Immune Dysregulation and Vascular Risk in HIV-Infected Patients: Implications for Clinical Care

Virginia A. Triant1 and Steven K. Grinspoon2

1Division of Infectious Diseases, and 2Program in Nutritional Metabolism, Massachusetts General Hospital, Boston, Massachusetts

(See the article by Kaplan et al, on pages 452–463.)

Epidemiological data from a number of cohorts suggest increased cardiovascular disease rates among human immunodeficiency virus (HIV)–infected, compared with non-HIV-infected, patients [1, 2]. Consistent with these observations, recent data from carefully conducted studies suggest increased atherosclerotic indices, including increased carotid intima-media thickness (IMT) [3] and coronary atherosclerotic plaque burden in HIV-infected patients [4]. Elevated rates of traditional cardiovascular disease (CVD) risk factors contribute to increased risk, and individual antiretroviral medications are likely to play a role [5]. In addition, emerging evidence suggests that HIV-related inflammatory and immunologic factors also contribute substantially to cardiovascular disease among HIV-infected patients.

Interest in inflammatory and immune-mediated mechanisms for HIV-related CVD was fueled, in part, by an unanticipated result from the SMART study, which randomized patients to a viral suppression or a drug conservation group, with treatment interruption occurring at prespecified CD4+ cell counts [6]. The hypothesis of SMART was that drug conservation would minimize the toxicity of antiretroviral therapy (ART) and reduce cardiovascular and other secondary events. In contrast to the hypothesized result, the study showed increased CVD rates in the drug conservation group compared with the viral suppression group [6, 7]. These data suggest the intriguing possibility that more consistent and prolonged ART is associated with less cardiovascular disease, suggesting a benefit of treatment that outweighs cumulative toxicity. Subsequent analyses demonstrated elevated rates of several inflammatory markers in the drug conservation/treatment interruption group [8], and further investigations have revealed associations between elevated inflammatory markers and all-cause mortality in patients with HIV infection [8, 9]. More recently, several cohort studies have shown a lower CD4+ cell count to be associated with increased rates of surrogate markers of atherosclerosis or of CVD event rates [10–13], adjusting for traditional CVD risk factors. Of note, recent studies have also suggested that CVD risk remains elevated for virologically suppressed HIV-infected patients. A study evaluating carotid IMT (cIMT) found that HIV controllers—patients with plasma HIV RNA levels of <75 copies/mL in the absence of ART—had higher cIMT, a marker of preclinical atherosclerosis, compared with HIV-negative patients. These findings suggest that factors intrinsic to controlled HIV infection or its accompanying low-level viremia may confer increased CVD risk [14].

Kaplan et al [15] offer further insight into factors that might drive this increased CVD risk in this issue of the Journal. Using data from the Women’s Interagency HIV Study (WIHS), the study investigates whether CD4+ and CD8+ T cell activation (defined by co-expression of CD38 and HLA-DR) and senescence (defined by absence of CD28 and presence of CD57) are associated with subclinical carotid artery disease among HIV-infected patients. As anticipated, HIV-infected women exhibited a significantly higher frequency of activated CD4+ and CD8+ T cells and of immunosenescent CD8+ T cells, compared with HIV-negative women; there was also a trend toward increased levels of immunosenescent CD4+ T cells. Of note, levels of immune activation and senescence were higher comparing treated and virologically suppressed
HIV-infected patients to HIV-negative controls.

Among the HIV-infected group, increased levels of T cell activation (both CD4\(^+\) and CD8\(^+\)) and of CD8\(^+\) T cell senescence were associated with an increased prevalence of carotid artery lesions, defined as focal lesions >1.5 mm in thickness in any segment. These effects persisted after adjustment for age, antiretroviral medication class, HIV RNA levels, and traditional CVD risk factors. The association between carotid lesions and activated and senescent CD8\(^+\) T cells persisted after further adjustment for CD4\(^+\) cell count or CD4\(^+\)/CD8\(^+\) cell ratio, but the association with CD4\(^+\) T cell activation became nonsignificant with this adjustment. In contrast, cIMT, a more global measure of thickness measured at the common carotid artery, was not associated with T cell activation or senescence.

The findings of this study support the emerging hypothesis that links immune dysregulation with cardiovascular outcomes among HIV-infected patients. Studies have shown low CD4\(^+\) cell count to be associated with carotid artery lesions [11] and low nadir CD4\(^+\) cell count to be independently associated with increased arterial stiffness [10]. Recent studies have assessed the relationship between CD4\(^+\) cell count and cardiovascular events, demonstrating CD4\(^+\) cell counts of <200 cells/\(\mu\)L to be independently associated with myocardial infarction rates [13] and CD4\(^+\) cell counts of <500 cells/\(\mu\)L to be associated with higher odds of a combined cardiovascular endpoint [12]. The study by Kaplan et al [15] further explores the relationship of immune dysregulation and cardiovascular disease, assessing specific effects of T cell activation and senescence in relation to a surrogate index of atherosclerotic disease. Although advanced immunodeficiency in HIV infection and AIDS is increasingly recognized to be a risk factor for adverse cardiovascular outcomes, the persistently increased risk even in patients who are virologically suppressed in the periphery by standard assays and who are immune reconstituted while receiving ART (or in the absence of ART, in the case of HIV controllers) has not been fully explained. Persistent immune activation and progressive immune senescence—the immunologic hallmark of aging—may provide an explanation. Markers of both of these processes are altered, even in virologically suppressed patients, and the current study is one of the first to show a link between these specific immunologic processes with vascular disease.

Although this study provides valuable insight into HIV-related factors that might be driving the atherosclerotic process, certain questions remain. T cell activation and senescence indices were associated with carotid lesion frequency. In contrast, T cell activation and senescence were not associated with global measures of carotid thickness, measured as IMT. Further investigation is necessary to determine the clinical and physiological implications of these findings. Perhaps an association was not detected with IMT because it was measured at the right distal common carotid artery only. Indeed, studies have shown that the presence of increased IMT—particularly as related to inflammatory changes—differs depending on the region of the carotid artery studied [3]. Furthermore, progression of IMT was not investigated longitudinally, and alterations might become apparent over time with immunologic aging. The study was limited to women, and whether the interactions between T cell activation, senescence, and vascular pathology are similar for men remains unknown. Finally, it would be interesting and important to relate the changes in T cell activation and senescence to circulating inflammatory markers and to the development of clinical events in a longitudinal cohort.

How do the emerging data linking immune dysfunction to CVD risk affect clinical practice? If immune activation and senescence are linked to markers of vascular disease, it is plausible that modifying these immune alterations may decrease cardiovascular risk. The most effective and practical intervention to reduce immune activation and senescence is treating HIV infection with ART [16]. Although treating HIV infection is of obvious paramount importance to suppress viral replication and reverse immunosuppression, emerging evidence suggests that this strategy is also likely to be a critical intervention to prevent chronic complications not traditionally related to AIDS. Recent HIV infection treatment guidelines have endorsed earlier treatment of HIV infection [17, 18], and in July 2010, the International AIDS Society–USA cited cardiovascular risk as a specific reason to initiate ART in updated HIV infection treatment guidelines [19]. However, future studies are critically needed to define the mechanisms of immune-mediated cardiovascular pathology, useful markers for immune dysregulation, and the optimal timing of and goals for ART treatment with respect to CVD.

Treating with ART, however, does not reduce levels of immune activation to those of HIV-negative patients, as suggested by findings of Kaplan et al [15] and others, and patients maximally treated with ART may not be free of risk for cardiovascular disease. If persistent immune alterations drive this residual yet significant risk, can these immune alterations be further modified? Specific immunomodulatory therapies targeting microbial translocation, one of the causes thought to underlie persistent immune activation, are under active investigation [20]. Included among these are nutritional supplements that restore normal gastrointestinal flora as well as interventions aimed at restoring T-helper 17 cells, which are thought to play a role in preventing microbial translocation, to the gut-associated lymphoid tissue [20]. Strategies to control immune senescence are also being explored and include immunosuppressive drugs.
inhibitors of pro-inflammatory cytokines, and telomere-based therapies [16], but the effects of such therapies will need to be balanced against potential negative immunological effects. Indeed, this balance may be difficult to achieve.

It is important to recognize that use of ART, though potentially beneficial to improve immune- and inflammatory-related CVD risk, may still carry with it effects on traditional risk factors, such as lipids, glucose, and body composition, that need to be managed. These effects may, in part, be class-specific, but they may also relate individually to specific drugs and combinations. Modifiable risks such as hypertension, diabetes, dyslipidemia, and, particularly, smoking should be universally assessed and aggressively treated among HIV infected patients. Several studies suggest CVD risk factors are not being adequately managed among such patients [21, 22], and increased provider education and screening strategies are likely to be beneficial. Traditional risk factors are likely only a piece of the complex puzzle of vascular risk in HIV infection, yet they are factors which must be addressed.

Our understanding of cardiovascular disease among HIV-infected patients has become more sophisticated in recent years, as we begin to understand the mechanisms by which chronic infection and ongoing immune activation can contribute to CVD. Despite rigorous interventions to minimize CVD risk factors and reduce viral replication, there appear to be residual immunologic effects that confer vascular risk. Studies investigating the mechanisms of these immunologic alterations in relation to cardiovascular events and exploring therapies to modify T cell activation and senescence will advance our understanding of this complex field and help to optimize the long-term care of HIV-infected individuals.

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References