Cytomegalovirus and Immunological Aging: The Real Driver of HIV and Heart Disease?

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(See the article by Parrinello et al, on pages 1788–96.)

Numerous studies have implicated cytomegalovirus (CMV) as the smoking gun in posttransplant atherosclerosis [1, 2]. Whether CMV is related to the initial development of atherosclerosis and onset of coronary heart disease is still unclear, however. Several epidemiologic studies, along with mechanistic animal studies, suggest some role for CMV in the development of cardiovascular disease [3–6], but the search for a causal link between CMV and heart disease continues today. Research on human immunodeficiency virus (HIV) has made great strides in identifying causal relations between various infections and manifestation of chronic diseases. Ultimately, studies of the impact of HIV on coronary heart disease may be the key to identifying whether CMV is an etiologic factor in the development of cardiovascular disease.

In this issue of the Journal of Infectious Diseases, Parrinello et al. [7] take us one step closer to understanding the relationship between CMV and development of coronary heart disease. By using data from the Women’s Interagency HIV Study, Parrinello et al. [7] found that higher CMV immunoglobulin G (IgG) levels were not associated with markers of subclinical atherosclerosis among HIV-uninfected women, suggesting that increased antibody levels did not increase the risk of atherosclerosis in their HIV-uninfected subsample. In contrast, HIV-positive women with increased CMV IgG levels were more likely to have carotid artery stiffness. These same individuals did not show greater intima-media thickness nor presence of carotid lesions, indicating that the relationship between CMV IgG levels and markers of cardiovascular disease was specific for carotid artery stiffness in HIV-positive subjects. The relation between increased CMV IgG levels and carotid artery stiffness was consistent across treated/aviremic, treated/viremic, and untreated HIV-infected groups. However, when examining the association between CMV IgG levels and presence of carotid lesions by treatment/viremia status groups, Parrinello and colleagues found that CMV IgG levels were associated with presence of carotid artery lesions only among HIV-infected persons who were receiving antiretroviral treatment and were aviremic, after adjustment for age, race, and smoking history. These results suggest that treatment/viremia status modifies the impact of CMV IgG level on carotid lesions.

Why would HIV-infected women who were treated and aviremic show the most robust relationship between CMV IgG level and carotid lesions in the study by Parrinello and colleagues? One possible answer, as Parrinello et al. [7] suggest, may lie in the magnifying effects of immune restoration inflammatory syndrome from antiretroviral therapy. Immune restoration inflammatory syndrome occurs in up to 25% of HIV-infected persons after the initiation of highly active antiretroviral therapy (HAART), when there is a surge in reconstitution of effector and regulatory T cells [8]. Inflammation and T-cell activation are well established in the etiology of atherosclerosis among immunocompetent populations [9]. In HIV-positive populations, it is thought that an exacerbated tissue-specific inflammatory immune reaction may occur when CD4+ T cells are redistributed from the lymphatic tissue to the periphery are activated by presentation of antigens at sites of preexisting persistent infections, such as CMV [8]. T-cell activation, in concert with decreased ability of regulatory T cells to downregulate the consequent inflammatory response, results in immune reconstitution inflammatory syndrome in individuals who are undergoing HAART [8]. A study by Naeger et al. [10] found that CMV-specific CD8+ T cell responses among HIV-infected individuals was highest among those who had received long-term antiretroviral treatment, supporting a role for modification of the impact of CMV on subclinical atherosclerosis by HIV treatment status. Naeger
and colleagues hypothesized that an increased proportion of CMV-specific T cells in those receiving antiretroviral treatment may be due to dysregulated and/or heightened response to normal levels of subclinical CMV replication [10, 11]. In a study by Hsue et al. [12] that examined CMV-specific T-cell response and intima-media thickness among HIV-infected individuals, the relationship between HIV and carotid intima-media thickness did not remain after control for CMV-specific immune responses, suggesting that CMV specific T-cell response may be the driving force linking HIV and carotid intima-media thickness. Taken together, T-cell activation and expansion by CMV during immune reconstitution and subsequent inflammatory dysregulation may represent a pathway by which individuals who are undergoing HIV treatment and are aviremic experience accelerated detrimental effects of CMV reactivation on cardiovascular health. Earlier work [10, 12], together with the study by Parrinello et al. [7] in this issue of the Journal, suggest that CMV and possible interactions with HIV treatment may influence cardiovascular risk.

Ongoing work has implicated chronic CMV infection with immunological aging, or immunosenescence. Research has shown that T cells from immunocompetent CMV-seropositive individuals have a more differentiated phenotype and altered functional capacity. Interestingly, these signs of immunosenescence in otherwise healthy older individuals mirror changes that occur in younger HIV-infected individuals [13–16]. We recently demonstrated an association between CMV IgG antibody level and T-cell markers of aging in a cohort of adults ≥18 years of age in the Detroit Neighborhood Health Study [17]. In our study, increased CMV IgG level was associated with increased proportions of CD28–, CD27–, CD57+, and KLRG1+ T cells. Of note, Kaplan et al. [18, 19] have shown that the expansion of CD28– and CD57+CD28– T cells has been implicated in cardiovascular disease in HIV-positive populations. In our study, the association between CMV IgG levels and immune parameters of aging were observed even after adjustment for chronological age, medication status, and seropositivity to herpes simplex virus 1 (HSV-1). The relationship between CMV and T-cell markers of aging appears specific, as HSV-1, another herpesvirus, was not significantly associated with any of the T-cell markers in our work. Similarly, Parrinello and colleagues demonstrated that their observed relationships were specific only to CMV and not to another herpesvirus, Epstein-Barr virus, further strengthening evidence of a CMV-specific response. Together, these findings lend support to the role of CMV infection in both accelerated immunological aging and cardiovascular disease [7, 17–19].

Although Parrinello et al. [7] did not find a relationship between CMV and their outcomes among HIV-uninfected subjects, a relationship between CMV and cardiovascular outcomes has been noted in general population-based samples in our work and work by others [5, 6, 20]. The relationship between CMV and cardiovascular disease identified in population or community-based samples has predominantly been shown among older individuals, whereas the subgroup of HIV-uninfected subjects in the study by Parrinello et al. were younger [7]. Therefore, statistical power to identify significant strata specific effects of CMV on cardiovascular health in a relatively young HIV-uninfected subgroup sample may have been limited in their study. If CMV contributes to immunological aging, as hypothesized, and if HIV augments the CMV contribution or independently contributes to immunological aging, then comparing the effect of CMV IgG titer on cardiovascular health across strata of HIV status, among individuals of the same chronological age may be equivalent to comparing older subjects in one strata with much younger subjects in the other strata, based on their immunological age. Identification of the ideal comparison group for these analyses is not straightforward and will require further studies of the correlation between chronological age and immunological parameters of aging in response to CMV in HIV-positive and negative populations. Such studies will allow researchers to identify how parameters of immunological aging covary with chronological age.

Given that CMV has been implicated in cardiovascular disease and immunological aging in immunocompetent populations and that HIV/CMV coinfection is highly prevalent [21, 22], one must question whether the association between HIV infection, immunosenescence, and atherosclerosis observed in previous studies of HIV in which CMV was not assessed is largely due to CMV coinfection in these study populations [13]. While it is possible that both CMV and HIV influence immunological aging and that the effects are additive, we must also consider that CMV may be the smoking gun in immunosenescence among persons coinfected with both pathogens, increasing the rate of immunological aging and the development of chronic diseases of inflammatory etiology, especially among those undergoing HAART. Future research should aim to elucidate whether CMV or HIV is driving immunosenescence in HIV-infected individuals, as reflected by the degree of pathogen-specific T-cell differentiation and functional capacity. Clearly, an important consideration will be the timing of infection. If CMV directly influences T-cell parameters of aging, then length of chronic CMV infection before acquisition of HIV infection may determine an individual’s T-cell repertoire before acquisition of HIV and how it is shaped during HAART treatment. For example, an individual infected with CMV early in life will have had more time for CMV to undergo oligoclonal expansion, altering the balance between mature and naive T cells and skewing the T cell repertoire toward more highly differentiated
cells. Such an individual will already have experienced significant immunological aging before acquisition of HIV infection, placing them at higher risk for progression to AIDS, for development of immune reconstitution inflammatory syndrome during HAART, and for increased CMV-specific T-cell responses, all of which appear to increase the risk for cardiovascular disease. Future studies that assess timing of CMV and HIV acquisition and monitor changes in markers of immunological aging over time are needed to clarify how timing and duration of CMV infection impact immune parameters and the development of CVD in HIV-infected individuals undergoing HAART. Moreover, further research is needed to identify whether treatment and control of HIV infection leads to aberrant control of CMV, such that it results in a chronic persistent subclinical reactive state that incites inflammation among aviremic individuals treated for HIV infection, as hypothesized by Parrinello et al. Overall, results from Parrinello and colleagues, along with those in a growing literature supporting a role of CMV in immunological aging, inflammation, and cardiovascular disease, suggest that further research on the immunologic and epidemiologic characteristics of CMV in HIV-infected and HIV-negative populations is crucial [7, 10, 17–19].

**Note**

*Potential conflicts of interest.* All authors: No reported conflicts.

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Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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