Reviewer's report

Title: Quality of life in Patients treated with first line antiretroviral therapy containing nevirapine or efavirenz in Uganda: a prospective non randomized study.

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Reviewer: Mark Siedner

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Review of: Quality of life in patients treated with first line antiretroviral therapy containing nevirapine or efavirenz in Uganda: A prospective, non-randomized study.

Summary:
The authors report data from a longitudinal cohort study of people living with HIV initiating anti-retroviral therapy. The primary outcome of interest in their analysis is quality of life, as measured by the MOS HIV scale and the Global Person Generated Index, assessed at the time of ART initiation, and again three, and six months later. The primary predictors are ART regimen (nevirapine versus efavirenz) and time since ART initiation. The authors make two primary conclusions in this paper: 1) that quality of life improved over time on ART; and 2) that there was no difference between regimens in quality of life. Overall, the study strengths include a prospective observational cohort design, large sample size, important public health question including regimens currently in use in the region. Weaknesses include some limitations to the current statistical methods and/or interpretations (as discussed below), short duration of follow-up, and English grammar/language which would benefit from some additional proofreading. My main concern is that the primary conclusions drawn by the authors (that quality of life improved over time and that there were no differences in quality of life by regimen) are not totally supported by the current data analysis and summarization.

Major Comments:

1) One of the two major claims in this paper is that quality of life scores improved during the study observation period. The authors state in the results section “regardless of the ART regimen there was a trend towards an increase in the mean scores from baseline to six-month visit,” and present in Table 2 crude changes in MOH MHS and PHS scores over 6 months of ART and present crude changes in both of 0.8 points in median scores over time. However, there is no statistical test to support that this increase in significant. Moreover, even if these changes were statistically significant, the clinical relevance of an increase in these scores of 0.8 (or approximately 2% change from baseline) is unclear. Prior studies have shown much greater changes in MOS scores (4-9 points) with ART (see van Leth et al Antiviral Therapy 2004, Pitt et al, J Int AIDS Soc, 2009),
making this finding difficult to interpret (and potentially a statistically significant finding without a clinically meaningful one). At the least I would suggest the authors consider presenting statistical tests which demonstrate a significant increase in scores over time. But a more thorough alternative would involve comparing these changes to prior data and reconsidering whether these changes are meaningful.

2) The second major point is that there was no difference in changes in quality of life over time on ART by regimen (nevirapine versus efavirenz). However, this conclusions is also limited by two issues. First, because of the contraindications for nevirapine, particularly in women with high CD4 counts, it may be impossible to separate the effects of regimen and CD4 count (i.e. only 11% of those on nevirapine had a CD4>350 whereas 66% of those on efavirenz did). Although they report there was no collinearity, they do not present multivariable models with their final model covariates. Stratified analyses by CD4 count (or limiting the analysis to CD4 strata that include sufficient numbers of both regimens). Second, the authors report global adjusted coefficients by regimen in Table 3, and report interaction terms in the results text, but some increased clarity on the methods used would be helpful. The most telling variable to report in the tables/results would be the test of significance for the global time*regimen interaction, such that coefficient at each time point and for each regimen can be demonstrated. It appears that the authors performed these tests, but it is not clear from the results section what they did, with separate phrases “There was no evidence of interaction between ART regimen and study visit in the PHS model (p=0.767), MHS model (p=0.699) and the GPGI model (p=0.956),” and “The differences in the mean/median scores by ART regimen were not statistically significant over the follow up period. PHS (p=0.138), MHS (P=0.850) and GPGI score (p=0.303).”

3) The by-regimen analyses are interesting and important additions (and resolve the issue discussed above regarding confounding between regimens by CD4 count). However, they also suffer from two issues: 1) the improvement in PHS on efavirenz is called significant, yet the magnitude of increase was only 0.6, so of unclear significance. Also, most of the covariates in the model could be more telling if a time-by-interaction term were added. For example, the authors report a global lower PHS score for those with Stage III/IV disease (as would be expected). However, it would be of interest if the change over time in quality of life scores were tested (time*WHO stage), such that although those with advance disease start out with lower quality of life, perhaps they increase at a faster rate on ART.

4) The conclusion section does not appear to be supported by the data in this paper as currently written. For example

a. The authors state: “This study supports the new WHO guidelines for resource limited settings to initiate ART and higher CD4 count (>500)” yet none of the patients in this study had a CD4 >500 and they do not demonstrate (or test for significance) of a difference in quality of life by CD4 count at CD4 intitiation (this would require a time*CD4 count interaction term).

b. “The study also supports the Uganda national guidelines where the EFV based
regimen is the preferred option.” However, the authors report no difference in quality of life or other outcomes by regimen.

Overall, the discussion and conclusions do not give the reader a strong sense of what should be taken away from this study. Are the major findings that there was no difference between regimens? How do the scores compare to other studies (since MOS is well validated and used in many other studies, it might be interesting to know if QOL appears similar to that in other studies, or if the trend in change is similar or different from prior studies)

5) For the figures, instead of including the SD on the figures the authors should consider adding error bars which demonstrate graphically, so the reader can see if there is overlap between the estimates. Also the graphs are potentially misleading because the y-axis is fit to the lines, making relatively minimal changes (e.g. 0.1 change in PHS/MHS) appear large over time. Instead a graph with the full range of possible values might be more appropriate

Minor Comments:

1) The authors state in the abstract that the primary exposures of interest are “patient and disease factors” but that they adjust for “clinical factors, socio economic [sic] status, socio-demographic and behavioral characteristics.” From this sentence it is not clear what the difference between the primary exposures and the adjusted factors are. It would be helpful to clearly define a primary exposure of interest: e.g. ART regimen? Duration of ART? What is the hypothesis they are trying to test?

2) The results section of the abstract does not specify what the primary exposure of interest is in the sentence: “PHS unadjusted # coefficient…” coefficient for which covariate? Time on ART?

3) The background section is long and much of it (review of prior literature) can likely be moved to the discussion (and/or is already included in the discussion section). The background might be easier to follow if largely focuses on the public health problem being discussed, what data is lacking, and how the current study will address that deficit.

4) Did the authors consider fixed-dose combination or total pill burden as an alternate predictor of interest. While side-effect profile could be a major determinant of quality of life, dosing regimens might also be. So comparing TDF/3TC/EFV versus all others (e.g. NVP/3TC/AZT and EFV/3TC/AZT which are both twice daily) would also be of interest

5) Line 156 should read “the final” instead of “final the”

6) Line 183 would be clearer if it ended after the term “hypersensitivity rash (3.8%)”

7) The authors state a randomized trial comparing EFV and NVP should be considered, however, many of these have been done and meta-analysis on this subject has been published (see Pillay et al, Plos One 2013)

Grammatical comments:
The manuscript in general requires careful proofreading and editing. Some examples:

1) Quality of life should be abbreviated on its first use in the abstract if the acronym will be used here.

2) The Methods section of the abstract ends without a period.

3) The last sentence of the methods section does not read clearly. I believe it is meant to state: Data were analyzed using generalized estimating equations to identify associations between patient and disease factors and quality of life, adjusting for clinical factors…

4) Line 33: non-nuceloside reverse transcriptase inhibitor. Also in that same line the actual recommendation (this is a semantic point) is for nucleoside (AZT/ABC) or nucleotide (TDF) reverse transcriptase inhibitors.

5) Line 47: use of “I” to represent 1? – although not clear what is mean by less than I copy/mL

6) Line 50: due to the lower risk of virologic failure

7) Line 124 is missing a final period (full stop).

8) The 185 appears to be a sentence which should conclude the prior paragraph instead of start the one it is in.

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

**Quality of written English:** Needs some language corrections before being published.

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.