterol Education Program guidelines. In the JUPITER study [21], rosuvastatin therapy was effective in reducing event rates and CRP, even among HIV-uninfected individuals with LDL cholesterol levels <1.8 mmol/L. While the benefits of statin therapy have not been established in HIV-infected individuals with normal LDL cholesterol levels, they have recently been shown to reduce T-cell activation in untreated HIV disease [119] and, in a recently published observational study [120], have been associated with a decreased risk of all-cause mortality in HIV-infected individuals.

CONCLUSION

While HIV-infected individuals with access to antiretroviral therapy are living longer and AIDS-defining events are much less common, these individuals remain at higher risk than the general population for non-AIDS morbidities, including cardiovascular disease. In addition to lifestyle factors and medication toxicities, persistent HIV-associated immune activation and chronic inflammation likely contribute significantly to this increased cardiovascular risk. Studies systematically assessing the relative prognostic usefulness of markers of the many immunologic pathways potentially mediating this risk will help identify and prioritize targets for novel therapeutic interventions to be tested in pilot clinical trials. Many such trials are already underway and are the first steps toward the next frontier of HIV therapy, which will include therapies to treat non-AIDS conditions such as cardiovascular disease.

Supplementary Data

Supplementary materials are available at The Journal of Infectious Diseases online (http://www.oxfordjournals.org/our_journals/jid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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