Author's response to reviews

Title: Incidence and risk factors for AIDS-related mortality in HIV patients in China: a cross-sectional study

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Author's response to reviews: see over
Dear editors:

We are grateful to your and other reviewers’ critical comments and thoughtful suggestions. Based on these comments and suggestions, we have made extensive modifications to the original manuscript (Manuscript ID: 1920346582122278). All changes made to the text are highlighted by using the annotation mode in MS Word. We hope that the new manuscript will meet your journal’s standards. Below you will find point-by-point responses to the reviewers’ comments/questions:

Part A (Reviewer: 1)

1. Comment: General comment is that the English language of this manuscript should be checked more carefully, some statements do not feel correct.
   Reply: We have gone over the English with the help of a native English speaker and then corrected the spelling and syntax errors.

2. Comment: The title of this manuscript does not according to the results, suggest re-evaluate.
   Reply: We have rephrased the title as suggested.

3. Comment: Other confounding factors should be considered in investigation of Risk factors for mortality in HIV infected patients.
   Reply: Many thanks for the reviewer’s comments. Similar to previous studies (Fujie Zhang, Zhihui Dou, Ye Ma, et al., Effect of earlier initiation of antiretroviral treatment and increased treatment coverage on HIV-related mortality in China: a national observational cohort study. The Lancet Infectious Diseases, 2011, 11(7):516-524.; Jiang H, Xie N, Cao B, Tan L, Fan Y, Zhang F, et al. Determinants of Progression to AIDS and Death Following HIV Diagnosis: A Retrospective Cohort Study in Wuhan, China. PLoS ONE 2013,8:e83078.; Wong KH, Chan KCW, Lee SS. Delayed Progression to Death and to AIDS in a Hong Kong Cohort of Patients with Advanced HIV Type 1 Disease During the Era of Highly Active Antiretroviral Therapy. Clinical Infectious Diseases 2004,39:853-860.), we have analyzed factors associated with mortality including: gender, age, transmission routes, marital status, received highly active antiretroviral therapy or not. We considered the influencing factors included are enough.

Results

4. Comment: The logic of results is poor, suggest re-evaluate.
   Reply: We thank the reviewer for this suggestion. We have re-sorted the contents of the results. The content of the results has now been divided into four parts, including: General characteristics, Characteristics according to time since HIV diagnosis and HAART, Underlying cause of death and Characteristics of treated deaths by baseline CD4 cell counts. (P7, L94; P8, L130; P9, L159 and L164)

5. Comment: Description in second and third paragraphs does not fit very well with Table 1, should be re-structured.
   Reply: The paragraphs have been restructured to be compatible with Table 1.

6. Comment: -“An upward trend was found in the sex ratio (male: female) of deaths from 2006 to 2010, and 79 during this time the mean age of death age increased from 39.2 to 44.2”. The
information of this sentence should be corrected according to table 1. How the significance of trend?

**Reply:** We have revised this sentence as follows: “The median age of death was 38.5 years old, 38.4 years for males and 38.7 years for females”, according to Table 1. (P7, L103 and L104)

7. Comment: Sixth paragraph, the meaning of this paragraph is complicated, should be re-written.

**Reply:** The sixth paragraph has been revised as follows: “The median time between diagnosis and death for patients receiving treatment was 1.6 years (IQR: 0.44, 3.62), while the median time between diagnosis and death for untreated patients was 0.5 years (IQR: 0.1, 2.2).”

8. Comment: Percentage should be added in table 2 and table 3 to show the trends clearly.

**Reply:** We thank the reviewer for this suggestion. We have added percentages to Tables 2 and 3.

**Discussion**

9. Comment: Suggest discuss more and exactly on the risk factors of mortality.

**Reply:** We have added three risk factors for mortality according to the results of our statistical analysis by logistic regression. The three risk factors are age, route of infection and whether the patient accepted HAART or not. We also have added a discussion in detail on why these are risk factors for mortality.

**Part B (Reviewer: 2)**

**Title and objective**

1. Comment: It seems that the study focused on the AIDS-related mortality rather than the overall mortality of the reported HIV-infected cases. Rephrasing is suggested.

**Reply:** We have rephrased the title as suggested.

**General**

2. Comment: Standardize the terms HIV/AIDS deaths, HIV deaths, AIDS deaths, AIDS-related deaths throughout the text.

**Reply:** We are grateful for your instructive suggestion and have standardized the term as “AIDS-related deaths.”

**Abstract-Results**

3. Comment: First sentence, define exact period with which data is extracted from the databases, instead of "by the end of December 31, 2010"

**Reply:** We have added the exact period “in January 2011” to the revised manuscript to describe when data was extracted from the databases. (P3, L8)

4. Comment: Report of change in annual incidence during the period would be useful.

**Reply:** We have added the estimated annual number of new infections during the study period in the part of results. (P6, L97-99) Data is collected on the number of new report cases every year, but it is difficult to determine the exact number of actual new cases in that year because many cases are unreported. In the revised manuscript, we have provided an estimated number of new
infections each year.

5. Comment: Last sentence, revise "death" to "AIDS-related death".
Reply: It has been revised to "AIDS-related death". (P3, L12)

Methods - Cause of death
6. Comment: Tuberculosis is prevalent in China, should those deaths be taken out from the analysis of AIDS-related death if the last CD4 did not fall below 200/µl? Otherwise the no. of AIDS-related deaths may be overestimated.
Reply: We agree that those deaths should be taken out from the analysis. We previously considered this problem but neglected to include it in our original manuscript. Therefore, we have added the related content at the end of “Cause of death”. (P6, L69-72)

Methods - Identify key variables
7. Comment: Line 50, first sentence is hard to be understood. Does it mean late diagnosis of HIV is defined as diagnosis of AIDS and death happened within one year from HIV diagnosis?
Reply: We have revised this phrase in the manuscript to read as follows: “A late diagnosis of AIDS-related death was defined as a diagnosis of AIDS (CD4 < 200 cells/µL or AIDS-related clinical symptoms) [26] where death occurred within one year after an HIV diagnosis.” (P6, L74-76)

8. Comment: prospective data is available in the database since 2004, why data in 2004 and 2005 not included in the analyses.
Reply: We are grateful for the suggestion. We have added the following explanation in the part of “Methods- Data collection”: “HAART was scaled up nationwide in 2003, with data prospectively included in the database after 2004. However, the data collected from 2004 to 2005 covered only part of the provinces, and nationwide collection was not yet initiated; for this reason, the mortality data did not start until 2006.” (P5, L52-54)

Methods - Statistical analyses
9. Comment: Why compare late diagnosis cases with untreated cases, but not treated vs untreated cases? That would lead to a more logical conclusion on the effect of HAART on survival
Reply: We found that there was very low mortality in the treatment population. HAART was scaled up nationwide in 2003 in China so the period available for study was relatively short. Therefore the significance of analysis in the information about death in treated patients is not very large. We have also added results and discussions on the association between mortality and whether the patient initiated HAART or not.

10. Comment: Line 61, something missing after "Chi-square tests"? Statistical analyses other than chi-square such as t test performed for comparison of continuous variables?
Reply: We have revised this sentence to read as follows: “A logistic regression was applied to determine the risk factors of HIV/AIDS mortality”, to make the representation more concise and exact. (P13, L87-88)
Results
11. Comment: Line 68 - 70, better state the total number of AIDS-related death among all reported cases and the range of annual incidence during the period.
Reply: We have added the number of AIDS-related death during the period. Data is collected on the number of new report cases every year, but it is difficult to determine the exact number of actual new cases in that year because many cases are unreported. In the revised manuscript, we have provided an estimated number of AIDS-related deaths each year.

12. Comment: Line 79, delete "age" after death
Reply: We have deleted the extra term.

13. Comment: Revise title of Table 2 as "The provincial statistics of the cumulative reported cases and the cumulative death cases with HAART".
Reply: We have revised the title of Table 2 as "The provincial statistics of the cumulative reported cases and the cumulative AIDS-related death cases with HAART".

14. Comment: Put down the day range between diagnosis and death clearly in Table 3
Reply: We have added more detailed content in Table 3. (P9, L139-142)

15. Comment: Line 117, rephrase "Most of the death cases who had not initiated HAART .."
Reply: We have rephrased the line as follows: “Patients aged 50 years old or older (AOR: 3.41, CI: 1.47-7.91) and those who had not received HAART were also significantly likely to have a high mortality.” (P10, L168-169)

Discussion
16. Comment: Line 134-135, the manuscript does not provide data on the no. of reported HIV cases by gender. More importantly, comparison of death rates rather than the absolute no. of deaths between the two gender is required to substantiate the statements.
Reply: Although female gender had a high risk of mortality in the unadjusted analysis, this risk factor was not included in the adjusted analysis. Therefore we have deleted this part of the discussion.

17. Comment: Line 153-154, the sentence is not quite relevant, as higher rate of HIV transmission does not equate to higher mortality.
Reply: We have added three risk factors of mortality according to the results of our statistical analysis by logistic regression. The three risk factors are age, route of infection and whether the patient accepted HAART or not. We have removed the discussion on the association between marital status and risk factors of morality in the revised manuscript.

Conclusion
18. Comment: Line 196, rephrase "early diagnosis maximize the effectiveness of HAART"
Reply: We have revised the line as follows: “In summary, early diagnosis of HIV can maximize the effectiveness of HAART.” (P14, L262)
Yours sincerely,
Zhihang Peng