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Inflammation in Chronic HIV Infection: What can we do?

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Effective antiretroviral therapy has dramatically improved the life expectancy of persons living with human immunodeficiency virus (HIV). However, even with long-term, effective antiretroviral therapy, 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 events and mortality [8,9]. For example, a recent analysis in the Multicenter AIDS Cohort Study found that levels of soluble CD14, a marker of monocyte activation, were significantly higher in HIV-infected compared to HIV-uninfected men, but did not differ between HIV-infected men with or without effective antiretroviral therapy and changed very little in the years following antiretroviral initiation [10]. Given the long-term consequences of chronic inflammation, there is an urgent need to better understand the causes and to 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 on antiretroviral therapy, but the independent role of each factor is difficult to discern. HIV-infected persons with residual HIV-1 replication, immune depletion, or with hepatitis B or C co-infection, especially among those with underlying fibrosis, exhibit higher levels of inflammation and immune activation [11,12]. Other chronic viral co-infections are similarly associated with inflammation or immune activation: greater high sensitivity C-reactive protein (hs-CRP) and T-cell activation (%CD38 HLA-DR expression) were seen in subjects with HIV and human herpesvirus 8 co-infection [13], and elevated interleukin (IL)-6 and tumor necrosis factor (TNF)-alpha were associated with higher quantitative cytomegalovirus

immunoglobulin in older, HIV-uninfected populations [14]. Microbial translocation persists to some degree despite suppressive antiretroviral therapy, and is associated with both immune activation and inflammation [15,16]. Lifestyle factors (e.g.., smoking, sedentary habits, or intravenous drug use) can further increase immune activation and inflammation: HIV-infected smokers had higher T-cell activation, soluble CD14 and lipopolysaccharide compared to HIV-infected non-smokers, [17]; increased injection drug frequency in a cohort with or at risk for HIV was associated with higher IL-6 and CRP [18]. Whether concomitant comorbidities are the consequence or cause is a matter of debate, but heightened 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 valganclovir, which has broad antiviral activity against herpesviruses including CMV, led to a decrease in CD8+ T-cell activation (%CD38 HLA-DR expression), 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 sevalamer or rifaximin have not proven successful [24,25], whereas 12 weeks of the probiotic *Saccharomyces boulardii* produced significant reductions in systemic IL-6 and lipopolysaccharide binding protein (LBP) [26]. Treatment with vitamin D, omega-3 fatty acids, and statins have reduced CD38 expression on CD8 T-cells [27], decreased IL-6 and TNF-alpha [28], and decreased lipoprotein-associated phospholipase A2 (Lp-PLA2) [29], respectively, among HIV-infected, antiretroviral-suppressed individuals. A recent observational study found that initiation of antiretroviral therapy together with rosuvastatin was associated with significantly greater decreases in both hs-CRP and TNF-alpha compared to antiretrovirals alone [30]. Lifestyle changes, including exercise, can also

reduce inflammation [31-33] and have proven clinical benefits beyond just a reduction in inflammatory biomarkers.

Over the past 27 years, the United States Food and Drug Administration has approved 25 antiretroviral drugs for treatment of HIV-1 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 antiretroviral therapy regimens be associated with a greater decline in 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-blind randomized trial, 48 weeks of co-formulated elvitegravir/cobicistat/emtricitabine/tenofovir-DF produced a significantly greater reduction in soluble CD14, hsCRP, and Lp-PLA2 compared to a co-formulated efavirenz/emtricitabine/tenofovir-DF regimen in antiretroviral-naïve 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+ lymphocyte count and plasma HIV-1 viral load responses were not significantly different between study arms. Moreover, the efavirenz/emtricitabine/tenofovir-DF arm actually had increased soluble CD14, hs-CRP, and Lp-PLA2 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, where a change to raltegravir from enfuvirtide decreased IL-6, hs-CRP, and d-dimer [38]; a change from a protease inhibitor or nonnucleoside reverse transcriptase inhibitor decreased soluble CD14 [39]; and a change from efavirenz decreased soluble CD14 and hs-CRP [40]. Thus, the authors demonstrate the potential benefit on inflammation and immune activation of a fixed dose, single-tablet integrase inhibitor-based regimen for the initial treatment

regimen in antiretroviral-naïve 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 to other gut sites [41]. Similarly, intensification with raltegravir decreased unspliced HIV RNA in the ileum, but not in other small or large bowel sites [42]. Although raltegravir intensification has been extensively tested to further decrease virologic replication, findings have primarily demonstrated a rapid increase followed by a decrease of 2-long terminal repeat circles, but no further reduction in HIV 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 over-generalization of these results. First, soluble CD14, hs-CRP, and Lp-PLA2 are measures of immune activation and inflammation 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, elevated Lp-PLA2 (also known as platelet-activating factor acetylhydrolase or PAF-AH) is associated with increased cardiovascular disease risk in both HIV-infected and uninfected adults, 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 III clinical trial of recombinant Lp-PLA2 to increase systemic Lp-

PLA2 levels, but was stopped early due to a lack of efficacy [51]. Thus, whether there is actual clinical benefit with reduction of these markers is unknown, and improvement in clinical outcomes should be demonstrated before clinical care is altered. A second key point in interpreting the finding of Hileman, et al. is that the results are specific to the comparison of co-formulated elvitegravir/cobicistat/emtricitabine/tenofovir-DF to efavirenz/emtricitabine/tenofovir-DF. Whether similar effects would be demonstrated with alternate integrase inhibitor-based regimens is unknown. The two 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 antiretroviral therapy without contraindications, elvitegravir/cobicistat/emtricitabine/tenofovir-DF 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 if these effects are clinically meaningful.

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