Author's response to reviews

Title: High T-cell immune activation and immune exhaustion among ART-treated patients with suboptimal CD4 recovery despite long-term viral suppression in an African cohort

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Author's response to reviews: see over
Response to reviewers’ comments

Reviewer 1

Following needs to be considered:
The authors chose to divide the cohort into 3 groups based on the current CD4 count. However, in the remaining manuscript only increase in CD4 count from baseline is used. Most studies choose to define immunological non responders as persons with CD4 counts less than 200 and responders as persons with CD4 counts > 500. Using the increase in CD4 count actually results in groups that overlap (suboptimal with increase 94-298, optimal 94-435). It is fine to present data on increase in CD4 count, it would provide additional information though to present the association between immune activation/exhaustion and the actual CD4 count. This would also make comparison with previous findings easier.

Explanation: We explain on page 6 under the subheading “Definition of suboptimal CD4 reconstitution” that we used the CD4 increase (difference between baseline and 4 years) and these are the categories used throughout the analysis. We do not use absolute CD4 counts.

The typing or transcription error on the group cut-offs has been corrected and the groups do not overlap.). The edited cut-offs for the CD4 increases are as follows; suboptimal responders -43-199, optimal responders 200-282, super-optimal 417-878 (as reported in Figure 1).

The patients included are not very well described. The authors provide information on age, sex, and antiretroviral treatment.
Did any of the patients have AIDS-defining illness? The patients with poor immune recovery and immune activation - could that be due to co-infections such as TB or HCV? Were any of the patients actually treated for TB during the 4 years of HAART? Patients are tested for concurrent infections. Surprisingly few patients were found HBsAg positive. Even more surprisingly is the finding of no intestinal parasitic infections in the entire cohort. These findings need to be discussed.

On page 5 second last sentence, we mention that patients that had an opportunistic infection in the previous 6 months were excluded and Figure 1 shows in detail that there was no patient in this category. AIDS-related events including opportunistic infections were not significantly different in the subgroups and this is consistent with our previous report (Nakanjako et al AIDS Research and Therapy 2008, 5:23 doi:10.1186/1742-6405-5-23) that there were no statistically significant differences in the incidence of clinical events among patients with and without suboptimal CD4 reconstitution.
This has been discussed on page 12, second paragraph.

Reviewer 2

1. Although the authors looked across controls and cases, it would have been interesting to have a comparison group with on going viral replication (VL > 400 compies/ml) to compare the persistence of PD-1 and T cell activation. This should be highlighted as a limitation.
We have included this as a limitation in the last paragraph of the discussion on page 13. We did not compare levels of immune activation among patients with and without viral suppression however there is already evidence that ART decreases immune activation levels over time (Benito et al 2002; Lederman et al, 2006).

2. The authors conclude well about the relevance of their findings to the argument regarding early initiation of ART especially in settings where patients show up with Stage IV disease. Although this is explicitly mentioned in the conclusion, it is not clear whether this was a question that they had posed in the introduction. Namely, would the findings in this study be of use in contributing to the immunological argument for early initiation of ART.

This has been edited in the conclusion both in the abstract and main paper. As part of the conclusion we mention that regulation of these immune abnormalities may modify immune recovery among ART-treated patients with suboptimal CD4 reconstitution despite sustained viral suppression.

3. The authors also should note which facility was used for the analyses in this study. Otherwise methods used were appropriate.

This has been included on page 6; last sentence under the subheading “Definition of suboptimal CD4 reconstitution”.

4. The authors in reporting the results should have included a figure showing the actual fluorescence.

We have included this in Figures 3 and 4

5. In the discussion, the authors should include more detail on PD-1 and a reference to look at and include would be Michelle D'Souza et al Programmed Death 1 expression on HIV Specific CD4T cells is driven by viral replication and associated with T cell dysfunction. Journal of Immunology 2007; 179:1979-1987

We have included this in the discussion on page 12 second paragraph

6. Second paragraph under discussion should be under the limitations section of the discussion.

This is now the last paragraph of the discussion section before the conclusion

7. Perhaps the authors could report on any important clinical outcomes for the suboptimal responders e.g OIs/hospitalizations during the 4 years of ART.

Explanation about the AIDS-related events has been given on page 11 last paragraph

8. Suggest changing title to "High T-cell immune activation and immune exhaustion in an ART-experienced African cohort with suboptimal CD4 recovery."

Title has been edited to ‘High T-cell immune activation and immune exhaustion among individuals with suboptimal CD4 recovery after 4 years of antiretroviral therapy in an African cohort’.

9. Finally the authors need to proof read through the manuscript as there are various adjoining verbs missing.

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