Reply to Cannizzo et al

TO THE EDITOR—In their letter, Cannizzo et al [1] highlight an important issue in the interpretation of T-cell activation marker data in the context of human immunodeficiency virus (HIV) infection. CD38 has long been interpreted as a T-cell activation marker in HIV infection, but resting naive T cells may also express low-to-moderate amounts of this surface marker. Indeed, CD38 (then known as “T10”) was first demonstrated to be dramatically elevated on T cells from untreated HIV-infected individuals in 1981 [2], in one of the first published reports to describe AIDS and years before HIV was discovered as the cause of AIDS. Subsequently, work by Giorgi et al [3] demonstrated that higher CD38 expression (as measured by relative fluorescence intensity) on CD8+ T cells strongly predicted faster progression to AIDS and death in untreated HIV infection. In untreated HIV infection, the relative fluorescence intensity of CD38 on activated memory CD8+ T cells is dramatically higher than that on resting naive cells, and memory CD8+ T cells are dramatically expanded, so naive T-cell CD38 expression contributes negligibly to the prognostic capacity of this marker during untreated HIV infection. During antiretroviral therapy (ART)—mediated viral suppression, however, T-cell activation—in particular, CD38 expression on memory CD8+ T cells—declines markedly, such that activated memory CD8+ T cells no longer express CD38 at much higher levels than resting naive cells. For this reason, there is very little evidence for a relationship between CD38 relative fluorescence intensity and clinical outcomes in treated HIV infection.

Nevertheless, most studies of T-cell activation in treated HIV infection, including our own recent study [4] and the article by Tenorio et al [5] referred to in the letter by Cannizzo et al [1], use CD38 co-expression with HLA-DR to identify activated T cells. Since HLA-DR is not typically expressed on resting naive cells, co-expression of HLA-DR and CD38 typically identifies activated memory T cells. Thus, although Cannizzo et al [1] are correct that the CD38+ T-cell population is a mix of naive and activated cells in treated HIV infection, the CD38+HLA-DR+ population is largely a memory T-cell population. Indeed, in our study of the immunologic predictors of mortality among ART-suppressed participants in the Longitudinal Study of the Ocular Complications of AIDS cohort, we specifically assessed CD38 and HLA-DR co-expression not just on the entire CD8+ and CD4+ T-cell populations, but also on the central memory subsets (CCR7+ CD45RA−), specifically excluding naive T cells [4]. The mortality associations for the frequencies of CD38+HLA-DR+ T cells and CD38+HLA-DR+ central memory T cells were nearly identical for both CD8+ and CD4+ T-cell populations. It should also be noted that we observed a significant relationship between both CD4+ and CD8+ T-cell activation and mortality in this study, although these associations were attenuated after adjustment for current CD4+ T-cell count, suggesting that the relationship between T-cell activation and mortality may be at least in part mediated and/or confounded by the degree of ART-mediated CD4+ T-cell recovery. Nevertheless, markers of innate immune activation and inflammation predicted mortality much more strongly than T-cell activation in our study (as well as in the study by Tenorio et al), suggesting that innate immune activation may be a more appropriate target than T-cell activation for interventions to reduce mortality in this setting.

Last, while we do not believe that naive T-cell expression of CD38 affected the relatively weak association between T-cell activation and clinical outcomes in these 2 studies, we acknowledge the possibility that T-cell activation, as a marker of adaptive immune defects, may be a better predictor of AIDS and infectious complications than it is of cardiovascular and other causes of death that may predominate in North American studies. Indeed, recent work from the SUN study suggests that monocyte activation more strongly predicts progression of atherosclerosis progression (by coronary calcium score) than T-cell activation in treated HIV infection [6]. Conversely, we have observed much stronger relationships between T-cell activation and mortality in HIV-infected Ugandans during early ART-mediated viral suppression (a setting where individuals are more likely to die from infectious complications) than we have in the North American cohorts [7]. These observations underscore the need for parallel biomarker research in both resource-rich and resource-limited settings, as the specific immunologic pathways that are most important in driving morbidity and mortality (and the interventional targets they may suggest) may differ between these settings.

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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References


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