Title: CD4 cell count recovery among HIV-infected patients with very advanced immunodeficiency commencing antiretroviral treatment in sub-Saharan Africa

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Author's response to reviews: see over
Dear Editor,

Thank you for your e-mail on the 27.02.06 regarding the above manuscript. I am grateful for the comments of the two reviewers and for the invitation to revise this manuscript. I am hereby submitting a revised version of this paper and below I have itemised my responses to the reviewers:

Review by Robert Colebunders

1. **Potential survival bias.** We agree with both reviewers that the issues surrounding the potential for survival bias was insufficiently discussed in the original manuscript and this has now been much more adequately addressed in the revised manuscript (Page 12, paragraph 2). Survival bias could affect the results in two principal ways:

   a. Inclusion of early CD4 cell count data points for patients who subsequently died during follow-up could have affected the rates of CD4 cell recovery (CD4 cell slopes).

   i. However, all patients included had data points for both baseline and week 16, and so phase 1 slopes could not have been affected in this way.
ii. Phase 2 slopes would potentially be affected by this. However, only 11 deaths occurred during the phase 2 CD4 response. Secondly, as stated in the original manuscript, WHO stage of disease is the strongest predictor of death in this cohort and yet CD4 cell count recovery was independent of this variable. Moreover, on page 7 of the original manuscript, it was stated that “Baseline characteristics and rates of CD4 cell count change in phase 1 and phase 2 did not differ when comparing the results of analyses of all eligible patients with those restricted to subjects who had data for every time-point (n=292); this was also the case for all subsequent stratified analyses.” Thus, our original analyses took care to examine for such an effect.

b. Death of patients may have been more likely among those who did not have good immunological responses to ART. This would tend to bias towards apparently enhanced responses (greater rates of CD4 recovery and lower rates of immunological non-response) among those within the lowest baseline CD4 strata in which the death rate was highest.

i. We agree that this is possible and we include this in the revised Discussion. However, such an effect may have been minimised by two other factors. Firstly, the majority of deaths occur in the first few weeks of ART among those whose disease is simply too far advanced; such deaths probably do not reflect a lack of immunological response to ART. Secondly, we have previously reported in this cohort that over 20% of early deaths during ART were attributable to immune reconstitution disease (Lawn et al. AIDS 2005: 19:2141-8; Lawn et al. AIDS 2005: 19:2050-2). Such deaths typically occur among those with very low baseline CD4 cell counts and yet who have the greatest immunological response to ART. These deaths, would tend to have exactly the opposite survival bias effect on CD4 cell count responses, reducing the overall survival bias effect.

2. **Minor text change:** We have changed ‘advancing’ to ‘advanced’ in page 3, last paragraph.
Review by Manuel Battegay

1. **Causes of death.** We consider the request of the reviewer to include the ‘reasons of death’ in this paper to be beyond the scope and aims of this paper. However, the point is very well taken that when considering the potential for survival bias in the different CD4 cell count strata, some indication should be given as to the relative death rates in these strata. We have previously published detailed analyses of rates and causes of early mortality within this cohort (Lawn et al. AIDS 2005: 19:2141-8; Lawn et al. AIDS 2005; 19:2050-2) to which we refer in the revised manuscript (rather than replicating already published data). In these analyses, we indeed show that death rates are associated with baseline CD4 cell count strata in a manner that one might expect. Thus, as discussed above, this has implications for potential survival bias as outlined fully above and revised in the Discussion section (page 12, paragraph 2).

2. **Survival bias:** See responses above.

3. **Citation of 2 additional references by Kaufmann et al.** These references, which we had missed in our original literature search, provide further useful data from the Swiss HIV Study Cohort and have been cited in the revised Discussion as suggested.

4. **No. of individuals with CD4 cell counts remaining below 200; clinical data:** The data we have presented do not suggest “very low number of individuals remaining below 200”. Our point is simply that those with the lowest baseline CD4 cell counts are likely to have CD4 cell counts that remain <200 cells/µl for a longer period that those with higher baseline counts. However, the point the reviewer makes about correlation of CD4 responses with clinical outcomes is an important one. We have recently generated data that show that both risk of mortality and risk of incident TB during ART are dependent upon the current CD4 cell count during treatment ie. those with good responses have reduced risk or morbidity and mortality (unpublished data). We cite these unpublished observations in the revised Discussion (paragraph at bottom page 12, top of page 13) to substantiate the last sentence of the Abstract conclusions.

Other revisions
A statement that this research was conducted in compliance with the Declaration of Helsinki has been inserted into the revised Methods section.

I hope that these responses and the revisions to the manuscript are satisfactory and that the Editorial Board can now consider publication of this in *BMC Infectious Diseases*. Please note that the Tables inserted at the end of the text are pdf inserts and so there is not risk whatsoever of the data shifting between columns.

Yours sincerely,

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