Author's response to reviews

Title: Predictors of Suboptimal CD4 Response among Women Achieving Virologic Suppression in a Randomized Antiretroviral Treatment Trial, Africa

Authors:

Aida Asmelash (aasmelash@bhp.org.bw)
Yu Zheng (ezheng@sdac.harvard.edu)
Kara Wools-Kalaoustian (kwools@iupui.edu)
Douglas Shaffer (adx9@cdc.gov)
Fred Sawe (fsawe@hivresearch.org)
Anthony Ogwu (aogwu@bhp.org.bw)
Robert Salata (ras7@po.cwru.edu)
Judith Currier (jscurrier@mednet.ucla.edu)
Michael Hughes (mhughes@sdac.harvard.edu)
shahin Lockman (shahin.lockman@gmail.com)

Version: 4
Date: 31 March 2014

Author's response to reviews: see over
Predictors of Suboptimal CD4 response among Women Achieving Virologic Suppression in Randomized Antiretroviral Treatment Trial, Africa.

We thank the reviewers very much for their thoughtful comments. Please find below our responses to each of the questions or suggestions raised by the reviewers.

Response to reviewer Susan E Cohn

- The authors do not really explain why they chose to use this composite endpoint of SCR versus CD4<350 only or some other end point such as CD <less than 250 or 300. How did they come to this decision? Had they looked at other possibilities first or was these criteria for SCR set prior to the study (A5208)?

  \textit{Response: The definition of SCR (<100 CD4 cells/µL increase from baseline and absolute CD4 cell count < 350 cells/µL, both at 48 weeks after HAART initiation) was specified prior to performing any analyses of suboptimal immune response. This SCR definition was selected due to a combination of a) its clinical relevance, based on knowledge of significantly higher rates of HIV-associated morbidity and mortality associated with CD4<=350 compared with >350, and b) a conservative expectation (based on prior experience/literature) that the majority of patients starting ART with CD4<200 should experience CD4 increase of >100 and achieve CD4>350 by 48 weeks after treatment start. This information has been added to the Background section.}

- If they are interested in examining their populations of women at 48 weeks and at 96 weeks, why did they not chose a population of women all of whom had data at 96 weeks? Even though their population that had competed data through 48 weeks they then went on to address this population at 96 weeks despite where they had only 25\% drop out. The authors did not reveal how many women went on to develop detectable virus or clinical outcomes, and the reasons for why the women were not included and how many died, how many left due to lost to follow up and the like. It appears that according to fig 1 there were 625 women at week 48 but only 471(75\%) at week 96.

  \textit{Response: the A5208/OCTANE trial was designed to follow women for at least 48 weeks after the last participant was enrolled. We therefore chose to base the primary CD4 reconstitution analysis based upon analysis of data through 48 weeks (rather than 96 weeks) after HAART initiation, in order to optimize the amount of complete data available for this analysis, due to the design of the study. For the 154 women who did not have week 96 CD4 results, the main reason is study completion prior to week 96 follow-up: 140 (91\%) completed the study but were followed less than 96 weeks, 11 were lost to follow-up prior}
to study completion, and 3 were due to missing visits. Among the 625 women included in the analysis, 25 experienced virologic failure between week 48 and 96 (20 in non-SCR group and 5 in SCR group).

- Figure 1 is not clearly defined making it difficult to understand. It appears that all of the women with HIV viral suppression at week 48 were divided into SCR and non-SCR. 100% of the SCR group by definition had CD4 < 350 but only 46.2% of women with no SCR had CD4 > 350, not the vast majority as stated on PP 11 parag 2. Also why are their few patients at week 24 and 36 than 48? How many started with the study?

Response: We have added a footnote to Figure 1, with the definition of SCR, and noting that the denominators indicate the number of women with a CD4 measurement at that time point (the study included all women with baseline and 48 weeks CD4 measurement but some of these women did not have CD4 values at all other time points, such as 24 and 36 weeks).

- In their statistical methods section on p 7. They state that 'the selection of covariates in the final multivariate models was done by stepwise selection requiring p<0.05 for inclusion /retention of a variable. Except that the screening CD4 count was forced into the model to take account of the possibility that women with lower screening counts might be less likely to achieve the threshold of 350 cells/ by week 48. However in their baseline table they state that Hep B sag was more likely among the SCR versus non SCR population but the univariate P values was 0.10. They should clarify in more detail how the variables for inclusive in their multivariable analysis were selected.

Response: The inclusion/retention criteria for stepwise selection refer to the threshold for forward and backward selection. This procedure selects significant variables adjusted for other variables. A variable with P>0.05 in the univariate analysis could be included in the model because after adjusting for other variables in the model, it could become significant. The first two sentences of this paragraph have been added to the end of the Statistical methods section of the manuscript.

- On p 9 the authors state that other factors were not significantly associated with SCR. They should say which factors were specifically were examined. Were factors other than the ones listed in Table 1 examined?

Response: Baseline Body mass index, exposure to single dose nevirapine, treatment arm (nevirapine/tenofovir/emtricitabine versus lopinavir/ritonavir/tenofovir/emtricitabine) and adherence were not significantly
associated with SCR (P>0.05). This has been added to the 2nd paragraph of the results section.

- In the methods section they say that adherence was evaluated at week 4,12,24,48. Did adherence play a role even measured as crudely as all or none? How did the adherence variable play out over the 48-week study? Did it differ by week 96 if it was even measured? Did women burn out and stop their ART? Adherence a key factor in immunologic recovery did not appear in any of the tables.

  **Response:** 61% reported no missing dose by week 48 in SCR group and 67% reported no missing dose by week 48 in non-SCR group, but it is not significant in univariate analysis (P=0.42), and also not selected by stepwise procedure to the final model. This information was also added to the 2nd paragraph of the results section.

- Did the co-authors read and sign off on the manuscript? If so it would be helpful to state this in the manuscript.

  **Response:** Yes, co-authors read, contributed to, and signed off on the manuscript. This has been added to the Methods section.

**Reviewer 2: Anchalee Avihingsanon**

- In the second paragraph of introduction part: authors stated that there were no clear predictors of discordant responses. In fact increasing age, injecting drug use, hepatitis co-infection, and lower baseline CD4 cells and HIV RNA have been associated with discordant response. Please explain and look at more references.

  **Response:** References have added and the text modified, to say that prior results have been variable.

- In the result section the factors were not significantly associated with SCR P>0.05. Please be specific using boosted PI was it associated with better immune response or not.
Response: Baseline Body mass index, exposure to single dose nevirapine, treatment arm (nevirapine/tenofovir/emtricitabine versus lopinavir/ritonavir/tenofovir/emtricitabine) and adherence were not significantly associated with SCR (P > 0.05). This has been added to the 2nd paragraph of the results section.

- Table 1: The proportions/percentages in the table have been presented by categorical grouping and not by response group. Could this please be changed to make it easier for readers to understand? We want to know about the percentages of subjects in each response group who have a particular attribute represented by the categories which are described. Could the authors also confirm that when there are less than or equal to five subjects an any of the cells for any of the grouping that a 2 sided Fisher’s exact test has been used, and not a Chi-square test.

Response: the table has been changed per the comment. The Fisher’s exact test was used rather than Chi-square test for all categorical variables (noted in the statistical methods section).

Minor comment:

- In discussions part: please add reference for some studies have shown HCV and IDU to be related to level CD4 response while on therapy.

Response: These have been added

- Since antiHCV was not available what is the percentage of HCV co-infection in African women and how common of injecting drug user in this population.

Response: WHO estimated overall prevalence of HCV in Sub Saharan Africa as 3.0% (Lancet Infect Dis, 2002; 2(5): 293-302). Intravenous drug use is reportedly infrequent in this population. For this population the prevalence of HCV co infection and intravenous drug use was not looked at.