

sCD163 and Clinical Outcomes in Treated HIV: Insights into Mechanisms

Peter W. Hunt¹

¹Department of Medicine, University of California San Francisco

Corresponding author: Peter W. Hunt, MD
995 Potrero Avenue
SFGH Bldg 80, Ward 84
San Francisco, CA 94110
Office: (415) 476-4082 x345
Fax: (415) 476-6953
phunt@php.ucsf.edu

Accepted Manuscript

It is now well appreciated that HIV-infected individuals in the modern treatment era have an increased risk of morbidity and mortality compared to 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 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 on all participants. Thus, studies linking monocyte phenotypes to end-organ disease in treated HIV infection have largely been limited to surrogate markers of disease (e.g., coronary artery calcium scores [4]), instead of clinical events. Additionally, the phenotype and function of innate immune cells in circulation (e.g., monocytes) may not reflect the status of their more numerous counterparts (e.g., 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 (e.g., sCD14) that are often shed by activated monocytes and macrophages in response to lipopolysaccharide (LPS) 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 largely ART-suppressed HIV-infected individuals in Denmark, they found that each quartile increase in plasma sCD163 levels 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 endpoints 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 non-infectious 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 largely ART-suppressed HIV-infected individuals 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 article 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 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 Knudsen *et al* article provides some important evidence to the contrary. Indeed, the relationships between sCD163 levels and mortality in this study were significantly *stronger* among non-smokers than smokers, and among non-IDU than IDU, suggesting that smoking- and IDU-related increases in sCD163 were not likely to be driving the significant mortality associations observed.

Other interactions described by Knudsen *et al* are similarly enlightening regarding the mechanistic pathways linking monocyte and macrophage activation to mortality, and 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 pre-menopausal 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 gender 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 article. Nevertheless, higher sCD163 levels predicted mortality much more strongly among ART-suppressed individuals than among viremic individuals, suggesting that the mortality associations with sCD163 are not simply driven by untreated viral replication and/or poor adherence to antiretroviral therapy and that the ART-suppressed population 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 is 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 sCD163 elevations observed remain unclear. While continued HIV expression from infected cells in tissues, co-infections 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 fed by all the major roots and which 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.

Footnotes: The author has no conflicts of interest/funding to declare.

References

1. Hunt PW, Sinclair E, Rodriguez B, et al. Gut Epithelial Barrier Dysfunction and Innate Immune Activation Predict Mortality in Treated HIV Infection. *J Infect Dis* **2014**.
2. Tenorio AR, Zheng Y, Bosch RJ, et al. Soluble Markers of Inflammation and Coagulation but Not T-Cell Activation Predict Non-AIDS-Defining Morbid Events During Suppressive Antiretroviral Treatment. *J Infect Dis* **2014**.
3. Ford ES, Greenwald JH, Richterman AG, et al. Traditional risk factors and D-dimer predict incident cardiovascular disease events in chronic HIV infection. *AIDS* **2010**; 24:1509-17.
4. Baker JV, Hullsiek KH, Singh A, et al. Immunologic predictors of coronary artery calcium progression in a contemporary HIV cohort. *Aids* **2014**; 28:831-40.
5. Sandler NG, Wand H, Roque A, et al. Plasma levels of soluble CD14 independently predict mortality in HIV infection. *J Infect Dis* **2011**; 203:780-90.
6. Liu S, Khemlani LS, Shapiro RA, et al. Expression of CD14 by hepatocytes: upregulation by cytokines during endotoxemia. *Infect Immun* **1998**; 66:5089-98.
7. Knudsen TB, Ertner G, Petersen J, et al. Plasma CD163 independently predicts all-cause mortality from HIV-1 infection. *J Infect Dis* **2016**; in press.
8. Subramanian S, Tawakol A, Burdo TH, et al. Arterial inflammation in patients with HIV. *JAMA : the journal of the American Medical Association* **2012**; 308:379-86.

9. Wilson EM, Singh A, Hullsiek KH, et al. Monocyte-activation phenotypes are associated with biomarkers of inflammation and coagulation in chronic HIV infection. *J Infect Dis* **2014**; 210:1396-406.
10. Lee SA, Sinclair E, Jain V, et al. Low proportions of CD28- CD8+ T cells expressing CD57 can be reversed by early ART initiation and predict mortality in treated HIV infection. *J Infect Dis* **2014**; 210:374-82.
11. Meier A, Chang JJ, Chan ES, et al. Sex differences in the Toll-like receptor-mediated response of plasmacytoid dendritic cells to HIV-1. *Nat Med* **2009**; 15:955-9.
12. Hunt PW. HIV and Inflammation: Mechanisms and Consequences. *Curr HIV/AIDS Rep* **2012**; 9:139-47.

Accepted Manuscript