Author’s response to reviews

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

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Katie Wakeham; Richard Harding; Jonathan Levin; Rosalind Parkes; Anatoli Kamali; David Lalloo

Dear Editor of BMC Palliative Care,

We are very grateful for the opportunity to address reviewers comments on this manuscript. Please find responses below.

Yours sincerely

Katie Wakeham
Reviewer reports:

Reviewer 1: Thank you for this opportunity to review this manuscript on an important topic, palliative care in sub-Saharan Africa. The paper is well written. The references are substantive and represent a great synthesis of the current literature. The discussion was well done and placed the findings within the broader context of palliative care.

No comments.

Reviewer 2: 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.

The main RCT was referenced. Dates added.

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.

We stand by our representation of our data with ART initiation coded as day 0. The process of ART initiation is described in detail in the main RCT study paper (Parkes-Ratanshi R, Wakeham K, Levin J, Namusoke D, Whitworth J, Coutinho A, Mugisha NK, Grosskurth H, Kamali A, Laloo DG: Primary prophylaxis of crypto coccal disease with fluconazole in HIV-positive Ugandan adults: a double-blind, randomized, placebo-controlled trial. The Lancet infectious diseases 2011, 11(12):933-941.) ART was provided by local HIV care providers and had a set 6-week initiation process that involved counseling and education. It is possible that such an initiation process may change perception and reporting of symptoms, but this study presents real-life observational data and no-one would purpose not to council or prepare patients for ART. Days since HIV diagnosis is problematic in a cohort of individuals who are severally immunosuppressed and are likely to have had HIV infection for many years.
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.

It is highly likely that individuals approaching death have a higher symptom burden than those who are not. Indeed unsurprisingly the total number of symptoms and distress indices were higher in this study amongst those who went onto die during the study period. This observational study looked to describe symptoms and was not deigned to investigate symptom burden associated with imminent death.

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.

Methods

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.

Added and remains referenced in other publications.

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.

Yes this is possible. We did not collect data on access to food. We have expanded discussion on this subject.

Conclusions
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…

Have amended. Although we believe that the importance of reporting high symptoms burden is to push for more service and research provision in this area.

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.

I have removed the p values from table 2 and left the data as descriptive.