Reviewer's report

Title: Impact of antigen specificity on CD4+ T cell activation in chronic HIV-1 infection

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Reviewer: Nichole Klatt

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Here Smith et. al. assessed the specificity of antigen-specific cells in HIV-infected versus HIV-uninfected cells in order to address whether chronic immune activation during HIV infection is due to antigen-specific responses.

Major Compulsory Revisions

1. Page 9, first paragraph, the authors state they did not see any #7 expression on CD4+ T cells from either HIV+ or HIV- individuals, which is reported as data not shown. However, several reports have found #7 expression on peripheral CD4+ T cells. Did the authors use a positive control? The authors must demonstrate that their staining was accurate and indeed negative if they want to state this, and should consider including a positive control with the negative data in supplemental. Alternatively, the authors should consider removing these data to avoid reporting an inaccurate conclusion if no positive control was used.

2. The authors discuss PD-1 expression on CD4+ memory and “activated memory” cells, however do not show whether the antigen-specific cells in HIV+ individuals express PD-1. If these data are available, they should be included. Furthermore, the authors discuss the PD-1 expression relative to antigen-specific responses. However, it appears that the authors assessed antigen-specific responses from bulk PBMCs (if this is not correct, the authors also need to specify this in the figure legend). Thus, comparing PD-1 on RA- and CD38+HLA-DR+ CD4+ T cells relative to bulk PBMCs is inappropriate.

3. In the discussion (page 11), the authors state “This ‘hierarchy’ correlates well with the level of persistence or the likelihood of reactivation/re-encounter of the respective virus/antigen.” What is this sentence based on?? The authors need to provide data or references supporting this statement.

Minor Compulsory Revisions

1. The authors state (page 8, first paragraph) “The activation level of the CD4+CD45RA- population was significantly higher than the CD4+CD45RA+ population (p < 0.01), highlighting the influence of antigen encounter on activation levels in HIV+ individuals.” However, several groups have routinely demonstrated that memory cells are more prone to bystander activation, which is not, necessarily, antigen-specific. Indeed, this could alternatively reflect a greater propensity for activation in general, whether antigen-specific or bystander,
compared to naïve cells. The authors should tone down this comment.

2. The authors report the data as “RA+” or “RA-” in the graphs- they should change that to “Naïve” or “Memory/Effector” to make it more readily understandable.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests