

Soluble CD163 and Clinical Outcomes in Treated HIV Infection: Insights into Mechanisms

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It is now well appreciated that human immunodeficiency virus (HIV)-infected individuals in the modern treatment era have an increased risk of morbidity and mortality, compared with the general population, particularly among those who initiate antiretroviral therapy (ART) at advanced disease stages. Immune activation and inflammation persist despite suppressive ART and are thought to drive many of these complications. Nevertheless, there has continued to be uncertainty as to the most appropriate immunologic targets for therapeutic interventions. A key step in this process is demonstrating that biomarkers of a candidate interventional target predict subsequent clinical events in observational studies. Over the last few years, several studies in treated HIV-infected individuals have demonstrated that plasma markers of innate immune activation and inflammation tend to predict non-AIDS-defining morbidity and mortality more strongly than cellular markers of T-cell activation [1–3]. Yet, the specific cellular sources of those inflammatory mediators have been unclear. This is, in part, because most studies that are large enough to measure relatively uncommon clinical outcomes are typically too large to afford banking viably cryopreserved leukocytes from all participants. Thus,

studies linking monocyte phenotypes to end-organ disease in treated HIV infection have largely been limited to surrogate markers of disease (eg, coronary artery calcium scores [4]), instead of clinical events. Additionally, the phenotype and function of innate immune cells in circulation (eg, monocytes) may not reflect the status of their more numerous counterparts (eg, macrophages) in tissues, which may also contribute to soluble inflammatory mediators in plasma. Despite these limitations, several studies have highlighted the potential importance of monocyte and macrophage activation in predicting end-organ disease in treated HIV infection by assessing soluble receptors (eg, soluble CD14 [sCD14]) that are often shed by activated monocytes and macrophages in response to lipopolysaccharide and other stimuli [1, 2, 5]. Nevertheless, there is continued uncertainty as to whether sCD14 levels are specific markers of monocyte and macrophage activation, since it is shed not just by monocytes and macrophages, but also by other cell types, including neutrophils and even hepatocytes, in response to inflammatory stimuli [6].

In their cohort study in this issue of *The Journal of Infectious Diseases* [7], Knudsen et al present the first data linking plasma levels of the monocyte/macrophage activation marker soluble CD163 (sCD163) to clinical outcomes in treated HIV infection. In a sample of 933 HIV-infected individuals in Denmark whose viral loads were largely suppressed by ART, they found that each quartile increase in plasma sCD163 level was significantly associated with a 35% increased risk of

death. Unlike sCD14, sCD163 is relatively specific for monocyte/macrophage activation. Thus, this study provides the most compelling data to date linking monocyte and macrophage activation to clinical end points in treated HIV infection. While this relationship appeared slightly stronger for cardiovascular causes of death (as might have been predicted, based on earlier studies linking sCD163 to vascular inflammation [8]), a similar relationship was also observed with other noninfectious and infectious causes of death, potentially suggesting a role of monocyte and macrophage activation in contributing to multiple end-organ diseases in this setting. Interestingly, in another recent cohort study of HIV-infected individuals whose viral loads were largely suppressed by ART, conducted in the United States, higher plasma sCD163 levels were also linked to T-cell activation and expansion of poorly differentiated effector CD8⁺ T cells [9], a defect that also appears to predict mortality in treated HIV infection [10]. Whether monocyte and macrophage activation is a cause or consequence of adaptive immune defects in treated HIV infection (or confounded by some other related immunologic pathway) remains to be seen. Nevertheless, these prior observations linking sCD163 levels to adaptive immune defects in treated HIV infection provide a potential mechanistic link to the increased infection-related mortality seen in the current study by Knudsen et al.

A great strength of the study by Knudsen et al is its large sample size and linkage to the robust population-based Danish cohort study, which enabled the investigators to link sCD163 to not just clinical

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outcomes, but also a wide variety of potentially confounding clinical covariates and health-related behaviors. Indeed, many health-related behaviors are known to increase immune activation, including smoking and injection drug use. Since HIV-infected individuals are more likely to smoke and use injection drugs than the general population, some have argued that the increase in immune activation observed in treated HIV infection—and the relationship between immune activation and adverse clinical outcomes in this setting—might be largely or, at least in part, due to enrichment for these health-related behaviors. The study by Knudsen et al provides some important evidence to the contrary. Indeed, the relationships between sCD163 levels and mortality in this study were significantly stronger among nonsmokers than among smokers and stronger among non-injection drug users than among injection drug users, suggesting that smoking- and injection drug use-related increases in sCD163 levels were not likely to be driving the significant mortality associations observed.

Other interactions described by Knudsen et al are similarly enlightening with regard to (1) the mechanistic pathways linking monocyte and macrophage activation to mortality and (2) the subgroups of individuals most likely to benefit from interventions to reduce monocyte and macrophage activation. For example, women had greater sCD163 levels than men, reminiscent of the heightened responses of premenopausal women to Toll-like receptor ligands, reported in earlier studies [11]. Furthermore, the relationship between sCD163 levels and mortality was somewhat stronger in women than in men, suggesting not just that these sex-based differences in immune activation may be clinically relevant, but also that HIV-infected women may stand to derive even greater benefit from interventions to reduce monocyte and macrophage activation than HIV-infected men. Higher levels of HIV replication were also strongly associated with sCD163 levels

in this study. Nevertheless, higher sCD163 levels predicted mortality much more strongly among individuals with ART-suppressed viral loads than among viremic individuals, suggesting that the mortality associations with sCD163 are not simply driven by untreated viral replication and/or poor adherence to ART and that the population with ART suppression may well stand to benefit from interventions to reduce immune activation.

While the report by Knudsen et al is a major step forward in understanding the relationships between monocyte and macrophage activation and clinical outcomes in treated HIV infection, many unanswered questions remain. For example, since other biomarkers were not measured in this study, it is impossible to know whether sCD163 (or the monocyte/macrophage activation it represents) is causally associated with mortality or simply a marker for some other closely related inflammatory pathway that may be even more strongly predictive of and causally associated with mortality. Furthermore, the root drivers of the persistent elevations in sCD163 levels observed remain unclear. While continued HIV expression by infected cells in tissues, coinfections, including cytomegalovirus, and microbial translocation have all been implicated as potential drivers of the persistent inflammatory state in this setting [12], the most optimal targets for interventions remain unclear. It also remains unclear whether the contributions of each of these drivers to persistent immune activation will be evident even in those who initiate ART very early in the course of the infection and/or at high nadir CD4⁺ T-cell counts. Nevertheless, ameliorating the harmful effects of immune activation during treated HIV infection may be like cutting down a tree. One could try to cut away each individual “root” driver, and one could also try pruning each individual “branch” (representing the many parallel inflammatory pathways that contribute to morbidity and mortality). Alternatively,

one could cut the tree at the trunk, a common immunologic pathway that is fed by all the major roots and that gives rise to most of the parallel inflammatory pathways leading to disease. Perhaps monocyte and macrophage activation could be the tree trunk in treated HIV infection. Targeted interventions directed at monocyte and macrophage activation may well help answer this question in the future.

Note

Potential conflict of interest. Author certifies no potential conflicts of interest. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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