Reviewer's report

Title: Comparative impact of antiretroviral drugs on markers of inflammation and immune activation during the first two years of effective therapy for HIV-1 infection

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Reviewer: Kristine Erlandson

Reviewer's report:

This is an observational study investigating the impact of ART on markers of inflammation and activation. The study has several unique aspects including the selection of a cohort on suppressive ART, comparison of 2 NRTI and 3 additional treatment arms.

Major Compulsory Revisions:

1. It isn’t entirely clear to me what this manuscript offers beyond what is already published in the literature.

   a. The authors mention (in passing) in the last paragraph of the manuscript that “To our knowledge, the differential impact of antiretroviral drugs on markers of immune activation has not previously been studied”. IF this is true, this should be mentioned in the introduction as the reason for this paper. HOWEVER, I’m concerned about this statement--- the authors need to be VERY clear as to which markers of immune activation have not been explored because this statement is not entirely true. Prior studies have investigated the impact of some ART regiments on activation markers (Gupta, JAIDS 2013; Ghandi JAIDS 2012).

   b. The authors comment that the population is well balanced despite the lack of randomization. However they do not comment on differences that may not be recognized-- importantly, differences in unrecognized bias towards treatment selection that cannot be controlled for.

   c. The cohort is quite small compared to other studies (A5224, for example) and although not statistically significant, these differences could be relevant in terms of inflammatory differences.

   d. The authors did not consider post-treatment variables (ie, change in CD4, change in BMI that may have a greater influence on inflammatory markers than just the baseline covariates)—these post-treatment variables are considered in some of the other studies.

   e. The authors comment that they only include those that remain on treatment whereas this is not done in other studies. Other studies (A5224, for example again) do have an as-treated analysis, however, to account for this. Furthermore, the authors aren’t looking at the newer, better agents where providers might want to see data convincing them to switch agents for more effective suppression of inflammation/activation.
f. I think one aspect that the authors could really emphasize is that they have a "real-world" population that is not in the context of a clinical trial where compliance may be better, etc. Although small, this demonstrates changes in inflammatory markers that occur with “usual” care, not research/clinical trial care.

2. There are no details about the overall population from which this sample is drawn. How many total patients are in the clinic? How many started ANY therapy? How did those that had plasma stored differ from those that did not?

3. No p values or comparative statistics are provided for differences between groups. Age appears to be quite a bit different between groups. How might age have impacted the differences in ART selection or response? Furthermore, did the authors consider including age or smoking the multivariate analysis as covariates that differed between groups?

4. The authors should acknowledge the variability in the inflammatory markers in the limitations.

5. Do the authors have thoughts about WHY differences may be found between ART regimens? The change in CD4, change in BMI, etc would be helpful to see if this could be an explanatory factor. Do the authors have thoughts about WHY differences may be seen compared to other study populations? Healthier subjects? Greater age? Greater BMI? Greater CD4 reconstitution? How do these factors differ between study populations? If these findings are to add more to the available literature using randomized therapy with larger study populations, the unique aspects of this study should be emphasized.

6. Are there inflammatory markers presented here that have not been presented elsewhere? What would they suggest compared to what we know about other markers? The authors mention a little about this, but perhaps emphasizing this a bit more would be helpful (ie, that sCD14 may not change because of ongoing gut damage).

7. On table 2, it is unclear what the one-sample t test is indicating when shown next to 10 different potential comparisons (5 different baseline groups and 5 different fold changes).

Minor revisions:

1. I would move the specific discussion about the various studies (currently in the intro) to the discussion section. Way too much information in the introduction.

2. NRTI is spelled out again in the stats section but has already been abbreviated.

3. IP-10 isn’t defined before it is used.

4. More data on the lab assays could be provided if available (CVs, impact of freeze-thaw)

5. On page 9, 2nd section, the authors say “ATV/r was associated with a smaller fall in Il-6…” This is misleading, as the p value was not significant at all. The
sentence should read “No significant differences in the change in IL-6…” or something to that extent.

Discretionary revisions:
6. Did anyone quit smoking while on the study?

**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 below.