Reviewer's report

Title: Utility of CD4 cell counts for early prediction of virological failure during antiretroviral therapy in a resource-limited setting

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Reviewer: Maria A Munoz-Fernandez

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The objective of this work is to study the practical utility of CD4 cell count measurements as a substitute for viral load monitoring for predicting virological failure in a cohort of South African patients. The final conclusion is that CD4 cell count measurements cannot be used as a substitute for virological failure monitoring. The main problems of the article are in the methodology used and in the presentation of the results.

Table 1 provides little information; the following information should be added:

- Adherence. In methods appear: “adherence was monitored by clinic-based tablet refills”. However, in the results this parameter is not used and it is essential to predict virological failure. A multivariate model that does not include the adherence value is very poor.
- Follow-up time. Which is the minimal time that the patients than do not have virological failure are followed up? How many patients are followed up at 12, 24...months? What was the proportion of patients with undetectable VL at each time?. All these data can not be obtained from Kaplan Maier figures.
- Treatment. It is convenient to show basal treatment and change of treatment during follow up, combination of treatment, etc.
- How many patients are lost in the follow up (aids, death...)?.
- Other variables. CD8 cell counts, via of transmission, etc

The authors use the Wilcoxon test, but it is unknown between with variables, and the p is missed.

To measure correlation between CD4 and VL is more adequate to use the Spearman non parametric correlation coefficient than the Pearson test, because as you can observe in the figures 2A-C, there is a non-lineal association and, in addition, the VL is a truncated variable, in this case VL< 400 copies/ml or 2.6 LogVL.

In figure 2, the symbols do not represent patients, but observation pairs CD4-LogVL, thus, the same individual may be represented one or several times depending on when the virological failure is reached. This is an evident bias in the correlation between the absolute CD4 cell count values, increases in CD4 cell count and CD4 count slope. This figure should be substituted by a new figure
representing mean CD4 values or increases in CD4 from basal values taken every 3 months, for both virological failure and non virological failure groups. Moreover, the patients number at each time interval should be added.

The figures 2 D-F only show that the different measures of CD4 cell count have a normal distribution in both groups. The authors compare the CD4 cell count from patients, at the moment of virological failure, with the CD4 cell count from patients without virological failure. But, at what time are they using the CD4 cell count from the patients without virological failure? Basal time?. During all follow up?. If the values of all patients during all follow up are used, this is a bias.

Figure 3, Which is the significance of ROC curve?. It does not include patients, but observation of the slopes (consecutive differences of CD4 cell counts) that, in a same patient, can change of sign several times. The ideal is to represent the ROC curve with variables measured at basal time (at moment of undetectable VL) or with determinations performed before the basal time if possible, for example: nadir CD4 cell counts, VL and CD4 cell count median a year before to obtain undetectable VL, etc and of course only one observation for patient.

Minor comments: the number of decimal digits in p values should be consistent along the article. I would suggest 3 decimal digits.