Inflammation and Complications of HIV Disease

Michael P. Dubé and Fred R. Sattler
Department of Medicine and Division of Infectious Diseases, Keck School of Medicine, University of Southern California, Los Angeles

(See the article by Neuhaus et al, on pages 1788–1795, and the article by Kalayjian et al, on pages 1796–1805.)

It is becoming increasingly clear that even prolonged effective antiretroviral therapy (ART) may not repair all the damage done by human immunodeficiency virus (HIV) infection. As treating clinicians, we may tell patients that their disease, which previously was associated almost universally with a progressively fatal downhill course, can now effectively be considered to be in remission when their viral loads become undetectable and their CD4 cell counts improve, often to a reasonable or even normal range. We may even say that so long as patients do as they are told, they really should be fine. All they need to do is take all their pills; use condoms, sunscreen, and seat belts; quit smoking; eat 5 servings of fruits and vegetables per day; and exercise. However, there are a number of adverse outcomes associated with inflammation that initially may improve with effective ART but then may fail to normalize or may recur; in addition, other complications may appear later. Examples of such complications include changes in subcutaneous fat, muscle wasting, opportunistic infections, neurocognitive dysfunction, cancers, increased coagulability, impaired endothelial function [1], low levels of high-density lipoprotein cholesterol [2], and increased risk of cardiovascular disease in association with certain ART components [3].

In this issue of the Journal, Neuhaus et al [4] and Kalayjian et al [5] contribute to our understanding of the relationships of HIV infection, inflammation, and complications of chronic HIV infection. In a carefully performed comparison of HIV-infected participants without advanced HIV disease and population-based controls unlikely to have HIV infection, investigators from the Strategies for Management of Anti-Retroviral Therapy (SMART) study reported increased levels of inflammatory biomarkers in association with HIV infection [4]. These biomarkers included high-sensitivity C-reactive protein, interleukin (IL)–6, and D-dimer, the levels of which were measured in the same central laboratory. Statistical adjustment for key covariates failed to attenuate the relationship between the inflammatory biomarkers and HIV infection, when compared with the ostensibly noninfected controls in the Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Development in Young Adults (CARDIA) cohorts. Although their role in the causal pathway of cardiovascular disease may be subject to debate, these markers have been associated with adverse clinical outcomes, such as cardiovascular disease, diabetes, and death, in HIV-uninfected populations [6, 7]. Thus, elevated levels of these markers/mediators represent an important potential explanatory variable in understanding the increased incidence of complications related to chronic inflammation among HIV-infected persons.

As reported in previously published research from this group [8], and consistent with findings for other cohorts, increased levels of these biomarkers were associated with both all-cause mortality and cardiovascular disease events in HIV-infected participants. Moreover, among those assigned to have CD4 cell-guided treatment interruption, IL-6 and D-dimer levels changed in an unfavorable direction with treatment interruption. These increases in both IL-6 and D-dimer levels were particularly marked in the large subgroup receiving ART who had suppressed HIV RNA levels at study entry [8], and higher biomarker levels were associated with greater increases in HIV RNA levels. These findings provide a rationale to study the use of ART or other anti-inflammatory interventions to modify cardiovascular disease risk and other complications that may be associated with chronic inflammation.

Although improvement of biomarker levels with ART is encouraging, crucial to the understanding of long-term prognosis is the observation of failure of inflammatory biomarker levels to normalize with prolonged ART. In the current investigation of the SMART cohort, even with viral suppression (de-
fined by an HIV RNA level <400 copies/mL), these biomarkers were elevated compared with levels in age and sex-matched HIV negative controls [4]. Although this study did not evaluate changes over time, there was no trend for more-favorable levels of high-sensitivity C-reactive protein, IL-6, or D-dimer among subjects receiving prolonged ART at the time of study entry. Thus, we are again left with the dilemma of a short-term improvement but a failure to normalize in spite of years of receipt of ART.

The study by Kalayjian et al [5] addresses a different question in a more advanced, initially ART-naive population. This study provides preliminary insights into how baseline pre-ART levels of the proinflammatory mediators soluble tumor necrosis factor receptor–1 (sTNFR-1), sCD27, sCD40L, and IL-6 may be associated with HIV complications, including opportunistic infections plus death, and independently with malignancies or death after initiation of effective ART.

Nearly one-half of the opportunistic infections occurred in the first 2 months, before complete viral suppression would have occurred. It is possible that a sizable portion of the baseline inflammation measured before receipt of highly active antiretroviral therapy was associated with subclinical manifestations of these imminent comorbid events, thus limiting the usefulness of baseline levels in predicting events occurring substantially later during treatment. It would have been helpful to examine outcomes if opportunistic infections diagnosed in the first 4–8 weeks after initiation of ART were censored. If the relationship persisted, this would have provided compelling evidence that attenuation of inflammation or immune activation, as is expected to occur with effective ART [9], was not primarily operative, and that other immunopathogenic mechanisms or pathways were responsible for these later complications. In this context, a major limitation of the study, as acknowledged by the authors, is that these mediators were not measured at serial time points after ART was initiated, which makes it difficult to understand the ultimate relationship of mediators to complications occurring later in the course of HIV infection. Indeed, the fact that these events were not associated with the incident HIV load at their occurrence suggests that there probably was substantial attenuation in inflammation, which up-regulates HIV replication via nuclear translocation of nuclear factor–κB [10].

Of particular interest and importance was the observation that, in models that excluded opportunistic infections, the occurrence of malignancies or death was still associated with levels of the same inflammatory markers at baseline. These malignancies or death occurred at a median time of 51 weeks after initiation of ART, and CD4 cell counts demonstrated an average increase to >200 cells/mm3. Again, we do not know the levels of inflammatory mediators at these later time points. It is possible that such malignancies are merely a consequence of generalized, impaired immune surveillance not directly related to suppression of HIV load and enhancements in circulating CD4 cell counts, because patients were still immunocompromised despite their response to ART. It is possible that inflammation at baseline was merely a marker of other immune mechanisms unrelated to tumor necrosis factor (TNF)–α or IL-6 but, nonetheless, predisposed these patients to later complications. Furthermore, death appeared to occur at a relatively even rate across the 100 weeks of follow-up, suggesting that the early burst of opportunistic infections and elevation of proinflammatory mediators at baseline may not have been related to these later events.

Regardless, the study by Kalayjian et al [5] provides the impetus to conduct prospective studies in patients initiating ART complicated by incident opportunistic infections and malignancies, to understand longitudinal effects of high levels of inflammatory mediators at baseline, the natural history, whether there is attenuation of these markers, and whether other immunoregulatory mediators may become operational later in the course of effective ART.

So what factors are primarily responsible for longer-term adverse outcomes in HIV-infected patients receiving effective ART? In the short term, it may be viral replication; however, in the long term, persistent immune activation/inflammation may be the key. One leading hypothesis holds that persistent translocation of bacterial products across a damaged gut lining may be responsible for persistent immune activation/inflammation [11, 12] that could ultimately lead to inflammation–based complications. It is possible that delayed immune recovery may lead to opportunistic complications and that persistent inflammatory stimuli are central to ongoing endothelial dysfunction, increased cardiovascular risks, and other chronic disease risks. It will be critical that future studies examine mechanisms underlying persistent immune activation/inflammation, as well as test strategies for modulating inflammation, to effectively intervene in these long-term complications that are holding our patients back from more complete recovery from HIV infection.

References

5. Kalayjian RC, Machekano RN, Rizk N, et al. Pretreatment levels of soluble cellular receptors and interleukin-6 are associated with HIV.

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