PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	HIV virologic failure and drug resistance among injecting drug users receiving first-line ART in China
AUTHORS	Leng, Xuebing; Liang, Shujia; Ma, Yanling; Dong, Yonghui; Kan, Wei; Goan, Daniel; Hsi, Jenny; Liao, Lingjie; Wang, Jing; He, Cui; Zhang, Heng; Xing, Hui; Ruan, Yuhua; Shao, Yiming

VERSION 1 - REVIEW

REVIEWER	Ping Zhong Shanghai Municipal Center for Disease Control and Prevention, China
REVIEW RETURNED	21-Jun-2014

GENERAL COMMENTS	1) In order to make the readers clearly understand the distribution of the studied IDU subjects, please describe the geographic distribution of 929 IDU persons receiving first-line HAART, and the propotion of the cases especially in Yunnan, Guangxi and Xinjiang provinces. A map displaying the distribution would be suggested. 2) On analysis of ART adherence based on provinces,this manuscript indicated a better organisation and good adherence in both Yunnan and Guangxi provinces, however, besides the detailes for Yunnan, no conclusive description was seen for Yunan province. Therefore, please add these information in the present manuscript. 3) If in this study, Xingjiang IDU population had a severe virologic failure , please show readers the detailed data including drug resistance.

REVIEWER	Rudi Wisaksana Internal Medicine Department, Padjadjaran University, Bandung, Indonesia
REVIEW RETURNED	30-Jun-2014

GENERAL COMMENTS	In general, this manuscript is well written, using data with large samples from China. My concern is that this manucript analyzed data not from prospective cohort, but from series of cross sectional between 2004 and 2012, which might had different methodology and potential biases. The authors should add information reasons for serial cross sectional and process of analyzing data. 1. In general, this manuscript is well written, using data with large

	samples from China. My concern is that this manucript analyzed data not from prospective cohort, but from series of cross sectional between 2004 and 2012, which might had different methodology and potential biases. The authors should add information reasons for serial cross sectional and process of analyzing data. 2. Many countries have negative policy to IDU, which might limit access to care. Please describe situation in China regarding IDU and PLWHIV in introduction section. 3. Please describe in methodology section assessment to identify IDU 4. To reduce biases between several cross sectional. I strongly suggest to do sensitivity analysis between the series of cross sectional. 5. In my opinion choosing p<0.05 as criteria for multivariate analysis could lead to over adjustment. Please add reason for choosing this p value as a cut-off. 6. Information regarding HAART regimen during virological failure is as important as HAART in initial baseline. Please also add information on HAART regimen during virological failure and any previous subtitutions. 7. In many countries PLWHIV among IDU had same response to HAART compare to non IDU [Addiction. 2010 Jun;105(6):1055-61]. Can the author add an explanation why this study found the opposite? 8. Only half of patients with virological failure have drug resistance. Please add explanation on this finding. 9. Based on the study finding, can the authors give recommendation regarding 2nd HAART regimen in China?

VERSION 1 – AUTHOR RESPONSE

Comments from the Reviewer Ping Zhong:

1、In order to make the readers clearly understand the distribution of the studied IDU subjects, please describe the geographic distribution of 929 IDU persons receiving first-line HAART, and the proportion of the cases especially in Yunnan, Guangxi and Xinjiang provinces. A map displaying the distribution would be suggested.

Thank you for the comment. I have added the details of geographic distribution in table 1.

2、On analysis of ART adherence based on provinces, this manuscript indicated a better organization and good adherence in both Yunnan and Guangxi provinces, however, besides the details for Yunnan, no conclusive description was seen for Yunnan province. Therefore, please add this information in the present manuscript.

Thank you for the comment. I have added a conclusive description about Yunnan in paragraph 5 in “discussion”.

“Large-scale ART treatment had been implemented in Yunnan province since 2004, patients receiving free antiretroviral treatment in Yunnan had better survival effects [30]. In our study, the prevalence of virologic failure among IDUs in Yunnan was low, which was supported by a local research[31].”(Line 14, paragraph 5, “Discussion”)

3、If in this study, Xingjiang IDU population had a severe virologic failure , please show readers the detailed data including drug resistance.

Thank you for the comment. I have added some details about Xinjiang in paragraph 5 in “discussion”. “in our study of 306 patients from Xinjiang, 87 (28.4%) had virologic failure, of which 85 were successfully genotyped and 28 were found to have drug resistance. This finding indicated that Xinjiang had worse effectiveness of treatment, which was convinced by a previous study showed that patients from Xinjiang were 12.6 times more likely to develop virologic failure when compared to those from Guangxi and Yunnan”(Line 3, paragraph 5, “Discussion”)

Comments from the Reviewer Rudi Wisaksana:
In general, this manuscript is well written, using data with large samples from China. My concern is that this manuscript analyzed data not from prospective cohort, but from series of cross sectional between 2004 and 2012, which might had different methodology and potential biases. The authors should add information reasons for serial cross sectional and process of analyzing data.

1、Many countries have negative policy to IDU, which might limit access to care. Please describe situation in China regarding IDU and PLWHIV in introduction section.

Thank you for the comment. I have added details with the situation in China regarding IDU and PLWHIV in “introduction”.
“In 2003, the “four free one care” policy was introduced, which provided free antiretroviral treatment for all eligible HIV patients in China. According to the analysis of the 2013 HIV/STD epidemic in China, more than 278,000 patients had received the free antiretroviral treatment [8]. Since 2004, methadone maintenance treatment, needle exchange and harm reduction have gradually expanded in China, this has improved the adherence of IDUs to treatment and reduced HIV transmission[16].”(Line 5, paragraph 2, “Introduction”)

2、Please describe in methodology section assessment to identify IDU

Thank you for the comment. I have added the definition in “study design and study participants” “Injecting drug users (IDUs) were defined as patients who had a history of self reported drug injection.”(Line 6, “Study design and study participants”)

3、To reduce biases between several cross sectional. I strongly suggest to do sensitivity analysis between the series of cross sectional.

Thank you for the comment. I have added sensitivity analysis in “result” and “discussion.” Some details will be seen in table 4.

“Sensitivity analysis
Table 4 presents factors associated with HIV viral suppression failure at time of starting ART from 2003-2007 and 2008-2011 respectively. Only residence outside of Guangxi and Yunnan provinces was observed at lower risk than other provinces during 2003 and 2007 (OR=0.4, 95% CI 0.2 – 0.6, P<0.01) after adjusted for initial ART regimen, ART regimen at survey, self reported missing doses in the past month, and CD4 cell counts before ART. During 2008 and 2011, four factors were associated with virologic failure, including province. Patients who were minorities (OR=2.3, 95% CI 1.3 – 4.0,

P<0.01), farmers (OR=2.1, 95% CI 1.2 – 3.8, P=0.01), CD4 200-349 or 0-199 (OR=3.2, 95% CI 1.3 - 7.9, P=0.01 and OR=4.1, 95% CI 1.6 -10.3, P<0.01) were more likely to be virologic failure, and residence outside of Guangxi and Yunnan provinces was a protective factor (OR=0.3, 95% CI 0.1 – 0.8, P=0.01).”(“Sensitivity analysis”)

“Through the sensitivity analysis, some details would be presented. Before 2008, province was the only factor associated with virologic failure, however, besides province, three more factors were significantly with virologic failure after 2008: ethnicity, occupation, and CD4 cell counts at survey. Enlarging sample size is an effective way to reduce biases. After combining the several cross-sectional surveys, education and self reported missing doses in the past month were into the final multivariate logistic regression models.”(Paragraph 7, “Discussion”)

4、In my opinion choosing p<0.05 as criteria for multivariate analysis could lead to over adjustment. Please add reason for choosing this p value as a cut-off.

Thank you for the comment. I have added reason for choosing p<0.05 as a cut-off in “data analysis”.
“Due to large sample and according to some previous studies [9,10,13,14], P < 0.05 was defined as statistically significant, and all tests were two sided.”(Line 7, “Data analysis”)

5、Information regarding HAART regimen during virological failure is as important as HAART in initial baseline. Please also add information on HAART regimen during virological failure and any previous subtitutions.

Thank you for the comment. I have added the last HAART regimens at table 1 and table 3, and some details in “results”.
“HAART regimens at survey were AZT+3TC+NVP/EFV (52.3%), D4T+3TC+NVP/EFV (34.8%), DDI based regimens (9.7%), and second-line regimens (3.2%).”(Line 3,”HAART regimens and virologic profiles”, “results”)

6、In many countries PLWHIV among IDU had same response to HAART compare to non IDU [Addiction. 2010 Jun;105(6):1055-61]. Can the author add an explanation why this study found the opposite?

Thank you for the comment. I have added an explanation in paragraph 4 in “discussion”
“Except one study from Indonesia showed that adherence to ART was not different between IDUs and non-IDUs[17], some international studies have found that IDUs tend to have lower ART adherence rates than do non-IDUs [18-19].”(Line 3, paragraph 4, “Discussion”)

7、Only half of patients with virological failure have drug resistance. Please add explanation on this finding.

Thank you for the comment. I have added some explanation in paragraph 2 in “discussion”
“Of the 193 patients who experienced failed viral suppression, 175 were successfully genotyped and 68 were identified as having drug resistance mutations. The prevalence of HIVDR among patients with virologic failure was 38.9% (68/175), which suggested that HIVDR was one of the most important factors associated with virologic failure, further researches should be focused on other potential factors.”(Line 1, paragraph 2, “Discussion”)

8、Based on the study finding, can the authors give recommendation regarding 2nd HAART regimen in China?

Thank you for the comment. The findings in our study can indicate that the importance of adherence and adherence education should be strengthened. Whether patients should be switched to 2nd HAART regimens depends on the WHO standards.

VERSION 2 – REVIEW

REVIEWER	Rudi Wisaksana TB-HIV Research Center, Medical Faculty, Padjadjaran University, Hasan Sadikin Hospital Bandung, Indonesia
REVIEW RETURNED	15-Aug-2014

- The reviewer completed the checklist but made no further comments.