Reviewer’s report

Title: The impact of antiretroviral therapy on symptom burden among HIV outpatients with low CD4 count in rural Uganda: nested longitudinal cohort study

Version: 0 Date: 24 Jan 2017

Reviewer: Victoria Simms

Reviewer's report:

General comments

The data must have been collected in 2007 or 2008, but the paper does not say so. It needs to be made explicit, because it's part of the setting, like the location. I think you should make the age of the study into a strength. Place it in context. For example, you could discuss what we know about retention in care of Ugandan patients over the past 10 years and point to unmanaged symptoms as a possible cause of attrition.

I am concerned that all observations prior to ART initiation are coded to day 0, given that so much is made of the relationship between symptom burden and time in days. Looking at Figure 1, the pre-ART data seems to have a big effect on the shape of the curve, especially when you use square-root terms. It is possible that some of the change over time can be attributed to other time-changing factors, e.g. counselling and adjustment to diagnosis. These factors may be at work before ART initiation. If all the pre-ART measurements are close together (within a few days of ART initiation) then coding them all to be day 0 is fine, but if they are further apart the effect of time from diagnosis as distinct from time since ART initiation is lost. It would be possible to separate them by changing the time term to 'days since HIV diagnosis' and using ART initiation as a random effect.

The paper does not discuss the fact that 22% of participants died. Possibly some of the change over time can be attributed to survival bias, if participants who died had higher symptom burden at baseline. There's no indication of whether these deaths could have been prevented, or whether symptoms were different between those who died and those who didn't.

Abstract

It should be made clear that participants had a CD4 count<200, because that is no longer the expected population for ART initiation. 'Low CD4' is unclear.

In the list of symptoms that have changed, weight loss is named but the results are not given.
Methods

Sample selection criteria are missing. Every participant has at least 2 post-ART datapoints, so you must have dropped participants who had fewer observations. They may have been different from those who survived and stayed in follow-up. Without understanding how this group of 97 was selected we can't know whether their experience can be generalised to a wider group.

Details missing: How was data collected? On paper or electronically, and completed by the participant or by a nurse/counsellor? If electronic, what software was used? If on paper, how was data transferred to Access? It would be OK to refer to another publication and say the details are given there.

Results

The fitted equation for number of symptoms has some terms missing. Right now it says the answer is 400, regardless.

The GDI uses the same symptoms as the PHYS and PSYCH, so to some extent Figure 1 shows multiple testing. The graphs are not independent of each other. That's fine but should be acknowledged.

Discussion

In the paragraph on hunger, is it possible that participants remained hungry because they did not have enough food? You have a reference on that.

Could any of the symptoms actually be side effects of ART? E.g. fatigue can be caused by efavirenz. I'm not suggesting you start analysing all the symptoms by ART regimen, just mention the possibility of side effects.

Reference 11 was published in 2010 but is described as 'recent'.

Conclusions

'Commencing ART heralds the mark of personal acceptance of HIV status' - strong statement, could do with a reference. It ought to be true, but I don't think it necessarily is.

The last five sentences are not supported by the rest of the paper and should be cut. They are a stand-alone push for more palliative care research with 9 new references, 6 of them self-citations. If these references were relevant they would have been brought up earlier. Palliative care is not
even mentioned in any other part of the paper except as a keyword. You may want to consider sending the paper to an HIV journal.

Table 1

The MSAS-SF question originally was not 'I don't like myself', it was 'I don't LOOK like myself'. Check which version was used for data collection.

Table 2

I am not convinced about the use of p-values here. Firstly it is not clear what kind of test you have used to obtain them, although I'm guessing it was a McNemar test. Secondly, you are trying to use lack of evidence for change as evidence of changelessness. To take itching as an example, the meaning of the test result is 'If in reality itching did not change over time, there would have been a 20% probability of this study finding results of 65% at baseline and 57% at endline, or two numbers even further apart.' But you never had any reason to believe itching would remain constant over time, so evidence that the observed result might happen were that the case doesn't tell you much. It certainly doesn't tell you that there is no change over time, so the interpretation '31 symptoms remained unchanged' (page 7) is not supported.

I think a visual representation like a bar chart would more effectively make the point that symptoms persist on ART.

If you do want to use p-values, 3 decimal places is more than enough. There's no point implying a greater level of precision than you can really achieve.

The last column should say 'prevalence of high distress', not frequency. You are using the words frequency, burden and prevalence somewhat interchangeably, which is confusing because the MSAS-SF measures burden and frequency.

Table 3

Seems to be missing some footnotes. Be consistent about the number of decimal places. Are these variables Normally distributed?

Proofreading, not a complete list:

Page 5 line 51, 'respondent'
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
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