Author's response to reviews

Title: Prevalences and associated risk factors of HCV/HIV co-infection and HCV mono-infection among injecting drug users in a methadone maintenance treatment program in Taipei, Taiwan

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Author's response to reviews: see over
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Dear Editors,

We appreciate sincerely Reviewers’ detailed comments on our previous manuscript entitled “Risk of HCV/HIV co-infection and HCV mono-infection among injecting drug users in a methadone maintenance treatment program in Taipei, Taiwan” (9380398237351505). We also appreciate your inviting us to resubmit our revised manuscript to *BMC Public Health*. We have carefully reanalyzed our data as recommended and responded to each comment from the Reviewers. Below, please find our detailed responses. The reviewers’ inputs much improved the manuscript and we look forward to publishing this article in *BMC Public Health*.

Please let me know if you have any questions or additional comments.

Sincerely,

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Reply to the Reviewer #1 Comments

Major revisions:
1. The Abstract first sentence emphasize that ‘Taiwan has a growing HIV/AIDS epidemic that has recently shifted to injection drug users (IDUs).’ Well, this might be true before 2007 but as authors cited in instruction that the numbers associated with injection drug user has slowed for the past 5 years, with the newly reported cases among IDUs dropped sharply to 115 infected IDUs for the year of 2011.

   Reply 1: We really agree with your advice. We revised the first sentence in the Abstract “Taiwan has a growing HIV/AIDS epidemic that has recently shifted to injection drug users (IDUs)” into “Injecting drug users (IDUs) in Taiwan contributed to an HIV/AIDS epidemic in 2005.” Please see Page 3 (first paragraph, line 1-2).

2. Background: It is obviously that authors did not review articles related to behaviors that transmit HIV and HCV amongst drug users in literature. In addition, the second sentence ‘HCV and HIV are the principal causes of morbidity and mortality in this population.’ needs citations since I am not sure this is true after considering overdose, suicide, and accidents associated with drug dependence. Moreover, for the last paragraph, I would suggest that authors specify the reasons about disclosing factors related to HIV/HCV co-infections in clinical practices in addition to few studies has been conducted in this topic.

   Reply 2: We really agree with your advice. We added literature information regarding behaviors that transmit HIV and HCV amongst drug users in the background section, “Many human behaviors, such as unsafe injection practices and unsafe sexual behaviors, are associated with HCV [3] and HIV [4, 5] infections among IDUs.” Please see Page 5 (first paragraph, line 3-5). We also added two citations for information “HCV and HIV contribute substantially to morbidity and mortality in this population [2, 6].” Please see Page 5 (first paragraph, line 6-7). Moreover, a statement was added to specify the reasons about disclosing factors related to HIV/HCV co-infections, “Investigations about factors associated with HCV and HIV mono-infection and HCV/HIV co-infection among IDUs are needed to control the epidemic.” Please see Page 6 (second paragraph, line 10-11).

3. Methods: I suggest that authors explain why chose the HIV and HCV seronegative group as the reference? There is no way to know what factors
differentiated HIV/HCV coinfection and HCV mono-infection when authors tried to explain in discussion that associated risk factors were different.

Reply 3: We really agree with your advice. We explained why chose the HCV/HIV seronegative group as the reference as follows: “Since the HCV and HIV co-infection is not uncommon in IDUs and these two infections shared the similar route of transmission, this study used HCV/HIV seronegativity as the reference group to determine the factors associated with HCV mono-infection and HCV/HIV co-infection.” Please see Page 9 (third paragraph, line 2-4) and Page 10 (first paragraph, line 1). We also revised the explanation regarding the factor associated with HCV/HIV co-infection, “Syringe sharing in the 6 months before MMTP enrollment was strongly associated with HCV/HIV co-infection in this study. This finding may reflect that injection practices were the major transmission route of HCV and HIV infection among IDUs [3, 5]. Because co-infection with HCV and HIV in IDUs has become a rapidly emerging global public health problem [8, 9], interventions including syringe exchange services and drugs substitution treatments are imperative to prevent IDUs from HCV and HIV infections [31].” Please see Page 16 (second paragraph, line 2-7).

4. Although authors have explained risk factors of HIV/HCV coinfection that they found in this paper, discussion and suggestion may need to go deeper instead just mentioned the results are consistent to other studies. Authors need to articulate how and why their study findings are important and in what way can help HIV/HCV coinfection patients? Or is there any comprehensive policy suggestion for the prevention of HIV/HCV coinfection?

Reply 4: We really agree with your advice. The statements in the discussion section were added to emphasize policy implications of findings associated with HCV/HIV coinfection, “This finding may reflect that injection practices were the major transmission route of HCV and HIV infection among IDUs [3, 5]. Because co-infection with HCV and HIV in IDUs has become a rapidly emerging global public health problem [8, 9], interventions including syringe exchange services and drugs substitution treatments are imperative to prevent IDUs from HCV and HIV infections [31].” Please see Page 16 (second paragraph, line 2-7).

Minor suggestions:
1. Page 7 authors mentioned that methadone is free for heroin patients. Is this true in Taiwan?
Reply 1: Yes, it is true; methadone is free for heroin patients in Taiwan. Methadone clients have to pay US$25 for a clinic visit monthly according to the regulation of Taiwan’s CDC, however.

2. Page 10 first line the authors set the type III error (alpha) 0.10 in bivariate analysis. Can the authors explain why 0.10?

Reply 2: We really appreciate your advice. Although we found many factors associated with HCV mono-infection and HCV/HIV co-infection in univariate analysis, we further conducted backward stepwise multivariable regression to determine factors associated with each outcome. Following prior study, the backward stepwise multivariable regression only included variables found to be associated with HCV or HCV/HIV co-infection at alpha level (p<or =0.1) in bivariate analysis [22]. Please see Page 10 (first paragraph, line 4-5).

3. English editing may be necessary.

Reply 3: We really appreciate your advice. This paper had been edited by a professional editor whose native language is English.
Reply to the Reviewer #2 Comments

Major Compulsory Revisions

1. Background: It is not supported by the way that you interpret bibliography why HIV/HCV co-infection is important (it is, but going through your justification, it is not obvious. Maybe you can add more details in the treatment of the co-infection)

Reply 1: We really agree with your advice. The statements in background section were added to emphasize the importance of investigating factors associated with HCV/HIV coinfection, “HCV and HIV contribute substantially to morbidity and mortality in this population [2, 6]. Moreover, co-infection with HCV and HIV is not uncommon and has become a global public health problem, causing an increased rate of progression to cirrhosis, decompensated liver disease, hepatocellular carcinoma, and death [8, 9].” and “Investigations about factors associated with HCV and HIV mono-infection and HCV/HIV co-infection among IDUs are needed to control the epidemic. Please see Page 5 (first paragraph, line 5-9) and page 6 (second paragraph, line 10-11).

2. Discussion: Some of the comparisons with the bibliographic references are not satisfactory interpreted (i.e page 14, at the end: A literature review showed that the prevalence of HCV/HIV co-infection was higher among TCH IDUs (13.1%) than among IDUs in China in 2007 (12.7%). Is a 0.4% difference so much higher? Were the settings of the study the same?)

Reply 2: We really agree with your advice. We revised the statement regarding the comparisons of HCV/HIV prevalence in this study with prior reports, “the prevalence of HCV/HIV co-infection among TCH IDUs (13.1%) was not much different from that among whole IDUs population in China in 2007 (12.7%) [26].” Please see Page 15 (third paragraph, line 1-2).

3. HCV and HIV incidence: Despite the small number of sero-conversions, at least a descriptive analysis of the sero-converted individuals is needed, especially in terms of risk factors such as sharing syringes.

Reply 3: We really appreciate your advice. We added descriptive analysis regarding the factors associated with the HCV or HIV sero-converters, “3 (21.4%) of the 14 HCV seroconverters and 2 (20%) of the 10 still HCV negativities had syringe sharing
in the last 6 months prior to reentry into the MMTP.” and “The 2 HIV seroconverters denied sharing syringes in the last 6 months prior to reentry into MMTP.” Please see Page 14 (first paragraph, line 2-3).

Minor Essential Revisions

1. Statistical analysis section: In the 2nd paragraph you state: Logistic regression… HIV mono-infection. However, in your analysis, HIV mono-infected individuals are excluded, so this method described here does not apply to that group.

   Reply 1: We really agree with your advice. We revised the statement “Study participants were divided into four groups: HCV/HIV co-infected, HCV mono-infected, HIV mono-infected, and seronegative (i.e., negative for both HCV and HIV)” into “Study participants were divided into three groups: HCV/HIV co-infected, HCV mono-infected, and seronegative (i.e., negative for both HCV and HIV).” Please see Page 9 (third paragraph, line 1-2).

2. Results: Lines 6-9: You should report either mean ±SD or median with range or IQR, depending on the distribution of the data (i.e if they meet the normality assumption) and not both.

   Reply 2: We agree with your advice. We revised the description of numerical data,”
   The mean age of the clients was 41 years (standard deviation, sd: 10); 86% were male; and the mean years of injecting drug use was 14.3 (sd: 9.7).” Please see Page 11 (first paragraph, line 6-9).

3. Results: Table 1 should be removed since all information in the Table is given explicitly in the first 3 lines of the results (it is duplicated information)

   Reply 3: Yes. Table 1 was removed from the text.

4. Methods, study population: What was the re-enrolment rate? Do sero-negatives at baseline that re-enrolled differ statistically significant to those sero-negatives at baseline that drop off or finish the treatment? Were these sero-negatives at baseline that finish the treatment also tested for HIV/HCV and if no; why?

   Reply 4: We really appreciate your advice. We added the information regarding the
re-enrollment rate in IDUs, “294 (20.4%) of the 1,443 study subjects were admitted to the TCH MMTP twice or more, including 64 HCV/HIV co-infections (33.7%, 64/190), 217 HCV mono-infections (19.2%, 217/1128), and 13 seronegativities (10.4%, 13/125) (Chi-square test for p value <0.001).” Please see Page 11 (first paragraph, line 10-12).

According to Taiwan’s CDC, maintained methadone clients with HIV negativity at admission are required to have an HIV testing every 6 months. But because of budget constraints, no such a requirement is for maintained methadone clients with HCV negativity at admission in Taiwan.

5. Discussion: You don’t need to report numerical results again in the discussion, since they were already mentioned in the results session

Reply 5: We really agree with your advice. We revised the description of numerical data, “the prevalences of HCV/HIV co-infection and HCV mono-infection were high among IDUs enrolled in the Taipei City Hospital MMTP between 2006 and 2010.” Please see Page 15 (first paragraph, line 1-3).

6. Results- Covariates of infections: In backward-stepwise multinomial regression, after controlling for other variables... which variables? State, in specific, which are the other variables that you are controlling for (either here or in Table 3)?

Reply 6: We really appreciate your advice. We revised the description of multinomial regression as “In backward-stepwise multinomial regression, after controlling for study subjects’ sociodemographics and substance use histories….,” Please see Page 13 (second paragraph, line 1-2).

Discretionary Revisions
1. Title: To my understanding is ‘prevalence and associated risk factors’ of HCV/HIV co-infection and HCV mono-infection among injecting drug users in a methadone maintenance treatment program in Taipei, Taiwan instead of ‘Risk’

Reply 1: We really agree with your advice. We revised the title, “Risk of HCV/HIV co-infection and HCV mono-infection among injecting drug users in a methadone maintenance treatment program in Taipei, Taiwan” into “Prevalence and associated risk factors of HCV/HIV co-infection and HCV mono-infection among injecting drug users in a methadone maintenance treatment program in Taipei, Taiwan.” Please see
2. Results- Covariate of infections:… (Table 2 and 3): Please remove ‘(Table 2 and 3)’ from the subtitle and put in the correct place in the text

Reply 2: We agree with your advice. The subtitle in the result section was revised, “Covariates of infection: univariate and multinomial regression analyses.” Please see Page 11 (second paragraph, line 1).

3. Methods: Can you please describe what method did you use to locate re-enrolled individuals since the enrolees were anonymous?

Reply 3: Thank you for pointing this out. Each enrollee who was treated with Methadone has been assigned with a Methadone treatment code. Thus re-enrolled individuals can be identified based on this treatment code. However, to ensure protection of individual privacy, the link between this code and individual ID were scrambled upon the data release, and hence researchers were left with only an item created by the Drug Prevention Center at TCH to indicate whether an individual was a re-enrollee. We have added an explanation in the manuscript to clarify this. More specifically, we added: “The existing dataset contains an identifier to indicate whether an individual was a re-enrollee. This identifier was coded by TCH prior to the data release and not by the researchers.” Please see Page 8 (second paragraph, line 1-3).

4. Methods: Was it not possible for the 125 sero-negative individuals to undergo HIV/HCV test also so that to have a better estimate of the incidence (instead of the re-enrollers only)?

Reply 4: We really appreciate your advice. Since HCV testing was not repeated among maintained methadone clients according to Taiwan CDC regulation, this precluded this study from using the 125 sero-negative individuals to estimate the incidence of HCV or HIV infection.

5. Results - Covariates of infections: Line 1: you are mentioning chi-square test here, but it is not mentioned in the ‘statistical analysis’ section. Is this Table a result of univariate logistic regression? Then it should be better stated as such.

Reply 5: We really appreciate your advice. We revised the statistical description, “The chi-square test was used to assess bivariate associations of selected factors with
HCV/HIV co-infection and HCV and HIV mono-infection.” Please see Page 10 (second paragraph, line 2-3).

6. Methods- Data collection: Why ‘sexual work’ was not included as principal source of income and homeless as a living situation since they are both possible risk factors for HIV/HCV infection?

Reply 6: We appreciate your advice. Because of only one homeless IDU in this study, we added this information into the footnote of table 1, “Live alone ab. bIncluding one homeless injection drug user.” Please see Page 25 (table 1).

Since the information regarding the sexual occupation of the study participants was not available in this study, we included this limitation into the text, “First, we analyzed secondary data; information on the sexual behaviors and occupation of the study participants was not available.” Please see Page 18 (second paragraph, line 1-2).

7. Results: Table 2 is too large. You can consider either splitting it in two (Table 2i for the demographics and 2ii for the substance use) or alternative change the way you are reporting the data for the dichotomous variables i.e shared syringes: you can report n(%) yes only (% of no would be the reference category for the ORs). This would make your tables much smaller and easier to follow.

Reply 7: We really agree with your advice. We revised the table 2 according to your suggestion. Please see Page 24 (revised table).

8. Results, HCV and HIV incidence: Add ‘among re-enrollers’, since it does not apply to the whole sample.

Reply 8: We agree with your advice. We revised the subtitle in the result section, “HCV and HIV incidence among re-enrollers.” Please see Page 13 (second paragraph, line 1).

9. Results- Covariates of infections: When describing Table 2, you are just stating which variables are significant or not and in which direction, while it would be more interesting to state also the magnitude of the association, i.e sharing syringes increases the risk of co-infection by 27 times etc. In Table 3, all numerical information is included in both text and Table, so the text should be again rephrased to give some additional information regarding interpretation of the results.
Reply 9: We appreciate your advice. We revised the description of study results, “In backward-stepwise multinomial regression, after controlling for study subjects’ sociodemographics and substance use histories, the odds of HIV infection was 27 times higher (95% CI 13.30–57.76) among IDUs with syringe sharing in the 6 months before MMTP enrollment than among other IDUs without syringe sharing. Also HCV/HIV co-infection was significantly positively associated with number of MMTP enrollments (AOR=2.28, 95% CI 1.33–3.90), and number of times incarcerated (AOR=2.01, 95% CI 1.71–2.37) and significantly inversely associated with smoking amphetamine in the 6 months before MMTP enrollment (AOR=0.44, 95% CI 0.25–0.76; Table 2). Higher number of times incarcerated increased the risk of HCV mono-infection by 1.77 times (95% CI 1.52–2.06). Additionally, HCV mono-infection was significantly positively associated with duration of injecting drug use (AOR=1.04, 95% CI 1.01–1.07) and was significantly inversely associated with smoking amphetamine in the 6 months before MMTP enrollment (AOR=0.49, 95% CI 0.32–0.75) and amphetamine positivity on urine testing at MMTP enrollment (AOR=0.61, 95% CI 0.40–0.93).” Please see Page 12 (second paragraph, line 1-11) and page 13 (first paragraph, line 1-2).