Reviewer's report

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

Version: 2 Date: 19 November 2007

Reviewer: Margaret May

Reviewer's report:

General

1. This paper contains important data showing that anemia and low BMI at start of ART are predictors of early mortality in a rural hospital in Tanzania that did not have reliable CD4 count monitoring. Therefore a prognostic model based on haemoglobin and BMI could be a useful risk assessment tool in resource-limited settings. Currently there is not much information on the prognosis of patients starting ART in sub-Saharan Africa in centres that are not urban-based research orientated institutions and therefore this paper makes an important contribution to ideas on monitoring and evaluating ART in a rural settings.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

2. A cut off of 10 g/dL was used for haemoglobin (hb), but reference ranges of haemoglobin vary by sex with females having lower hb than males. Perhaps the statisticians should have used sex-specific cut-offs for hb. Not doing this might affect hazard ratios for other characteristics, particularly the HR for sex may be biased by ignoring the interaction between sex and hb. Is the hb distribution different between the sexes?

3. Statistical methods. It is a pity that the statistician has dichotomised age, hb, total lymphocyte count (TLC) and platelet count in the early stages of the modelling. It may be that TLC would be a better predictor of mortality if different cut-offs had been used, perhaps one considerably lower than 1.2 x 10^9/L might be appropriate. The distributions for platelet count and TLC above and below the cut-off are quite different eg platelet count splits 84:16 and TLC splits 55:45 so their predictive ability is likely to be influenced by the choice of cut-off. The authors also found that age dichotomised at 35 years was not associated with mortality, but this again may be due to the cut-off chosen. Background mortality would be expected to increase with age, but may not be evident until over, say, 50 years of age. Whilst dichotomised variables give a very simple prognostic model, one with more categories might be clinically more useful, although perhaps a bigger sample size is necessary to estimate this.

Reference:
Dichotomizing continuous predictors in multiple regression: a bad idea
Statistics in Medicine
Volume 25, Issue 1, Date: 15 January 2006, Pages: 127-141
Patrick Royston, Douglas G. Altman, Willi Sauerbrei

4. The finding that female sex is associated with better survival is interesting. However, it is likely that part of the association is due to female sex acting as a surrogate variable for younger age and less advanced disease stage. Females may also be more adherent to medication and receive more social support than males whilst on ART. A breakdown of variables by sex would improve the paper.

5. The graded association with haemoglobin across the quartiles is an important finding. However, it would have been better to look at 4 hb groups with fixed boundaries (perhaps different for males and females as appropriate and recommended by WHO) as using quartiles means that the results are more difficult to compare with other studies.

6. The prognostic model would have to be re-calibrated for use elsewhere or for patients starting ART in later years as within the cohort, prognosis improved with calendar time. As this may be due to health care givers gaining experience of ART, or the patients who received treatment more recently having less advanced HIV disease than in earlier years, it is difficult to see how the model could be used to make predictions in new patients or tested in other African settings. However, the concept of using haemoglobin and BMI for prognosis in those starting ART is useful. An important point is whether haemoglobin and BMI remain predictive for deaths after the first 6 months of ART or are only predictive for early deaths. This could be assessed by estimating a measure of discrimination, such as Harrell’s concordance statistic for the first 6 months and then in a second analysis from 6 months to 3 years.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

7. Typo P3 Background line 4 – live not lives.

8. Univariate and multivariate should be changed to univariable and multivariable throughout as they are referring to numbers of predictors and not numbers of outcomes in the regression models.

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Discretionary Revisions (which the author can choose to ignore)

9. It would be interesting to know how unreliable the measurement of CD4 cell count was using the manual system compared with the automated flow cytometer introduced in 2006. How reliable were measurements of haemoglobin or platelet counts? Would it be possible to use the data to compare how a model with and without CD4 count would perform in terms of predicting mortality?
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.