

Format for ANSWERING REVIEWERS



June 28, 2013

Dear Editor,

Please find enclosed the edited manuscript in Microsoft Word format (file name: 3360-review copy final 20130712.doc).

Title: Prevalence of Hepatitis C Infection Among Intravenous Drug Users in Shanghai

Author: Yanlin Tao, Yufan Tang, Jianping Qiu, Xiaofeng Cai, Xiaoting Shen, Yaxin Wang, Xuetao Zhao

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 3360

The manuscript has been improved according to the suggestions of the reviewers.

1. The format has been updated.
2. Revisions have been made according to the suggestions of the reviewers.

Reviewer 00506601's comments:

1. *How was that Medical Center selected?*

Answer: Thank you very much for this comment. There are 17 districts in Shanghai. In each district, there is one medical center established by the local government, where IDUs can receive diaminon therapy for heroin addiction on a regular basis. Our samples were collected from one center, located in Xuhui District.

2. *How representative is the Medical Center to all other IDU clinics in Medical Centers in Shanghai?*

Answer: Thank you very much for this comment. There are 17 districts in Shanghai. Xuhui is one of the central districts. There is one medical center for IDUs in each district. Based on our regular communications with all of the medical centers, the age, sex, route of administration, drug category and history of drug abuse were similar among these IDU clinics, so we believed that the IDU medical center in Xuhui District would be representative of all of these clinics.

3. *How generalizable is the data to Shanghai and to all of China?*

Answer: Thank you very much for this comment. We are confident that our results are most likely representative for Shanghai, but we are not sure whether our data could be generalized to the whole of China, as related data are scarce.

4. *How were the 421 individuals selected? Was it a probably sample of participants in the clinic or was it a convenience sample where these were the only people who would consent so there is some bias in the sample? Bias has not been mentioned but how do the authors plan on addressing the potential for selection bias?*

Answer: Thank you very much for this comment. All of the serum samples used in this study were collected in 2012. There are approximately 500 IDUs who visit this clinic annually, and we finally obtained the informed consent of 432 IDUs. Approximately 86% of the IDUs participated in this study,

so there was no selection bias in our study group. We have added this information to our revised manuscript.

5. *The laboratory screening is reasonable but I question why add HIV and T.pallidum to the testing and to the paper. It is not really discussed and only adds a distraction to the paper without adding any content. I think these two serological makers should be removed.*

Answer: Thank you very much. We have removed these data from the revised manuscript.

6. *In the discussion the authors mention the low rate of RNA infection in the population and compare their infection rate to experimental HCV infection studies in chimpanzees. I think the authors should be more cautious since this is one study in one Medical Center in one City with more than likely a convenience sample. A much larger population based sample needs to be undertaken in China before generalizable statements can be made.*

Answer: Thank you very much for your comment. We have deleted this claim and the related citation from our revised manuscript.

Reviewer 02441147's comments:

1. *In the section Abstract is recommended to include the numbers of male and female patients included in the study to understand the percentages of RIBA confirmation.*

Answer: Thank you very much for your comment. We have added this information to the revised abstract.

2. *In the Section Introduction, second paragraph say "HCV is highly heterogeneous; 11 HCV genotypes with several distinct subtypes have been identified globally [2]." This is not correct, because actually the number of genotypes accepted is 7. See <http://hcv.lanl.gov/content/sequence/HCV/classification/genotable.html> and references:*

Simmonds P, Bukh J, Combet C, Del'age G, Enomoto N, Feinstone S. Consensus Proposals for a Unified System of Nomenclature of Hepatitis C Virus Genotypes. Hepatol 2005;42:962-73.

Murphy D, Chamberland J, Dandavino R, Sablon E. A new genotype of hepatitis C virus originating from central Africa. HEPATOLOGY 2007;46:623A

Answer: Thank you very much for this comment. We have revised this point in the manuscript.

3. *In the Section Results, say "HCV infection rates among HCV seronegative subjects". In the study, the RNA of HCV was analyzed in SEROPOSITIVE patients.*

Answer: Thank you very much for this comment. We have corrected this mistake in our revised manuscript.

4. *In the section discussion, in last paragraph, line 1 say "The gold standard for diagnosis of HCV infection requires biopsy of the liver" This is not correct, because the confirmatory diagnostic of hepatitis C is nucleic acid testing. Liver biopsy is only necessary for the assessment of chronic hepatitis and treatment decisions.*

Answer: Thank you very much for this comment. We have revised this point.

Reviewer 00070913's comments:

This paper give important epidemiology information of the HCV infection in a index city of China. I suggest you should mention the total population in Shanghai as reference. Is there any similar drug rehabilitation program in shanghai? What is your serving proportion to the city? The Language is well written..

Answer: Thank you very much for this comment. We have added this information to our revised

MATERIALS AND METHODS section. There are 17 districts in Shanghai. In each district, there is one medical center established by the local government, where IDUs can receive diaminon therapy for heroin addiction on a regular basis. Our samples were collected from one center located in Xuhui District. The population of Xuhui district is nearly one-tenth of the total population of Shanghai.

Reviewer 00070913's comments

... This manuscript includes only a few information. Much more clinical parameters, such as serum transaminase levels, histological grade of liver fibrosis and inflammation, should be shown and analyzed in Tables. Genotype also should be shown in a table. Why did the author use RIBA instead of PCR method? PCR is more familiar and should be enough for confirmation of HCV infection. Also viral load should be calculated in the same time by quantitative PCR method.

Answer: Thank you very much for your comments. This was an epidemiological study and not a clinical study. Our goal was to address the "Prevalence of Hepatitis C Infection Among Intravenous Drug Users in Shanghai," which is very important to current HCV epidemiology. IDUs receive diaminon therapy for heroin addiction on a regular basis at clinics. It is impossible to perform biopsies in this context, so we regret that we could not collect these important data.

We have added a table on HCV genotypes to our revised manuscript.

According to the recommendations put forth by the United States Centers for Disease Control and Prevention (CDC) and the American Association for the Study of Liver Diseases (AASLD), supplemental testing with a more specific assay (i.e., recombinant immunoblot assay – RIBA) of a specimen with a positive EIA result prevents reporting of false-positive results, particularly in settings in which asymptomatic persons are being tested. In this study, the third-generation Elecsys Anti-HCV assay (Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim, Germany) was used to screen for antibodies against HCV. The RIBA strip, a supplemental anti-HCV test with high specificity, was performed on all of the samples that tested positive during the initial screening, to exclude false-positives for anti-HCV. In addition, the samples that tested positive for anti-HCV antibodies during the initial screening were all subjected to HCV RNA qualitative and quantitative assays.

We did perform quantitative PCR for HCV RNA-positive individuals, but given our research goals, we did not include these data.

3. The references and typesetting have been corrected.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in black ink, reading 'Xuetao Zhao'.

Xuetao Zhao MPH

Center for Disease Control and Prevention of Xuhui,
50 Yongchuan Road, Xuhui District, Shanghai 200237, China.
Email: zhaoxtc@gmail.com

