Author's response to reviews

Title: Long-term mortality in HIV patients virally suppressed for more than three years with incomplete CD4 recovery: A cohort study.

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Author's response to reviews: see over
To the Editor in chief.

10 September 2010

The BioMed Central Editorial Team.

Thank you for having reviewed our paper, which presents findings from the Danish HIV Cohort Study, and for giving us the opportunity to revise our paper.

We have read all the valuable comments carefully and hope that we have addressed the reviewers’ and the Associate Editors concerns satisfactorily.

Below you will find point to point answers to reviewers which are highlighted with italic. Changes in the manuscript are highlighted with yellow color.

We believe the manuscript has benefited from the review process and we hope you will find it suitable for publication in the revised form. We are of course willing to make further changes if necessary.

Should you have questions or concerns regarding the manuscript, please do not hesitate to contact me.

On behalf of all authors,

Frederik Neess Engsig
Response to editorial comments and reviewers:

Editorial comments:

* Please add a title to your Authors' Contributions section.

   Answer: This has now been done.

* Please add the email addresses of all authors to the title page.

   Answer: This has now been done.

Reviewer 1.

Reviewer: Robert Gross

Reviewer's report:

Major revisions:

although the authors state that HCV testing is "intended" to be done yearly, that
doesn't meant it actually happens. The authors need to acknowledge this
problem in their limitations section noting that the effect of HCV may be limited to
those in whom HCV was suspected and thus tested for.
Answer: This has now been added to the Discussion, page 13, last paragraph; “HCV testing in the cohort is “intended” and may only be performed yearly on known high risk groups in the cohort e.g. IDU why chronic HCV may be underestimated in the cohort”.

It is not clear how HCV status and IDU status were handled in the multivariable models. I presume they were extremely collinear and couldn't not go into the models simultaneously. The authors need to acknowledge this issue as well.

Answers: We agree and thank the reviewers for spotting this mistake on our behalf. We used binary logistic regression in order to identify predictors for immunological non-response. Selection of potential confounders was performed using the “change in estimate” method with age and gender forced into the model. IDU entered the model as part of a variable name “Route of infection” including Heterosexual, IDU and Other (homosexual transmission of HIV is the reference). By mistake “Route of infection” and “HCV” have been entered simultaneously in 2 of the adjusted estimates of predictors for immunological response (Caucasians and Route of infection). This has now been corrected, Table 1, Adjusted estimate for Caucasian and Route of infection. The estimate changed little and does not alter the conclusion.
The authors state that OIs are not different between the groups but the non-responders have a nearly 3x higher rate! This certainly suggests that the immunological non-response is biologically important—perhaps the study was just underpowered to find this different to be statistically significant.

Answer: We agree. As seen in Table 1 quite few patients have an AIDS defining event after index date (IRs; 3 (1.3%), INRs; 2 (3.6%)). It is certainly possible that there is a biological cause of the increased mortality in immunological non-responders related to immunodeficiency but that our study simply do not have power enough to demonstrate an association. The following sentence have been added to the Discussion, page 15, second paragraph; “Still, we cannot rule out that there is a biological cause of the increased mortality in immunological non-responders related to immunodeficiency and that our study simply do not have power to demonstrate an association”.

Minor revisions:

there remain several phrases that are awkward in English.

Answer: The paper has been edited by several persons fluent in English – in case the editor finds, that some phrases are “awkward” we will be happy to rephrase them – but then we would be pleased to have them further specified.
Reviewer 2.

Reviewer: Rui Wang

Reviewer’s report:

The authors have provided adequate responses to most of my previous comments in their revision.

I have two follow-up comments.

1. Regarding to the previous "Major Compulsory Revision" comment: To address the question whether the excess mortality seen among the INRs was mainly related to prolonged immunological suppression prior to successful HAART, a formal statistical test would be an interaction test. This can be done by putting an interaction term (INR status and yes/no to prolonged immunological suppression prior to successful HAART) in the Cox regression model. A significant interaction term would indicate that excess mortality seen in INRs among those with prolonged immunological suppression prior to successful HAART differs from that among those without.

   Answer: When performing analysis for interaction between non-immunologic response and time with prolonged immunological suppression prior to successful HAART adjusted for age and gender the MRR was 1.5 (0.3 – 8.5) for non-immunologic responders. The interaction
term was 1.9 (95%CI; 0.3 – 13.5). The result is close to our stratified analysis adjusted for age and gender which produces a MRR of 1.8 (95%CI; 0.3 – 10.2). We find, however that the stratified analysis is important to present why we keep that analysis and not the interaction term in the paper.

Similarly for IDUs. Please add these results in.

Answer: When performing analysis for interaction between non-immunologic response and IDU adjusted for age and gender the MRR was 1.4 (95%CI; 0.5 – 4.0) for non-immunologic responders. The interaction term was 10.0 (95%CI; 0.9 – 115.1). The result is quite close to our analysis stratified for IDU adjusted for age and gender which produces a MRR of 1.8 (95%CI; 0.6 – 5.1). As stated above we find that the stratified analysis is the most stringent way to present the data.

2. Regarding to the 1st "Minor Essential Revision" comment: Please incorporate the answers in the paper.

Answer: This has now been added under Methods, page 8, second paragraph; “(The cut point was based on the median age; IRs; 37.6 years (IQR; 32.1 – 45.3) and INRs; 42.6 years (IQR; 36.1 – 51.3))” and “(The cut point of one year was based on the median time from first CD4 cell count ≤ 200 to start of the suppressed period; IRs; 0.7 year (IQR; 0.3 – 2.2) and INRs; 1.5 years (IQR; 0.4 – 3.2))”.