PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Positive Percentages of Urine Morphine Tests among Methadone Maintenance Treatment Clients with HIV/AIDS: A 12-Month Follow-up Study in Guangdong Province, China
AUTHORS	Luo, Xiaofeng; Gong, Xiao; Zhao, Peizhen; Zou, Xia; Chen, Wen; Ling, Li

VERSION 1 - REVIEW

REVIEWER	Zunyou Wu National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China
REVIEW RETURNED	09-Oct-2016

GENERAL COMMENTS	The study reported extremely high heroin use rate among methadone maintenance treatment clients with HIV/AIDS in Guangdong Province, China. There are a few methodology issues need the authors to address. First, all the data used for the paper, if I understand correctly, were not directly collected by the authors. These data were actually collected based on the national MMT protocol by health providers at the MMT clinics. I presume that the authors got permission to use part of data and they were authorized to retrieve data for the nine selected MMT clinics from the Chinese National MMT Program data system. If this understanding is correct, then, the method section, particularly about data collection, need to be rewritten. Second, selection of MMT clinics and participants. There were 60 MMT clinics in Guangdong Province by the end of 2012. The authors selected 9 MMT clinics for the study. However, the authors has not described the how they selected these 9 clinics. They neither describe how they selected study participants. Did all eligible study participants recruited for the study, only partial of eligible subjects were selected. Third, definition of “heroin use” needs authors’ reconsideration. The author defines a “heroin user” as, I quote, “During the study period, a client was recognized as a heroin user as long as any urine morphine test result was positive.” end of the quote. They study period was “Between July 2006 and December 2013”, for 7.5 years. If “subject A” having an urine morphine test (+) only once in August of 2006 but having all negative tests throughout the study period, while, “subject B” having all urine morphine test (+), they were totally different, and should be treated differently in the data analysis. Suggest authors to delete those who had less than 2 urine morphine tests per year during the study period.

	Fourth, suggest authors to present details descriptive data analysis of urine morphine tests results, for example, the number of urine morphine tests, including the number of total tests performed and the number of (+) results, the minimum and maximum, and median, and these tests by total study period, and by each year from y1 to y7. Fifth, in table 1, the 100% by vertical is not appropriate. Suggest change to horizontal adding up to 100% that mean the proportion of urine test positive by variable characteristics.

REVIEWER	Na He Fudan University, China
REVIEW RETURNED	13-Oct-2016

GENERAL COMMENTS	Abstract Results on Page 2, line 11-15: The author stated “Higher percentages of continued heroin use were associated with being young (OR≤30=0.45, 95%CI:0.26-0.80; OR31-=0.63, 95%CI: 0.39-1.00; OR36-=0.65, 95%CI:0.42-1.01), having harmonious family relationship (OR=1.46, 95%CI:1.01-2.12), financial sources depending on family or friends (OR=0.71, 95%CI:0.51-0.98), higher maintenance doses (OR=0.49, 95%CI:0.36-0.68) and poorer MMT attendance (OR<20%=4.74, 95%CI:3.01-7.47; OR20%-=1.74, 95%CI:1.16-2.64)”. This statement needs to be corrected. Clearly, being young, financial sources depending on family or friends and higher maintenance doses were associated with LOWER percentages of continued heroin use given that the odds ratios were less than the null value which is 1.00. In fact, the authors correctly documented these results in the main text. Introduction Page 4, line 7-9: Better to cite another reference to reflect the recent HIV epidemic in China, or at least stated that the figures reflected the HIV epidemic by 2013 when the present study collected data. Page 5, line 4-5: There are some reported data on heroin use among MMT clients including those with HIV/AIDS in China, though. References should be cited for the author’s statement. Methods

	Page 6, line 20: there was a typo, “enrolment’ should be ‘enrollment’. Page 10, line 10: should be “Self-reported……” Page 10, line 11: The number of clients who were morphine (+) should be 632 but not 642. Some of the figures or proportions in this paragraph must be wrong. Discussion The participants were recruited during a 7-8 years study period. However, the study only examined the percentage of heroin use during the first 12 months after receiving MMT. There are several important concerns: (1) How many participants were there and what was the participation rate in each calendar year during the study period? This is important given that there might be secular trend in the percentage of heroin use during the MMT clients. (2) Is there any possibility to find out what were the percentages of continued heroin use after the first 12 months post-MMT? This is particular interesting and valuable since that there was possibilities for MMT clients to reduce heroin use along with increasing time or period of MMT.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Zunyou Wu
Institution and Country: National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China
Please state any competing interests or state ‘None declared’: None declared

Dear Reviewer,

We are very pleased to have the opportunity to revise our manuscript (Ms. No. bmjopen-2016-014237) entitled “Extremely High Heroin Use Rate among Methadone Maintenance Treatment Clients with HIV/AIDS in Guangdong Province, China”. In response to your questions and suggestions, we thoughtfully and carefully revised the manuscript and made corresponding corrections point-by-point in red. We hope the revisions and correspondences will satisfy you and meet the quality standard of the journal.

Thanks again for your reconsideration.

Sincerely Yours,
Xiaofeng Luo

Reviewers' Comments
The study reported extremely high heroin use rate among methadone maintenance treatment clients with HIV/AIDS in Guangdong Province, China. There are a few methodology issues need the authors to address.

1. First, all the data used for the paper, if I understand correctly, were not directly collected by the authors. These data were actually collected based on the national MMT protocol by health providers at the MMT clinics. I presume that the authors got permission to use part of data and they were authorized to retrieve data for the nine selected MMT clinics from the Chinese National MMT Program data system. If this understanding is correct, then, the method section, particularly about data collection, need to be rewritten.
2.Second, selection of MMT clinics and participants. There were 60 MMT clinics in Guangdong Province by the end of 2012. The authors selected 9 MMT clinics for the study. However, the authors has not described the how they selected these 9 clinics. They neither describe how they selected study participants. Did all eligible study participants recruited for the study, only partial of eligible subjects were selected.
R: We thank the reviewer for pointing out the need for clarification, and revised the description of data collection, selection of MMT clinics and participants accordingly:
“This study was conducted in 14 MMT clinics located in 9 cities of Guangdong (According to whether the 1-year retention rate is above or below 50%, the 61MMT clinics were divided into two groups, and seven clinics were randomly selected from each group [28].). We got permission and authorization to use and retrieve part of data for the selected MMT clinics from the Chinese National MMT Program data system. Between July 2006 and December 2013, there were 9,397 entrants; among them, 8,912 (94.8%) received HIV test at entry and 485 (5.2%) refused to be test. Of the remaining 805 MMT clients who tested HIV positive at MMT entry, 81.1% (653 of 805) participated in this study. In this study, participants were eligible if they were (1) diagnosed with opioid dependence according to the International Classification of Diseases (10th Revision); (2) 18 years or older; (3) tested to be HIV-positive at entry; (4) able to provide informed consent; and (5) able to provide urine specimen to morphine test.”

3.Third, definition of “heroin use” needs authors’ reconsideration. The author defines a “heroin user” as, I quote, “During the study period, a client was recognized as a heroin user as long as any urine morphine test result was positive.” end of the quote. They study period was “Between July 2006 and December 2013”, for 7.5 years. If “subject A” having an urine morphine test (+) only once in August of 2006 but having all negative tests throughout the study period, while, “subject B” having all urine morphine test (+), they were totally different, and should be treated differently in the data analysis. Suggest authors to delete those who had less than 2 urine morphine tests per year during the study period.
R: We do appreciate the points raised by the reviewer and agree that- If “subject A” having a urine morphine test (+) only once in August of 2006 but having all negative tests throughout the study period, while, “subject B” having all urine morphine test (+), they were totally different, and should be treated differently in the data analysis.

In fact, the study only mainly examined the positive percentages of heroin use during the first 12 months after receiving MMT. In accordance with high drop-out rates, our study period was classified into two categories: one was defined as the duration between enrollment and dropout, the other was defined as the duration between enrolment and the end of the first 12 months. To address the difference caused by times of urine morphine test (+) and observation period, we selected positive percentages of urine morphine tests as the dependent variable.

In addition, as we learned from CDC, the heroin use rate was reported on a monthly basis, while our date was presented on a yearly one. This different form might confuse the readers.
Given our study mainly focus on the positive percentages of urine morphine tests, we revised the manuscript as follow:

Title: We have revised the title as “Positive Percentages of Urine Morphine Tests among Methadone Maintenance Treatment Clients with HIV/AIDS during the First 12 Months after Treatment Initiation in Guangdong Province, China”

Abstract Section:
Objective: We have revised the objective as “We aimed to assess the positive percentages of urine morphine tests and correlates among MMT clients with HIV/AIDS in Guangdong, China.”
Primary and secondary outcome measures: We have revised the primary and secondary outcome measures as “The positive percentages of urine morphine tests were calculated and underlying predictors were estimated.”
Result: We have deleted the information about the heroin use rate and added “There were 38.4% participants with positive percentages of urine morphine tests over 80% during the first 12 months after treatment initiation.” in the revised manuscript.
Conclusion: We have revised the conclusion as “High positive percentages of urine morphine tests remain prevalent among MMT clients with HIV/AIDS in Guangdong. The present findings have implications for reconsidering adjusting the current MMT doses and taking effective measures to facilitate attendance in order to decrease heroin use and ultimately improve the effectiveness among these sub-group MMT clients.”

Method Section:
We have deleted the definition of heroin user from the manuscript.

Results Section
We have deleted the information about the heroin use rate.

Discussion Section:
We have deleted the information about the heroin use rate, and added the positive percentages of urine morphine tests as:
“Findings from the current analysis revealed that there were38.4% participants with positive percentages of urine morphine tests over 80% during the first 12 months after treatment initiation.”
In addition, we have acknowledged what you had mentioned as a study limitation and discussed this in the “Discussion” Section in the revised manuscript:
“Thirdly, frequent drop-out always exists among clients in MMT programs. Most of clients would drop out within a few months which had been widely noticed [17,46]. For the drop-outs who could not been followed 12 months, many of them probably were tested only once or twice but all these tests were positive, which might over-estimate the percentages of heroin use. In addition, we only examined the positive percentages of urine morphine tests during the first 12 months after receiving MMT due to the limited sample size and high drop-out.”

4.Fourth, suggest authors to present details descriptive data analysis of urine morphine tests results, for example, the number of urine morphine tests, including the number of total tests performed and the number of (+) results, the minimum and maximum, and median, and these tests by total study period, and by each year from y1 to y7.
R: The main outcome of our study is the percentages of heroin use during the first 12 months after receiving MMT. We have added table 2 and table 3 as detailed description on urine morphine tests results in the revised manuscript. In addition, we have added “The median positive percentage of urine morphine tests was 52.3% for 2006, 47.9% for 2007, 47.0% for 2008, 45.1% for 2009, 44.5% for

2010, 47.1% for 2011, 23.3% for 2012 and 55.4% for 2013, respectively (Table 2).” in the Result Section.

Table 2 Urine morphine tests results at the different entrant year and followed month (n=642)
Year Positive percentage of urine morphine tests by month (%, n/N) Median (IQR)
1 2 3 4 5 6 7 8 9 10 11 12
2006 88.3(53/60) 56.1(32/57) 47.3(26/55) 43.1(22/51) 53.3(24/45) 51.2(21/41) 56.4(22/39) 47.2(17/36) 54.3(19/35) 60.0(21/35) 37.5(12/32) 46.9(15/32) 52.3(47.0-56.3)
2007 90.8(118130) 56.3(71/126) 53.4(63/118) 45.1(51/113) 48.1(52/108) 53.5(54/101) 49.5(48/97) 43.0(37/86) 47.6(39/82) 46.2(36/78) 44.4(32/72) 44.3(31/70) 47.9(44.6-53.5)
2008 93.9(124/132) 52.3(56/107) 49.5(47/95) 51.2(43/84) 53.9(41/76) 44.9(31/69) 40.9(27/66) 38.5(25/65) 41.0(25/61) 39.7(23/58) 39.7(23/58) 49.1(28/57) 47.0(40.0-52.0)
2009 98.8(83/84) 68.0(51/75) 46.8(29/62) 43.9(25/57) 56.4(31/55) 46.2(24/52) 47.1(24/51) 33.3(16/48) 42.6(20/47) 37.2(16/43) 40.5(17/42) 31.7(13/41) 45.1(40.1-49.2)
2010 96.1(49/51) 50.0(22/44) 52.5(21/40) 46.2(18/39) 40.5(15/37) 42.9(15/35) 43.8(14/32) 45.2(14/31) 46.6(14/30) 40.0(12/30) 35.7(10/28) 37.0(10/27) 44.5(40.1-49.2)
2011 96.7(87/90) 57.0(45/79) 50.0(36/72) 44.1(30/68) 42.9(27/63) 46.6(27/58) 63.0(34/54) 55.3(26/47) 47.6(20/42) 42.1(16/38) 36.4(12/33) 41.9(13/31) 47.1(42.3-56.6)
2012 91.7(55/60) 40.4(19/47) 33.3(14/42) 21.6(8/37) 33.3(11/33) 32.0(8/25) 16.7(3/18) 20.0(3/15) 8.3(1/12) 18.2(2/11) 20.0(2/10) 25.0(2/8) 23.3(18.7-33.3)
2013 100.0(35/35) 55.4(10/18) 28.6(4/14) 25.0(2/8) 75.0(3/4) 33.3(1/3) 50.0(1/2) 100.0(1/1) 100.0(1/1) - - - 55.4(31.0-100.0)

Table 3 The distribution of positive percentages of urine morphine tests during the study period (n =632)
Positive percentage (%) Number (n) Percentage (%)
>0 22 3.5
10- 47 7.4
20- 59 9.3
30- 55 8.7
40- 31 4.9
50- 85 13.4
60- 56 8.9
70- 34 5.4
80- 32 5.1
90- 211 33.4
total 632 100.0

5.Fifth, in table 1, the 100% by vertical is not appropriate. Suggest change to horizontal adding up to 100% that mean the proportion of urine test positive by variable characteristics.
R: We have changed the percentage calculation by horizontal in the revised manuscript.

Reviewer: 2
Reviewer Name: Na He
Institution and Country: Fudan University, China

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

Dear Reviewer,
We are very pleased to have the opportunity to revise our manuscript (Ms. No. bmjopen-2016-014237) entitled “Extremely High Heroin Use Rate among Methadone Maintenance Treatment Clients with HIV/AIDS in Guangdong Province, China”. In response to your questions and suggestions, we thoughtfully and carefully revised the manuscript and made corresponding corrections point-by-point in blue. We hope the revisions and correspondences will satisfy you and meet the quality standard of the journal.

Thanks again for your reconsideration.

Sincerely Yours,
Xiaofeng Luo

Reviewers' Comments
Abstract
1. Results on Page 2, line 11-15: The author stated “Higher percentages of continued heroin use were associated with being young (OR≤30=0.45, 95%CI:0.26-0.80; OR31-=0.63, 95%CI: 0.39-1.00; OR36-=0.65, 95%CI:0.42-1.01), having harmonious family relationship (OR=1.46, 95%CI:1.01-2.12), financial sources depending on family or friends (OR=0.71, 95%CI:0.51-0.98), higher maintenance doses (OR=0.49, 95%CI:0.36-0.68) and poorer MMT attendance (OR<20%=4.74, 95%CI:3.01-7.47; OR20%-=1.74, 95%CI:1.16-2.64)”. This statement needs to be corrected. Clearly, being young, financial sources depending on family or friends and higher maintenance doses were associated with LOWER percentages of continued heroin use given that the odds ratios were less than the null value which is 1.00. In fact, the authors correctly documented these results in the main text.
R: We have corrected the mistakes in the revised manuscript:
“Lower percentages of continued heroin use were associated with being young (OR≤30=0.45, 95%CI: 0.26-0.80; OR31-=0.63, 95%CI: 0.39-1.00; OR36-=0.65, 95%CI: 0.42-1.01), financial sources depending on family or friends (OR=0.71, 95%CI: 0.51-0.98) and higher maintenance doses (OR=0.49, 95%CI: 0.36-0.68). Higher percentages of continued heroin use were associated with having harmonious family relationship (OR=1.46, 95%CI: 1.01-2.12) and poorer MMT attendance (OR<20%=4.74, 95%CI: 3.01-7.47; OR20%-=1.74, 95%CI: 1.16-2.64).”

Introduction
2. Page 4, line 7-9: Better to cite another reference to reflect the recent HIV epidemic in China, or at least stated that the figures reflected the HIV epidemic by 2013 when the present study collected data.
R: We have added some information to reflect the HIV epidemic, especially among IDUs in the revised manuscript:
“As of 2013, 437,000 people lived with HIV/AIDS in China (including 263,000 people living with HIV and 174,000 AIDS patients), accounting for 0.033% of the total population in China; and sentinel surveillance data showed the HIV/AIDS prevalence was 6.3% among IDUs [5].”

3. Page 5, line 4-5: There are some reported data on heroin use among MMT clients including those with HIV/AIDS in China, though. References should be cited for the author’s statement.
R: We have cited 2 references to support our statement.
14. Wang R, Ding Y, Bai H, Duan S, Ye R, Yang Y, et al. Illicit heroin and methamphetamine use among methadone maintenance treatment patients in Dehong Prefecture of Yunnan Province, China.

PLoS One. 2015;10:e0133431.
25. Luo X, Zhao P, Gong X, Zhang L, Tang W, Zou X, et al. Concurrent heroin use and correlates among methadone maintenance treatment clients: a 12-month follow-up study in Guangdong Province, China. Int J Environ Res Public Health. 2016;13:305.

Methods

4. Page 6, line 20: there was a typo, “enrolment’ should be ‘enrollment’.
R: We have corrected the typo in the revised manuscript.

5. Page 10, line 10: should be “Self-reported……”
R: We have corrected the typo in the revised manuscript.

6.Page 10, line 11: The number of clients who were morphine (+) should be 632 but not 642. Some of the figures or proportions in this paragraph must be wrong.
R: We have corrected the mistakes in the revised manuscript:
“Among the clients with urine morphine (+), 69.6% (440 of 632) and 47.0% (297 of 632) completed the 6th and 12th month follow-up interviews respectively.”

Discussion

7. The participants were recruited during a 7-8 years study period. However, the study only examined the percentage of heroin use during the first 12 months after receiving MMT. There are several important concerns: (1) How many participants were there and what was the participation rate in each calendar year during the study period? This is important given that there might be secular trend in the percentage of heroin use during the MMT clients. (2) Is there any possibility to find out what were the percentages of continued heroin use after the first 12 months post-MMT? This is particular interesting and valuable since that there was possibilities for MMT clients to reduce heroin use along with increasing time or period of MMT.
R: We do appreciate the points raised by the reviewer.
We have acknowledged this as a study limitation and discussed this in the “Discussion” section in the revised manuscript:
“Thirdly, frequent drop-out always exists among clients in MMT programs. Most of clients would drop out within a few months which had been widely noticed [17,46]. For the drop-outs who could not been followed 12 months, many of them probably were tested only once or twice but all these tests were positive, which might over-estimate the percentages of heroin use. In addition, we only examined the positive percentages of urine morphine tests during the first 12 months after receiving MMT due to the limited sample size and high drop-out.”

VERSION 2 – REVIEW

REVIEWER	Zunyou Wu National Center for AIDS/STD Control and Prevention, China CDC, Beijing, China
REVIEW RETURNED	18-Dec-2016

GENERAL COMMENTS	I am very happy to see that the authors have significantly revised the manuscript, particularly added more detailed presentations of urine morphine test positivity for newly enrolled opioid users to methadone maintenance treatment program by year from 2006 to 2013, Table 2. After reviewing the revised manuscript, I notice that there is some inconsistency. For example, in the abstract, authors present results

	of “There were 38.4% participants with positive percentages of urine morphine tests”, while, in the main body of manuscript Results Table 1, authors present 98.4% of urine morphine positivity. In addition, in Table 2, the most results suggest urine morphine test positivity in between 18% and 56%, noticing a few 100% positivity only have 1 test and 1 positive. My concern remains in the definition of “positive percentages of urine morphine tests” is not clearly defined in the revised manuscript. Though authors give the definition in Page 8, line 3 through 6, “The percentage of heroin use was calculated based on the number of positive urine morphine test results and the number of total urine test times during the study period. Based on the urine morphine tests, the clients were currently grouped as “urine morphine (+)” and “urine morphine (-)”. Additionally, the positive percentages were grouped as <40%, 40-80% and >80% based on the data distribution”, it is still not clear how to determine the status of urine morphine positivity for an individual subject. The first month of methadone maintenance treatment is to give doctor time to adjust appropriate dosage for a client. Usually the dosage starts from small, 20 mg to 40 mg per day, that is usually not enough for maintenance treatment. The dosage will gradually increase slowly to certain amount, usually average 60 mg per day. Most clients in the first month of MMT adjustment stage often use opioid to adjust themselves to methadone maintenance treatment. Therefore, the urine morphine test in the first month of MMT is usually high, should be excluded from data analysis. Some study subjects may only have one urine morphine test result, or a few urine morphine test results during the study period. It might be appropriate to exclude those clients who had less than 10 records of urine morphine tests. In short, I suggest authors exclude urine morphine tests in the first month; then, include MMT clients who have at least 10 records of urine morphine tests, or in other words, exclude those who have less than 10 records of urine morphine tests in order to have a minimum denominator for calculating percentage of urine morphine positivity. After having these basic data cleaning, clearly defining the urine morphine positivity, then, redo data analysis.

REVIEWER	Na He Fudan University, Shanghai, China
REVIEW RETURNED	11-Dec-2016

GENERAL COMMENTS	The author has addressed my concerns in this revised version of the manuscript and I have no more suggestions.

VERSION 2 – AUTHOR RESPONSE

Response to Reviewer:
After reviewing the revised manuscript, I notice that there is some inconsistency. For example, in the abstract, authors present results of “There were 38.4% participants with positive percentages of urine morphine tests”, while, in the main body of manuscript Results Table 1, authors present 98.4% of urine morphine positivity. In addition, in Table 2, the most results suggest urine morphine test positivity in between 18% and 56%, noticing a few 100% positivity only have 1 test and 1 positive. My

concern remains in the definition of “positive percentages of urine morphine tests” is not clearly defined in the revised manuscript.

Though authors give the definition in Page 8, line 3 through 6, “The percentage of heroin use was calculated based on the number of positive urine morphine test results and the number of total urine test times during the study period. Based on the urine morphine tests, the clients were currently grouped as “urine morphine (+)” and “urine morphine (-)”. Additionally, the positive percentages were grouped as <40%, 40-80% and >80% based on the data distribution”, it is still not clear how to determine the status of urine morphine positivity for an individual subject.
The first month of methadone maintenance treatment is to give doctor time to adjust appropriate dosage for a client. Usually the dosage starts from small, 20 mg to 40 mg per day, that is usually not enough for maintenance treatment. The dosage will gradually increase slowly to certain amount, usually average 60 mg per day. Most clients in the first month of MMT adjustment stage often use opioid to adjust themselves to methadone maintenance treatment. Therefore, the urine morphine test in the first month of MMT is usually high, should be excluded from data analysis. Some study subjects may only have one urine morphine test result, or a few urine morphine test results during the study period. It might be appropriate to exclude those clients who had less than 10 records of urine morphine tests. In short, I suggest authors exclude urine morphine tests in the first month; then, include MMT clients who have at least 10 records of urine morphine tests, or in other words, exclude those who have less than 10 records of urine morphine tests in order to have a minimum denominator for calculating percentage of urine morphine positivity.

After having these basic data cleaning, clearly defining the urine morphine positivity, then, redo data analysis.
R: We do appreciate the points raised by the reviewer.
1. We have given the definition that status of urine morphine for individual subject as:
“During the study period, a client was recognized as a heroin user as long as any urine morphine test result was positive (the first urine morphine test was excluded).”
2. The result of urine morphine test in the first month of MMT has been excluded from data analysis (including calculating heroin use and percentages).
3. MMT clients who have at least 10 records of urine morphine tests were included in the revised manuscript.
Now, we have redone the data analysis and revised the manuscript accordingly.

VERSION 3 – REVIEW

REVIEWER	Zunyou Wu National Center for AIDS/STD Control and Prevention, China CDC, China
REVIEW RETURNED	17-Feb-2017

GENERAL COMMENTS	I am glad to see that the authors have further revised the manuscript. It looks better. After reviewing the revised manuscript, I have a few more suggestions. First, clarification of study period on page 8/29, line 7 to 10, it says, “During the study period, a client was recognized as a heroin user as long as any urine morphine test result was positive” and “The percentage of heroin use was calculated based on the number of positive urine morphine test results and the number of total urine test times during the study period”, it is not clear what does the “study period” refer to. Does it mean “12 months” as stated on page 6/29, line 22, or between 2006 and 2012. Please clarify.

	Second, suggest to add one more row to total the column for each month in the bottom of Table 2, i.e., 95.9%(281/293) for month 1, 53.6%(157/293) for month 2, 46.1%(135/293) for month 3, 42.7% (125/293) for month 4, 48.8% (143/293) for month 5, 43.7% (128/293) for month 6, 45.7% (134/293) for month 7, 40.3% (118/293) for month 8, 42.7% 9125/293) for month 9, 43.0% (126/293) for month 10, 39.3%(108/275) for month 11, and 42.1% (112/266) for month 12. Third, in the Results section, "Positive Percentages of Urine Morphine Tests during the Study Period", suggest author to consider add descriptions similar like following: Between 2006 and 2012, there were 3471 urine morphine tests performed and 1580 were positive (45.5%). The highest positive percentage was observed in the first month (95.9%), then it remained as high as between 39.3% and 53.6% for month 2 to month 12. After excluding the highest percentage in the first month, the average positive percentage was 40.9% for month 2 to month 12. Fourth, the above description of positive percentage should be summarized and included in the Abstract section. Trust the authors will consider these suggestions and will revise the manuscript. No further review is required.

VERSION 3 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Zunyou Wu
Institution and Country: National Center for AIDS/STD Control and Prevention, China CDC, China
Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below
I am glad to see that the authors have further revised the manuscript. It looks better. After reviewing the revised manuscript, I have a few more suggestions.

First, clarification of study period on page 8/29, line 7 to 10, it says, "During the study period, a client was recognized as a heroin user as long as any urine morphine test result was positive" and "The percentage of heroin use was calculated based on the number of positive urine morphine test results and the number of total urine test times during the study period", it is not clear what does the "study period" refer to. Does it mean "12 months" as stated on page 6/29, line 22, or between 2006 and 2012. Please clarify.
R: We have clarified the study period by adding comment in the revised manuscript.
"A client was recognized as a heroin user as long as any urine morphine test result was positive within 12 months."
"The percentage of heroin use was calculated based on the number of positive urine morphine test results and the number of total urine test times within 12 months."

Second, suggest to add one more row to total the column for each month in the bottom of Table 2, i.e., 95.9%(281/293) for month 1, 53.6%(157/293) for month 2, 46.1%(135/293) for month 3, 42.7% (125/293) for month 4, 48.8% (143/293) for month 5, 43.7% (128/293) for month 6, 45.7% (134/293) for month 7, 40.3% (118/293) for month 8, 42.7% 9125/293) for month 9, 43.0% (126/293) for month 10, 39.3%(108/275) for month 11, and 42.1% (112/266) for month 12.
R: We have added the data in table 2 in the revised manuscript.

Table 2 Urine morphine tests results at the different entrant year and followed month (n=293)
Year Positive percentage of urine morphine tests by month (%, n/N) Median (IQR)
1 2 3 4 5 6 7 8 9 10 11 12
2006 97.1(34/35) 48.6(17/35) 45.7(16/35) 37.1(13/35) 60.0(21/35) 45.7(16/35) 54.3(19/35) 48.6(17/35) 54.3(19/35) 60.0(21/35) 37.5(12/32) 46.9(15/32) 48.6(45.7-58.6)
2007 92.3(72/78) 55.1(43/78) 50.0(39/78) 43.6(34/78) 47.4(37/78) 51.3(40/78) 50.0(39/78) 42.3(33/78) 50.0(39/78) 46.2(36/78) 44.4(32/72) 44.3(31/70) 48.7(44.3-51.0)
2008 96.6(56/58) 50.0(29/58) 46.6(27/58) 48.3(28/58) 51.7(30/58) 41.4(24/58) 34.5(20/58) 39.7(23/58) 39.7(23/58) 39.7(23/58) 39.7(23/58) 49.1(28/57) 44.0(39.7-49.8)
2009 97.7(42/43) 62.8(27/43) 41.9(18/43) 41.9(18/43) 58.1(25/43) 39.5(17/43) 44.2(19/43) 27.9(12/43) 37.2(12/43) 37.2(16/43) 40.5(17/42) 31.7(13/41) 41.2(37.2-54.6)
2010 96.7(29/30) 50.0(15/30) 53.3(16/30) 50.0(15/30) 40.0(12/30) 40.0(12/30) 43.3(13/30) 43.3(13/30) 46.7(14/30) 40.0(12/30) 35.7(10/28) 37.0(10/27) 43.3(40.0-50.0)
2011 100.0(38/38) 55.3(21/38) 47.4(18/38) 42.1(16/38) 39.5(15/38) 42.1(16/38) 57.9(22/38) 44.7(17/38) 44.7(17/38) 42.1(16/38) 36.4(12/33) 41.9(13/31) 43.4(42.0-53.3)
2012 90.0(10/11) 45.5(5/11) 9.1(1/11) 9.1(1/11) 27.3(3/11) 27.3(3/11) 18.2(2/11) 27.3(3/11) 9.1(1/11) 18.2(2/11) 20.0(2/10) 25.0(2/8) 22.5(11.4-27.3)
Total 95.9(281/293) 53.6(157/293) 46.1(135/293) 42.7(125/293) 48.8(143/293) 43.7(128/293) 45.7(134/293) 40.3(118/293) 42.7(125/293) 43.0(126/293) 39.3(108/275) 42.1(112/266) 43.4(40.0-51.0)

Third, in the Results section, “Positive Percentages of Urine Morphine Tests during the Study Period”, suggest author to consider add descriptions similar like following: Between 2006 and 2012, there were 3471 urine morphine tests performed and 1580 were positive (45.5%). The highest positive percentage was observed in the first month (95.9%), then it remained as high as between 39.3% and 53.6% for month 2 to month 12. After excluding the highest percentage in the first month, the average positive percentage was 40.9% for month 2 to month 12.
R: We have added descriptions suggested by the reviewer as:
“Between 2006 and 2012, there were 3471 urine morphine tests performed and 1580 were positive (45.5%). The highest positive percentage was observed in the first month (95.9%), then it remained as high as between 39.3% and 53.6% for month 2 to month 12. After excluding the highest percentage in the first month, the average positive percentage was 40.9% for month 2 to month 12. The median positive percentage of urine morphine tests was 48.6% for 2006,……..”

Fourth, the above description of positive percentage should be summarized and included in the Abstract section.
R: We have added description of positive percentage in the Abstraction Section in the revised manuscript.
“Results: The highest positive percentage (95.9%) was observed in the first month. After excluding the highest percentage in the first month, the average positive percentage was 40.9% for month 2 to month 12. Positive percentages of urine morphine tests that <20%,…….”