Reviewer's report

**Title:** Immune Activation and Microbial Translocation in Liver Disease Progression in HIV/Hepatitis Co-infected Patients: Results from the Icona Foundation Study

**Version:** 1  
**Date:** 21 November 2013

**Reviewer:** Victoria Best

**Reviewer's report:**

In the study by Marchetti et al., authors tested whether markers of microbial translocation would predict hepatic disease progression in a cohort of HIV-HCV/HBV co-infected patients. They observed an association between plasma TNF# levels and risk of Fib4>1.45, however no associations were observed between liver disease progression and markers of microbial translocation in this cohort. Authors also suggest that circulating levels of sCD14, a marker for inflammation similar to TNF#, may negatively correlate with liver fibrosis progression. Unfortunately, this conclusion is not only contradictory to other published works, but is it is contradictory to data presented in the current manuscript. One strength of the study is that it addressed a clinically relevant and important question, given that co-infected individuals have exacerbated hepatic illness. Previous reports have already tested this hypothesis, however, and an association between HIV-induced microbial translocation and liver disease severity was observed in at least one of the authors' listed citations. Therefore, lack of associations in the current study may be due to the fact that once an individual becomes co-infected, there is already an increased risk of exacerbated liver disease (compared to HCV or HBV monoinfection), and no further stratification of the co-infected cohort (by disease severity) is possible. Unfortunately, the study design does not allow for an adequate test of this possibility. Points of concern are listed below.

**Major Compulsory Revisions:**

1) In Figure 2, higher levels of sCD14 were shown to have an increased risk of Fib-4 elevation compared to lower levels of sCD14, an observation consistent with numerous other studies. Yet, you choose extrapolated analyses to conclude that higher sCD14 levels are beneficial through a proposed mechanism. How do Table 3 data relate to Figure 2 data? Please clarify this discrepancy.

**Minor:**

1) In the study by Balagopal et al. which encompassed a patient cohort of HIV+ and HIV- subjects, surrogate markers of microbial translocation were associated with the severity of liver disease. Is it possible that your lack of association is due to the fact that you are restricting your analysis to HIV+ subjects (no HCV or HBV mono), all having increased risk of exacerbated liver disease? One possibility is
that there is an association between severity of MT and severity of liver disease even in your co-infected cohort, but that your cohort is not large enough to include individuals with higher fibrosis scores, or a range of MT measurements, thus masking the association. Please address the limitation of your study in your discussion.

**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.

**Declaration of competing interests:**

I declare that I have no competing interests.