Inflammation in Chronic HIV Infection: What Can We Do?

Kristine M. Erlandson and Thomas B. Campbell
Department of Medicine, Division of Infectious Diseases, University of Colorado, Aurora

Effective antiretroviral therapy (ART) has dramatically improved the life expectancy of persons living with human immunodeficiency virus (HIV). However, even with long-term, effective ART, HIV-infected persons have persistent, low-grade inflammation and immune activation [1] that are strongly associated with a heightened risk for cardiovascular disease [2–4], osteoporosis [5], anemia [6], physical function impairments and frailty [7], among other non-AIDS–defining events and mortality [8, 9]. For example, a recent analysis in the Multicenter AIDS Cohort Study found that levels of soluble CD14 (sCD14), a marker of monocyte activation, were significantly higher in HIV-infected men, compared with HIV-uninfected men, but that they did not differ between HIV-infected men with and those without effective ART and changed very little in the years following ART initiation [10]. Given the long-term consequences of chronic inflammation, there is an urgent need to better understand the causes and develop interventions that attenuate the effects of inflammation and immune activation in people living with HIV infection. The study by Hileman et al in this issue of The Journal of Infectious Diseases offers insight into how the choice of the initial antiretroviral regimen affects subsequent changes in inflammation and immune activation markers.

Multiple factors likely contribute to the chronic inflammation and immune activation found in HIV-infected persons during ART, but the independent role of each factor is difficult to discern. HIV-infected persons with residual HIV type 1 (HIV-1) replication, immune depletion, or hepatitis B or C virus coinfection, especially those with underlying fibrosis, exhibit higher levels of inflammation and immune activation [11, 12]. Other chronic viral coinfections are similarly associated with inflammation or immune activation: greater high-sensitivity C-reactive protein (hsCRP) levels and greater T-cell activation (defined as an increased percentage of T cells expressing CD38 and HLA-DR) but not expressing CD38 and HLA-DR) were seen in subjects with HIV and human herpesvirus 8 coinfection [13], and elevated levels of interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) were associated with higher levels of cytomegalovirus (CMV) immunoglobulin in older, HIV-uninfected populations [14]. Microbial translocation persists to some degree despite suppressive ART and is associated with both immune activation and inflammation [15, 16]. Lifestyle factors (eg, smoking, sedentary habits, or injection drug use) can further increase levels of immune activation and inflammation: HIV-infected smokers had higher T-cell activation, sCD14 levels, and lipopolysaccharide levels than HIV-infected nonsmokers, [17]; increased injection drug frequency in a cohort with or at risk for HIV infection was associated with higher IL-6 and CRP levels [18]. Whether concomitant comorbidities are the consequence or cause is a matter of debate, but heightened levels of inflammation and immune activation during HIV infection are associated with several diseases, including depression [19], obesity [20], and diabetes [21].

In previous studies, interventions to attenuate inflammation and immune activation have targeted some of the inflammation-associated factors mentioned above. For instance, treatment with valganciclovir, which has broad antiviral activity against herpesviruses, including CMV, led to a decrease in CD8+ T-cell activation (defined as a decreased percentage of CD8+ T cells expressing CD38 and HLA-DR) but not other markers of inflammation [22], whereas acyclovir, which does not have activity against CMV, had no effect on markers of inflammation or activation [23]. Attempts to decrease inflammation by decreasing microbial translocation from the intestine with sevelamer or rifaximin therapy have not proven successful [24, 25], whereas treatment with the probiotic Saccharomyces boulardii for 12 weeks produced significant reductions in systemic levels of IL-6 and lipopolysaccharide.
Treatment with vitamin D, omega-3 fatty acids, and statins have reduced the prevalence of CD38 expression on CD8+ T cells [27], decreased the levels of IL-6 and TNF-α [28], and decreased the level of lipoprotein-associated phospholipase A2 (Lp-PLA2; also known as platelet-activating factor acetylhydrolase) [29], respectively, among HIV-infected individuals with an antiretroviral-suppressed viral load. A recent observational study found that initiation of ART together with rosvastatin therapy was associated with significantly greater decreases in levels of both hsCRP and TNF-α, compared with ART alone [30]. Lifestyle changes, including exercise, can also reduce inflammation [31–33] and have proven clinical benefits beyond just a reduction in levels of inflammatory biomarkers.

Over the past 27 years, the US Food and Drug Administration has approved 25 antiretroviral drugs for treatment of HIV infection [34]. Many well-designed clinical trials have compared the efficacy and safety of various antiretroviral combinations, but relatively little is known about the impact of contemporary antiretroviral regimens on markers of inflammation or activation, outside of a possible adverse effect of abacavir on cardiovascular disease risk markers [35–37]. Could certain ART regimens be associated with a greater decline in levels of inflammation or immune activation? The article by Hileman et al provides interesting results to address this question. Hileman et al found that, in the context of a double-blinded randomized trial, a 48-week course of coformulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/c/FTC/TDF) produced a significantly greater reduction in sCD14, hsCRP, and Lp-PLA2 levels than a coformulated efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF) regimen in antiretroviral-naive adults. It is well known that integrase strand transfer inhibitors, such as elvitegravir, produce a more rapid phase of initial plasma HIV-1 RNA decay; however, the CD4+ T-lymphocyte count and plasma HIV-1 RNA load responses were not significantly different between study arms. Moreover, the EFV/FTC/TDF arm actually had increased sCD14, hsCRP, and Lp-PLA2 levels from week 0 to week 24 that failed to decline by week 48. These findings are similar to those reported in prior switch studies with raltegravir, a different integrase strand transfer inhibitor, in which a change to raltegravir from enfuvirtide decreased IL-6, hsCRP, and d-dimer levels [38]; a change from a protease inhibitor or non-nucleoside reverse transcriptase inhibitor decreased the sCD14 level [39]; and a change from efavirenz decreased sCD14 and hsCRP levels [40]. Thus, the authors demonstrate the potential benefit of inflammation and immune activation of a fixed-dose, single-tablet integrase inhibitor-based regimen for the initial treatment regimen in antiretroviral-naive individuals, independent of virologic suppression or immune recovery.

Why might this be? The authors hypothesize that the effect could be due to a greater concentration of integrase inhibitors in the gut. Supporting this, a previous study showed that the integrase inhibitor raltegravir achieves higher gut tissue levels than other antiretrovirals, with the highest exposure following a single dose achieved in the terminal ileum, compared with other gut sites [41]. Similarly, intensification with raltegravir decreased the level of unspliced HIV-1 RNA in the ileum but not in other small- or large-bowel sites [42]. Although raltegravir intensification has been extensively tested to determine its ability to further decrease virologic replication, findings have primarily demonstrated a rapid increase followed by a decrease in the number of 2-long terminal repeat circles but no further reduction in HIV-1 single-copy RNA or DNA proviral levels [42–47].

The study reported by Hileman et al is another contribution supporting integrase inhibitors as a preferred component of initial antiretroviral regimens [48], although care should be taken to avoid overgeneralization of these results. First, sCD14, hsCRP, and Lp-PLA2 levels are measures of immune activation and inflammation levels that serve as markers for clinical outcomes. Although these specific biomarkers are associated with adverse clinical events in prior studies, whether a greater reduction in biomarker concentration with either of the single-tablet regimens tested by Hileman et al would result in an improvement in clinical outcomes has not yet been shown. Depending on the clinical context, changes in biomarker levels might be interpreted quite differently. For example, an elevated level of Lp-PLA2 is associated with an increased risk of cardiovascular disease in adults with and those without HIV infection, and Lp-PLA2 inhibitors are currently under investigation to improve outcomes following cardiovascular events, thus far with limited mortality improvement [49]. In contrast, in the setting of septic shock, markedly low levels of Lp-PLA2 in multiorgan failure [50] prompted a phase 3 clinical trial of recombinant Lp-PLA2 to increase systemic Lp-PLA2 levels, but the trial was stopped early because of a lack of efficacy [51]. Thus, it is unknown whether reduced levels of these markers are clinically beneficial, and improvement in clinical outcomes should be demonstrated before clinical care is altered. A second key point in interpreting the findings by Hileman et al is that the results are specific to the comparison of coformulated EVG/c/FTC/TDF to EFV/FTC/TDF. Whether similar effects would be demonstrated with alternate integrase inhibitor–based regimens is unknown. The 2 regimens compared by Hileman et al also differed by inclusion of the cytochrome P450 inhibitor cobicistat in the formulation with greater effects on inflammation and immune activation markers. Thus, whether elvitegravir or cobicistat affected the immune activation and inflammation markers is not proven.

In clinical practice, when considering the low transmitted resistance, similar barrier to development of resistance, availability of a single-tablet once-daily...
regimen, and the exceptional tolerability, for many patients initiating ART without contraindications, EVG/c/FTC/TDF is among the preferred first-line regimens [48], regardless of additional benefits on inflammation or immune activation. Longer-term follow-up from the study by Hileman et al will help determine whether these effects on inflammation and activation are sustained, but larger trials will be needed to determine whether these effects are clinically meaningful.

Notes

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