ABSTRACT

Background: LAG-3 is a potent negative regulator of the immune response but its impact in HIV infection is poorly understood. Unlike exhaustion markers such as PD-1, Tim-3, 2B4 and CD160, LAG-3 is poorly expressed on bulk and antigen-specific T cells during chronic HIV infection and its expression on innate lymphocyte subsets is not well understood. The aim of this study was to assess LAG-3 expression and association with cellular dysfunction on T cells, NK cells and iNKT cells among a cohort of healthy and HIV-infected female sex workers in Nairobi, Kenya. Results: Ex vivo LAG-3 expression was measured by multiparametric flow cytometry, and plasma cytokine/chemokine concentrations measured by bead array. Although LAG-3 expression on bulk T cells was significantly increased among HIV-infected women, the proportion of cells expressing the marker was extremely low. In contrast, LAG-3 was more highly expressed on NK and iNKT cells and was not reduced among women treated with ART. To assess the functional impact of LAG-3 on iNKT cells, iNKT cytokine production was measured in response to lipid (αGalCer) and PMA/Io stimulation by both flow cytometry and cytokine bead array. iNKT cytokine production is profoundly altered by both HIV infection and treatment, and LAG-3, but not PD-1, expression is associated with a reduction in iNKT IFN γ production. Conclusions: LAG-3 does not appear to mediate T cell exhaustion in this African population, but is instead expressed on innate lymphocyte subsets including iNKT cells. HIV infection alters iNKT cytokine production patterns and LAG-3 expression is uniquely associated with iNKT dysfunction. The continued expression of LAG-3 during treatment suggests it may contribute to the lack of innate immune reconstitution commonly observed during ART.