Reviewer's report

Title: A Prospective Study of Improvements in Endothelial Activation Biomarkers, Including Plasma Angiopoietin-1 and Angiopoietin-2, in Kenyan Women Initiating Antiretroviral Therapy

Version: 2 Date: 31 January 2013

Reviewer: Anne P Frosch

Reviewer's report:

This is an interesting paper examining the influence of ARV treatment on markers of endothelial activation in Kenyan women with HIV. Understanding of these markers may contribute considerably to the pathophysiology of a number of infectious diseases including HIV and may be valuable prognostic tools. As such, this paper examines a critical and interesting topic in HIV research and does it in a group that could benefit from further research demonstrating the value of early ART.

Major Compulsory Revisions:

1) There is a need for clarification of "advanced HIV" and immune activation from HIV replication and the discussion of this study's results with reference to these two concept. The paragraph with the hypothesis is an example of this. The hypothesis is expressed as "advanced HIV" which would be defined by low CD4 or in certain settings WHO criteria, not viral load. The next sentence the says that the aim is to look at the association of the study indicators with HIV viral replication.

The primary issue is that this study only examined individuals with low CD4 who are likely at risk for opportunistic infections. As their viral load is declining, their CD4 count is also rising, for many above 200. Therefore, in this group, you will not be able to clearly differentiate whether the changes in Ang2 and Ang2:Ang1 ratio is secondary to a decline in viral replication and associated immune activation or the resolution of opportunistic infection and immune reconstitution. Perhaps Ang2 is a predictor of mortality in women with IRIS. The persistence of elevated Ang2 and Ang2:Ang1 ratio with virologic suppression while these population continues to have a relatively low CD4 counts may also be explained by this.

In the discussion and conclusions, there should be a explicit discussion of these issues and more conservative interpretation of the relationship of virologic suppression and changes in biomarkers in light of the fact that this study is only conducted in persons with advanced HIV and therefore limited conclusions on the role of virologic suppression. More analysis on the association of CD4 count and Ang-1, Ang-2, other biomarkers may also shed light. I do not suggest that this makes the findings less important, just that the etiology behind this change is
not clearly identified in this study.

Discretionary Revisions:
1) Clarification on reason behind the intention to treat analysis as a study aimed at examining the pathophysiologic role of these biomarkers in HIV infection, not the use of ARVs in achieving a change in the level of these biomarkers.

3) Consider malaria in pregnancy as a possible etiology for findings of elevated Ang-2 in pregnant women.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

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