Author’s response to reviews

Title: Risk factors associated with prevalent and incident syphilis among an HIV-infected cohort in Northeast China

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Version: 3 Date: 6 November 2014

Author’s response to reviews: see over
Dear Editor:

Thank you for your kind letter of “MS: 1464855116143622 - Risk factors for prevalence and incidence of syphilis among a HIV-infected cohort in Northeast China” on October 14, 2014. We revised the manuscript in accordance with the reviewers’ comments, and carefully proof-read the manuscript to minimize typographical, grammatical, and bibliographical errors. We have modified the manuscript accordingly, and detailed corrections are listed below point by point:

**Part A (Reviewer 1)**

**Major Compulsory Revisions**

1. this manuscript discussed the factors correlated with prevalence case and incidence cases. However, the author did not discussed the difference in term of risk factors between this two different but somehow overlap populations.

**Response:** We had revised. Please check in the third paragraph in the discussion section (line 15 of page 12).

2. In the limitation part, the author did not mention the possible bias induced by loss to follow up, the author also did not mention the possible information bias.

**Response:** In the limitations part, we had added” Thirdly, higher loss to-follow-up is another challenge of our study. By the end of the study period, about 21.7% of the participants were lost to follow-up, and this may cause selection bias. Fourthly, because HIV and syphilis are sensitive topic for participants, so this study cannot exclude social desirability bias.” (line 8 of page 14)

**Minor Essential Revisions**

1. add ref in line 18 of page 4, line 13 of page 5, line 1 of page 11

**Response:**


12countries/ce_CN_Narrative_Report%5B1%5D.pdf]" (line 21 of page 4)


**line 1 of page 11:** add ref 20-21. (line 8 of page 12)

2, for the inclusion criteria, the author excluded those who were illiterate, which may introduce important selection bias for the assessing factors correlated with prevalence cases,;

**Response:** We had substituted with “were 18 years or older and were able and willing to provide written informed consent”, because all of participants are literate. (line 22 of page 6)

3, Please give definition of HIV history;

**Response:** We had added"HIV infection status was based on positive test results from two peripheral blood samples by HIV ELISA and confirmed by western blot(Genelabs Diagnostics, Singapore). All HIV testing sites were certified by the National AIDS Reference Laboratory at China CDC. "(line 10 of page 6)

4, Please delete the sentence of "The prevalence....." at line 21-23 at page 10.

**Response:** We had deleted.

5, What does "The porportion...." at line 8-9 at page 11 mean?

**Response:** We had substituted with “In China MSM accounted for 0.3% of the total reported HIV/AIDS cases in 2006. This figure rapidly increased to 13.0% in 2011”. (line 13 of page 13)
Part B (Reviewer 2)

Major Compulsory Revisions

#1. It was clearly stated in the limitations section that the researchers were unable to evaluate health behaviors, only demographic and serologic predictors. However, this is not clear in the introduction and especially the first sentence of the conclusion.

Response: In the part of conclusions, we revised the first sentence with “The prevalence and incidence of concurrent syphilis were moderately high among PLWHA in Northeast China.” (line 17 of page 14)

#2. Once participants developed syphilis, did the researchers continue to follow them? This is unclear in the manuscript.

Response: During the follow-up, we calculated survival as time from baseline initiation to syphilis seroconversion or censoring. Patients were censored at dropout, loss to follow-up, or on May 31, 2013, whichever came first. Those who were diagnosed with syphilis infection were referred to the STI clinic in the same hospital for treatment. (line 3 of page 7)

#3. Who were the 292 who did not take the syphilis test? Was this because they refused blood testing for syphilis or were they not tested as a result of a health systems error? Does this include patients who did not give informed consent?

Response: We had revised with “As shown in Figure 1, 1302 PLWHA who were registered at the HIV clinic were invited to participate in the study, 243 did not meet enrollment criteria, 46 declined enrollment and 3 did not return for enrollment. Therefore a total of 1010 participants were included in the analysis of estimating HIV prevalence at baseline.” (line 16 of page 9)

#4. How did the researchers obtain adjusted odds ratios? There is no mention of what was controlled for in the multivariate logistic regression. This should be clearly explained.
Response: In the data analysis part, we added “We analysed covariates including sex, age (≤24, 25–39, and ≥40 years), ethnicity, marital status, occupation, education, HIV transmission route (heterosexual, homosexual and others), HIV diagnosis clinic (VCT, hospital, others and unknown), baseline CD4 count (<200, 200–349, 350–499, and ≥500 counts/mL), baseline VL (≤100000 and >100000 copies/mL).”

(line 19 of page 8)

#5. Receiving ART appears to be associated with lower rates of syphilis at time of enrollment but higher risk of developing syphilis during study period. This is not adequately discussed or explained. Why would it be both a protective but also a risk factor?

Response: we had revised in the third paragraph of discussion “Conflicting results are provided by studies analyzing the association between ART and STIs[34-36]. Our research data show that the syphilis seropositive rate within ART patients was significantly lower than treatment naïve patients. The possible reasons for this finding include: yet unrecovered immune status, degenerative sexual desires and lower frequency of unprotected sexual behaviour. Our study further shows that ART had significantly higher risk for syphilis seroconversion compared to untreated PLWHA. This is consistent with the results of Stolte in Amsterdam[34], but Huang[37] showed that ART was not statistically significant in decreasing syphilis incidence. Though ART have substantially lowered HIV RNA levels and decreased HIV infectiveness considerably among PLWHA [38], apart from beneficial clinical effects, treatment advances may have unintended effects on sexual behavior. Some evidence suggests that since ART became available, the prevalence of unprotected sex[34, 39] have increased. Sexually transmitted co-infections increase HIV infectiveness through local inflammatory processes and offset the ART treatment effect about HIV secondary prevention. These findings suggest that, with the expansion of ART in China, health education, behavior interventions and STI monitoring should be strengthened among ART patients.” (line 15 of page 12)
#6. Not only was the syphilis prevalence high, but also the incidence was also incredibly high. This should be discussed in greater detail. I would have liked to see some more references comparing both the prevalence and incidence to other studies, either inside or outside of China. Why do the author’s think that incidence rate was so high (>20% seroconversion during a median follow up of 9.4 months)? This is probably one of the strongest findings of the paper and should be expanded upon.

**Response:** We had revised in the second paragraph of discussion “The clear possibility that spreading of HIV with high syphilis prevalence and incidence may occur represents a new threat. Our findings provide important information to implement a syphilis screening and treatment program for PLWHA across China. Syphilis is a marker of unsafe sex practice[20, 21], the high syphilis prevalence and incidence mean PLWHA who had yet known their were HIV+ still engaged in unprotected sex in our study. Behavioral intervention can reduce HIV transmission risk among HIV+ MSM[33], consequently more efficient education programs, particularly safer sex behavioral intervention are urgently needed to reduce risk of acquiring STI and transmitting HIV among PLWHA in China.” (line 4 of page 12)

#7. In what ways did participants self report that they were homosexuals and/or MSM? These terms should not be used interchangeably. Was this self-report of sexuality or was this a self-report of sexual behaviors? If it was based on behaviors, then homosexual and heterosexual should be changed to men who have sex with men and men who have sex with women.

**Response:** We judged the infection route based on behaviors, so homosexual was changed to men who have sex with men(MSM).

#8. The first sentence of the conclusion claims that they have the first study reporting upon syphilis and risky behaviors. Is this in reference to syphilis incidence being a surrogate for risky sexual behavior? This paper did not investigate risky behaviors. The first sentence of the conclusion cannot make claims about things the study did not investigate.
Response: In the part of conclusions, we revised the first sentence with “The revalence and incidence of concurrent syphilis were moderately high among PLWHA in Northeast China.” (line 17 of page 14)

#9. Figure 1 is unclear. Why were 376 excluded? Only 200 were syphilis positive at the beginning of the study. Also, the formatting could be improved; part of the text is cut-off in the figure.
Response: We had revised Figure 1.

Minor Essential Revisions

#10. What are the syphilis rates of other low and middle-income countries as well as other East or Southeast Asian countries? More comparison is needed than just United States and United Kingdom.
Response: We added “In 2008, the prevalence of active syphilis among MSM was 12.2% in China, which was lower than that in Thailand (21.6%) but higher than that in Indonesia (4.0%) [6].” (line 17 of page 4)

#11. The introduction could have a stronger description on the role of treatment as prevention. This is a very innovative idea and could have more emphasis. There has been much literature in recent years and a few seminal studies that the authors could refer to.
Response: HIV-1 RNA in seminal plasma may decline more slowly than in blood[15] and could be detected with undetectable HIV-1 RNA in blood plasma[16], which suggest that there is potential transmission risk via unprotected sexual behaviour. (line 12 of page 5)

#12. Is the use of hazard ratio appropriate in this case? Hazard ratios tend to be used with survival data for clinical trials. They are associated with time to event, but the authors seem as if they are presenting hazard ratio as a relative risk ratio. Were participants removed from the analysis after syphilis seroconversion?
**Response:** In order to calculate the risk factors of syphilis seroconversion, we only followed patients who did not infected syphilis at baseline. During the follow-up, we record patients syphilis serostatus and time. Patients infected syphilis as outcome event. Then the COX proportional hazards regression model was used to analysis the risk factors with syphilis seroconversion. Therefore, HR was selected to analysis in our paper.

#13. The paper could also benefit from another English-language edit. There are a number of minor errors still in the paper. For example
Page 4 Line 22 “in” replace with “at”
Page 5 Line 2-3 Sentence is unclear
Page 10 Line 11 “we first evaluated” replace with “we report on the first evaluation of”
Page 12 Line 7 “convenient” replace with “convenience”
Page 12 line 15: “RAT” replace with “ART”
**Response:** We have revised as your advice.

**Discretionary Revisions**

#14. Some readers will not know what the criteria are for ART eligibility in China. It might be good to explain why individuals in China would not be eligible for ART.

**Response:** Since 2002, PLWHA in China with a CD4 count of 200 cells per µL or less, total lymphocyte count of less than 1200 cells per µL, or WHO disease stage 3 or 4 have been eligible for free combination antiretroviral therapy. In 2008, the CD4 count threshold for treatment was increased to 350 cells per µL [Zhang F. China Free Antiretroviral Therapy Manual, 2012 edn. Beijing: People’s Medical Publishing House, 2012.]. (line 15 of page 6)

#15. Page 11 line 4: There should be a reference supporting the role that safe sex counseling would play in this population. There has been conflicting evidence throughout the years about the role of safe sex counseling and this paper would
benefit from a reference showing the role of safe sex counseling to prevent STD acquisition in HIV+ individuals.

**Response:** We had added “Behavioral intervention can reduce HIV transmission risk among HIV-positive MSM [33].” *(line 10 of page 12)*

#16. The nearly 40% loss to follow up should be discussed in the limitations.

**Response:** In the limitation part, we had added “Thirdly, higher loss to-follow-up is another challenge of our study. By the end of the study period, about 37.2% of the participants were lost to follow-up, and this may cause selection bias.” *(line 8 of page 14)*

Many grammatical or typographical errors have been revised. All the lines and pages indicated above are in the revised manuscript.

Thank you and all the reviewers for the kind advice.

Sincerely yours,

Hong Shang