Author's response to reviews

Title: The risk of AIDS-defining events is decreasing over time in the German HIV-1 Seroconverter Cohort

Authors:

Mathias Altmann (altmannm@rki.de)
Matthias an der Heiden (anderheidenm@rki.de)
Ramona Scheufele (scheufeler@rki.de)
Katrin Hartmann (katiliba@aol.com)
Claudia Houareau (claudiahouareau@web.de)
Barabara Bartmeyer (Gunsenheimer-BartmeyerB@rki.de)
Osamah Hamouda (hamoudao@rki.de)

Version: 4 Date: 2 March 2012

Author's response to reviews: see over
We would like to thank all reviewers for their positive evaluation of our manuscript, the very thorough review and their helpful comments that, in our opinion, contribute to further improving our manuscript. Please find below our answers to each of the reviewers’ comments.

We hope that the revised version satisfactorily addresses all issues raised by the reviewers and now is acceptable for publication in the BMC Infectious Diseases JOURNAL.

Item-wise reply

**Reviewer: Maria Dorrucci**

**Comments to the Author**

This study shows that free-AIDS survival following HIV seroconversion has continued to improve (even if not linearly) over calendar time with an overall 80% reduction in the risk of AIDS defining events compared with pre-1997 (when mono- or dual- therapies were used). And this is in part confirmed by other studies. Besides this is the first study that shows a significant reduction in the risk of AIDS after 2007. The draft is well written and presented; methods are appropriated. However, one main question arise about important data not shown in the draft.

The main issue that authors should address regards the follow-up: for how many person years of follow-up individuals have been followed in each calendar period? And how many events for each calendar period? In table 1 only 214 individuals have been followed in the pre-1997 that is really much lower than those followed in recent years at least n=465 in 2005-2006 and n=731 in 2007-2010. The doubt is: was the pre-1997 cohort representative of those seroconverted before 1997?

**Reply by the authors**

We thank both reviewers to have raised the issue on follow up / lost to follow up. Compared to other studies, our analysis was not based on a fixed date for the right censoring, but on the last medical visit of each patient. Therefore, we were confident that events during this period were not missed. At the time of the first analysis (up to February 2011), due to delays in follow up visits and in reporting, follow up data for the last calendar period (2007-2010) were missing. For the present analysis, we completed our dataset with more accurate data (up to February 2012). Inclusion of these data on follow up had some implications on our results –e.g. more AIDS defining events and changes in point estimates. We think these changes have increased the quality and the reliability of our manuscript.

Data for the pre-1997 period was retrospective collected, and therefore, have a lower number of recruited seroconverters compared to after 1997. A discussion regarding the reliability of this period was added (p. 16, line 346).

**Modification of the manuscript**

Number of AIDS events and follow up/lost to follow up rates were added for each calendar period (p. 21, Table 1).

**Discussion section** (p. 16, line 346)
“[…] data for the pre-1997 period are retrospective and may not be as reliable as the data from the prospective period. Patients in this period were included regardless of their AIDS outcome; a survivorship bias might have been introduced as patients have to sign an informed consent at study entry. Regarding the pre-AIDS mortality, this bias might have been limited as the pre-AIDS mortality rates were relatively stable and at a very low level during the prospective periods. Regarding the lost to follow up, rates were relatively stable over the time periods but were at a high level. If lost to follow up subjects have a more rapid progression, the pre-1997 period in our study might underestimate the risk of AIDS in comparison to the other periods but our results remain conservative to this regard. Alternatively, we might have overestimate the first decrease in the AIDS risk if lost to follow up subjects have a slower disease progression.”

A second issue about data: no mention of the number of deaths has been done. Which is the trend of pre-AIDS mortality? pre-AIDS mortality is a competing-event that can affect results.

**Reply by the authors**

Data on mortality were not shown because mortality data were not available for the pre-1997 period. Indeed, informed consent is needed at study entry. Now, we included information on pre-AIDS mortality for the prospective periods (Table 1) and added text in the method (p. 8, line 150), results (p.10, line 205) and discussion (p.15, line 338) sections.

**Modification of the manuscript**

**Method section** (p. 8, line 150)

“Individuals with pre-AIDS mortality were censored as AIDS free at the moment of death.”

**Result section** (p.10, line 211)

“Death without AIDS, which accounted for 27 of the cases, had a relatively stable rate over calendar periods after 1997 (as this information was not retrospectively collected for the pre-1997 period), from 0.6 per 100 PY in 1997-2000 to 0.3 per 100 PY in the following periods.”

**Discussion section** (p.16, line 350)

“Regarding the pre-AIDS mortality, this bias might have been limited as the pre-AIDS mortality rates were relatively stable and at a very low level during the prospective periods.”

Another issue regards statistical analysis: no clear definition of follow-up has been given. I suppose that individuals were censored at last visit? Or when?

**Reply by the authors**

Indeed, individuals were censored at the last medical visit or at their first AIDS event. We think that the introduction of the follow up and lost to follow up discussion will make this censoring
strategy clearer. Furthermore, we changed the sentence and his position in the method section (statistical analyses, (p. 8, line 148) as follow:

Modification of the manuscript (p. 8, line 148)

“Individuals were censored either by the day of the last medical visit or by the date of the first AIDS-defining event, […]”

Minor essential revisions

Methods

-table 1 1997-2000 was repeated twice

Reply by the authors

We have corrected this mistake.

Statistical analysis

-The presence of HCV or HBV infections were not considered as a covariate and authors should add in the model. If they have no information about these infections, they would consider as a limit in the discussion.

Reply by the authors

We agree that non-AIDS-related competing mortality such as hepatitis B and C could bias the results. However, the pre-AIDS mortality in our cohort is so small that is should not affect our results (see added text for the pre-AIDS mortality question). Furthermore, we added a text in the limitations.

Discussion section (p.16, line 359)

“Further analyses (e.g. competing risk analysis) should be performed to better answer that issue.”

Results

-The follow-up distribution was not well described. Median follow-up and range should be shown.

Reply by the authors

As for the first question, we added information regarding time of follow up for each calendar period. In the result section, we also added median time and range of follow up for the whole cohort.

Modification of the manuscript

Table 1 (p. 21)

Result section (p. 10, line 194)
“Over the 8906 person-years (PY) of follow up (median = 2.8 years; range 1 day – 23.9 years), […]”.

Reviewer 2: Patrizio Pezzotti

Comments to the Author

The study evaluates the change on the risk of AIDS by 4 different calendar periods, defined on the basis of the availability of combination antiretroviral therapy, in a German cohort of HIV-positive individuals. The cohort includes only individuals with well estimated date of seroconversion. The study question is well defined and overall I have a positive opinion of the manuscript. However, the manuscript should be improved in several sections before acceptance.

Major Compulsory Revisions

The methods section is lacking information about death cases without AIDS and lost to follow-up and details should be given to better understand the magnitude of these problems that can bias the obtained results. Furthermore, in my past experience with similar data I used different ways to define the date of "administrative" censoring for those alive and still AIDS-free and there was debate in the past in literature on how to deal with these problems (see for example: Cozzi Lepri A, Phillips AN, Pezzotti P, Rezza G. Is the clinical course of HIV infection changing? Study's censoring strategy may be source of bias. BMJ 1997;315(7117):1237). Information about influence of censoring strategies and death without AIDS should be given in the results section and in the discussion section.

Reply by the authors

Thanks for raising this important issue. As we replied previously (see first question of Ms. Maria Dorrucci), our analysis does differ from other studies because we did not use a fixed date for the right censoring but the last medical visit of each patient. Time periods at risk are not missing AIDS events but we have to discuss the lost to follow up rates for each period.

At the time of the first analysis (up to February 2011), follow up data for the last calendar period (2007-2010) were missing due to delays in follow up visits and in reporting. For the present analysis, we completed our dataset with more accurate data (up to February 2012). Inclusion of these data on follow up had some implications on our results –e.g. more AIDS defining events and changes in point estimates. However, we think these changes have increased the quality and the reliability of our manuscript.

Modification of the manuscript

Method section (p. 8, line 150)

“Individuals with pre-AIDS mortality were censored as AIDS free at the moment of death. Lost to follow up was defined as the number of last medical visits in each calendar period. Due to a delay of reporting, last medical visits in 2010 were not considered as lost to follow up but as unknown status.”

Results section (p. 21, Table 1)
Results section (p. 10, line 213)

“Pre-AIDS mortality and lost to follow-up

Death without AIDS, which accounted for 27 of the cases, had a relatively stable rate over calendar periods after 1997 (as this information was not retrospectively collected for the pre-1997 period), from 0.6 per 100 PY in 1997-2000 to 0.3 per 100 PY in the following periods. The lost to follow up rate was also relatively stable over the calendar periods, except for the pre-1997 period where it was lower (0.4 per 100 PY) (Table 1). “

Discussion section (p.16, line 349)

“[…] data for the pre-1997 period are retrospective and may not be as reliable as the data from the prospective period. Patients in this period were included regardless of their AIDS outcome; a survivorship bias might have been introduced as patients have to sign an informed consent at study entry. Regarding the pre-AIDS mortality, this bias might have been limited as the pre-AIDS mortality rates were relatively stable and at a very low level during the prospective periods. Regarding the lost to follow up, rates were relatively stable over the time periods but were at a high level. If lost to follow up subjects have a more rapid progression, the pre-1997 period in our study might underestimate the risk of AIDS in comparison to the other periods but our results remain conservative to this regard. Alternatively, we might have overestimate the first decrease in the AIDS risk if lost to follow up subjects have a slower disease progression. Considering only the periods after 1997, a bias might have been introduced if lost of follow up subjects differ between the periods. Further analyses (e.g. competing risk analysis) should be performed to better answer that issue.”

Another aspect not discussed is the change of risk by calendar period due to change in the characteristic of the circulating virus. By the way I highlight that the cohort is characterized by a surprising very large number of enrolled seroconverters in the most recent calendar period. Is this due to the inclusion in the cohort of new clinical centres or due to other reasons? Please provide information about this point and in case add some comments in the discussion section.

Reply by the authors

Changes in the characteristic of the circulating virus in this cohort have been described elsewhere (Bartmeyer B. et al. Prevalence of transmitted drug resistance and impact of transmitted resistance on treatment success in the German HIV-1 Seroconverter Cohort., PLoS One. 2010 Oct 7;5(10):e12718). Results indicate that the prevalence of transmitted drug resistance remained stable over time. We added this information on our discussion.

The number of recruited seroconverters increased over time because the study became better established and not because of an increased number of inclusion centres.

Modification of the manuscript

Results section (p.9, line 182)

“Both the number of included patients and follow-up increased largely after 2001, when the study was better established.”

Discussion section (p.13, line 280)
“[…] this association between HAART uptake and AIDS risk. Increasing HAART uptake benefits could have been balanced by an increasing prevalence of Transmitted Drug Resistance (TDR) over the calendar periods. However, one previous study in the same cohort of seroconverters indicated a stable prevalence of TDR over the time [13]. Other factors related to the improvements in drug quality […]”

The authors should also discuss their results comparing with those reported for other cohorts not based on seroconverters.

Reply by the authors

Because estimates of changes in survival (time to AIDS) might be biased when duration of HIV-1 infection is not known, it is very difficult to compare with other cohorts not based on seroconverters. Therefore, we did not introduce such comparisons.

The results section would be improved if data about specific drugs and combinations mainly used in the different calendar periods were given.

Reply by the authors

We added some information in the result section. However, the Seroconverter study does not differ from the other countries in that regards. We do not want to give much more details as it would confuse more than highlight our main results.

Results section (p.12, line 245)

“While mono and dual NRTI therapy were mostly used before 1997, main combinations of HAART included 2 NRTI/PI till 2001 and a mixed of 2 NRTI/PI and 2 NRTI/NNRTI after this date. “

I suggest to use as reference category the 1997-2000 period instead of pre-1997. This will permit to highlight the most important results.

Reply by the authors

This is true. We changed the reference category as suggested.

Modification of the manuscript

Method section (p.8, line 146)

“The second calendar period (1997-2000) was used as reference period in the Cox proportional hazard model.”

Results section (p.11, line 221)

“Compared to 1997-2000, hazard rations were 2.6 (95%CI, 1.6-4.8; p=0.000) in pre-1997 and 0.5 (95%CI, 0.3-0.8; p=0.007) in 2007-2010 (Table 2).”

Minor Essential Revisions

Abstract
I suggest to add a sentence in the results section that the effect of age (although not statistically significant) is decreasing over time.

Reply by the authors
As this result was not statistically significant, we think it might only stay in the discussion.

For documented seroconverters in the methods section is described that the cohort may include individuals with an interval between negative and positive test up to three years; however, in the results section it is reported that this interval varied between three and 12 months. This is not substantial for the manuscript but unusual in practice.

Reply by the authors
The delay of three years between the last negative and the first positive test in the method section corresponds to the inclusion criteria. However, this delay is lower in the reality as shown in the results section. This result might indicate that our study population is very keen to be medically followed-up, which is often the case when considering seroconverter studies.

HIV exposure categories (rows 149-152)
I suggest to revise the sentence that sounds inappropriate combining behaviours with origins of patients. I feel that some readers could find it not very nice.

Reply by the authors
You are right. We rephrased it.

Modification of the manuscript
Method section (p.8, line 159)
“HIV exposure categories included, in the following order of priority: injecting drug users (IDU), men who have sex with men (MSM), heterosexuals, other (including blood transfusion and occupational acquisition), and unknown. Among heterosexuals, a new group including people originated from high prevalence countries (HPC) was created.”

Results section: AIDS defining events (rows 186-189)
Are they only the first ADEs or all those observed? Please specify. It will be useful to provide numbers of ADEs per period and the percentages of some of them to provide information about the change of the AIDS spectrum.

Reply by the authors
This is only first AIDS defining events. We corrected this sentence.

Modification of the manuscript
Result section (p.10, line 198)
“Over the 8906 person-years (PY) of follow up (median = 2.8 years; range 1 day – 23.9 years), 196 first AIDS-defining events were reported, […]”
Methods and results section

It is written in the methods that documented seroconverters may have an interval between negative a positive test up to three years. In the results you reported that the enrolled documented seroconverters had an interval between 3 and 12 months. This is not substantial for the manuscript but unusual in practice. Please provide clarifications.

Reply by the authors

Already answered previously

Additional comments from the Associate Editor:

I recommend the authors pay particular attention in replying to the major comments of the reviewers. In the methods it is stated that the German seroconverter cohorts collects baseline CD4 and viral load data. Did the authors observe changes in these parameters over the different calendar year periods? Did these variables correlated with the outcomes analyzed?

Reply by the authors

These two markers are strong prognostic markers in people with HIV-1 and are widely used in RCT and in seroprevalent cohort. For seroincident cohort with persons at equal duration of infection, adjustment is made on the duration of infection. Therefore, we have not adjusted for changes in CD4+ cell count and HIV RNA since this would, in effect, only estimate any part of the population effect of HAART not mediated through these two disease markers.