Reviewer’s report

**Title:** Predictors of mortality in HIV-infected patients starting antiretroviral therapy in a rural hospital in Tanzania

**Version:** 2  **Date:** 4 December 2007

**Reviewer:** Nicholas Paton

Reviewer’s report:

The authors have conducted a prospective observational study of 366 adults starting ART in Tanzania to determine the baseline factors associated with subsequent mortality. Although a number of similar studies have been conducted previously, this study is noteworthy because it is prospective and has been conducted in a rural setting. It is also one of the better studies in that appropriately normalised nutritional data (in particular BMI) has been collected. The main weaknesses are that the follow up is quite short (less than a year), about 20% of patients were lost to follow up or transferred to care elsewhere, CD4 counts were essentially not available, and the likelihood of critical confounding in the analysis.

Major Compulsory revisions

The authors note that all patients receiving ART from this clinic have been included in the analysis, and point to this as being a strength of the study. Whilst in principle this is a good thing, in this circumstance it represents a major weakness of the study by introducing a real possibility of major confounding. This is because most people initiated ART - with a therapeutic intent - based on clinical criteria (i.e. had stage III or IV disease), but the cohort also included pregnant women who initiated ART with a transmission prevention intent irrespective of disease stage. A proportion of the pregnant women will have had less advanced immunodeficiency (and therefore would have a better outcome) which can only be partly adjusted for by observed disease stage. Essentially these pregnant women are a completely different group and including them may, in particular, confound the associations between anaemia (probably negative confounding), BMI or gender and outcome that were found in the study. If CD4 measurements had been available, it would have been possible to adjust at least in part for this confounding effect, but this was not possible. The authors in part recognise this problem (in relation to BMI and pregnancy) by reporting the association of BMI and outcome with the 46 women excluded (the adjusted hazard ratio was reduced). However, I think the issue of confounding extends beyond this. I think it would be much better to exclude these pregnant women from the analysis altogether.

The unreliable CD4 count measurements that affected both entry to the ART programme and also prevent adjustment for immune-deficiency are also a concern, although I realise that this is a problem that cannot be avoided. Flow
cytometry measurements became available just 2 months before the end of the study. I think it is unnecessary to detail the methods of CD4 count analysis, given that there results are essentially disregarded.

Given that most patients started ART based on the criterion of stage of disease rather than on CD4 count, the best approach might be to restrict the analysis to those patients who started ART with stage III or IV disease. I realise that this means there may be further attrition in the study cohort size which may mean that some associations may no longer be significant. But the real associations are likely to become clearer and some of the (many) others which are perhaps artefactual, are likely to be weeded out. This analysis might also, if the authors wished, include the few pregnant women who started ART on the basis of having stage III or IV disease (rather than those who just started for PMTCT purposes) although this would still have the potential for confounding on some parameters as described. A secondary analysis with pregnant women included (or perhaps better, a separate analysis for the pregnant women alone could be described in a sentence or two of the results).

Given that the authors stratify the BMI into mild, moderate and severe malnutrition it is important to have some indication of the adjusted HRs for each of these specific strata. Mild to moderate malnutrition may also be associated with increased mortality, and it is of practical value to break this down further. Currently the analysis lumps together normal, mild and moderate malnutrition, and so it is not possible to ascertain the effects of moderate malnutrition, and it may also lead to an underestimate the HR associated with severe malnutrition. There are 134 patients with normal nutritional status, so this should be an adequate comparison group on its own. If numbers in the other strata really are insufficient to permit separate analysis, perhaps mild to moderate malnutrition could be grouped together.

It is important for interpretation to know how many people started on an ART regimen containing AZT and for how many patients overall (and of those on AZT) a post-treatment haemoglobin was used in the analysis. This needs to be mentioned in the results and addressed in the discussion as a potential confounder for the association with anaemia, if only to be dismissed.

Subjects who stopped ART were censored. Although this represents a minority of patients, this could create a bias e.g. patients may stop treatment because their condition is perceived to be deteriorating, and they may thus be censored just before death occurs. It would be better to use an intent-to-continue-treatment approach in the analysis (i.e. do not censor those who stop treatment).

It would be worth stating the level of univariable significance used for entering the variables in the multivariable analysis. It is implied that this is 0.05, but sometimes a higher value for this (e.g. 0.1) may be used to select variables so it is important to state clearly what was used.

It needs to be made clear in Table 2 what the HRs have been adjusted for. Is it all the other variables in the table? What about total lymphocyte count, which is
not significant in the multivariable analysis?

Discussion section: Para 1, reference to the ART-LINC data would be appropriate here (Egger M, Lancet 2002; 360: 119-129, or a more updated comparison from this cohort, if published).

Para 3 discussion on malnutrition cites several old (mostly pre-ART) studies from industrialised countries that are of limited relevance to the present study. However, there are two directly relevant studies from non-African settings that have identified a relationship between malnutrition and outcome in patients starting ART (i.e. identical approach to the present study) and these need to be cited in the discussion: Severe P, NEJM 2005; 353: 2235-2334; Paton NI, HIV Med 2006: 323-330. It might also be worth commenting on the fact that the hazard ratios for malnutrition and death are quite similar between the present study and the other studies that have used BMI to normalise for body weight.

Minor essential revisions
Background, line 4â#.. live (singular) rather than lives
Discussion, para 2â#). Change â##materialâ## to â##patientsâ## or â##studyâ##

Discretionary revisions
It would be helpful to have more detail on the percentage of patients prescribed each ART regimen
ZDV is sometimes preferred to AZT for abbreviation. Need to check BMC journal policy.

The finding of thrombocytopenia is interesting. Perhaps it could be due to marrow infiltration with TB or MAC. Some comment in results or discussion about the proportion of patients with an opportunistic infection at the time of starting ART would be helpful. Also some comment about the causes of death would be helpful, or some statement about the usual causes of death in this setting if there is no information on the actual causes of death in these patients.

Some comment on standardisation of weight measurements (e.g. was the same set of electronic scales used, or were they cross calibrated in any way) and height measurements (e.g. was a wall-mounted stadiometer used) would be informative.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

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

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:

I declare that I have no competing interests