Reviewer's report

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

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Review

Review of Predictors of Suboptimal CD4 Response among Women Achieving Virologic Suppression in a Randomized Antiretroviral Treatment Trial, Africa by Aida Asmelash et al.

Overview

This paper addresses a potentially important topic of suboptimal CD4 recovery in patients with HIV viral suppression on HAART, and specifically examines a population of women treated in resource-limited areas in Africa. They chose to examine a subset of women enrolled in A5208 (OCTANE Study) who were HIV+, with screening CD4<200 who were randomly assigned to start open labeled nevirapine or lopinavir/rit both with tenofovir/emtricitabine, all of whom had suppressed VL at week 48. They then looked at the predictors of “suboptimal CD4 response” (SCR) which they define as CD4 less than 350 at week 48 and <100 cell CD4 increase since baseline. They looked at univariate and then multivariable predictors of suboptimal CD4 response, as well as potential clinical outcomes among the population with and without SCR over the study.

Review

Overall, this paper is well written and relatively easy to follow. There are some areas that if clarified, would make it a much stronger paper.

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

2. If they are interested in examining their population 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 completed data through 48 weeks, they then went on to address this population at 96 weeks despite where they had only 25% drop out. They authors did not without 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 left due to death, lost to follow-up and the like. It appears that, according to Figure 1, there were 625
women at week 48 but only 471(75%) at week 96.

3. 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 non-SCR had CD4>350, not the “vast majority” as stated on p. 11 parag 2. Also, why are their few patients at week 24 and 36 than 48? How many started the study?

4. 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 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/µL by week 48”. However, in their baseline table, they state that “Hep B sAg was more likely” among the SCR vs non-SCR population, but the univariate P value was 0.10. They should clarify in more detail how the variables for inclusive in their multivariable analyses were selected.

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

6. In the methods section, they say that adherence was evaluated at week 4, 12, 24, and 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.

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