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Extremely High Heroin Use Rate among Methadone Maintenance Treatment Clients with HIV/AIDS in Guangdong Province, China

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4 1 **Extremely High Heroin Use Rate among Methadone Maintenance Treatment Clients with**
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6 2 **HIV/AIDS in Guangdong Province, China**
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4 **Abstract**

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6 **Objective:** Little is known about the heroin use and correlates among MMT clients with HIV/AIDS in
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3 Guangdong, China. We aimed to assess the rate of continued heroin use and related predictors among
4 these sub-group clients.

5 **Setting:** Fourteen MMT clinics located in 9 cities of Guangdong were chosen as study sites.

6 **Participants:** In this study, we reviewed retrospectively 642 clients with opioid dependence, HIV
7 seropositive, 18 years or older and providing informed consent during 2006-2013.

8 **Primary and secondary outcome measures:** The continued heroin use rate and underlying predictors
9 were estimated using ordinal logistic regression.

10 **Results:** Of the participants, approximately 98.4% continued using heroin during the first 12 months
11 after treatment initiation. Higher percentages of continued heroin use were associated with being young
12 ($OR_{\leq 30}=0.45$, 95%CI:0.26-0.80; $OR_{31-35}=0.63$, 95%CI: 0.39-1.00; $OR_{36-40}=0.65$, 95%CI:0.42-1.01), having
13 harmonious family relationship ($OR=1.46$, 95%CI:1.01-2.12), financial sources depending on family or
14 friends ($OR=0.71$, 95%CI:0.51-0.98), higher maintenance doses ($OR=0.49$, 95%CI:0.36-0.68) and
15 poorer MMT attendance ($OR_{<20\%}=4.74$, 95%CI:3.01-7.47; $OR_{20\%-40\%}=1.74$, 95%CI:1.16-2.64).

16 **Conclusions:** Heroin use rate is extremely high among MMT clients with HIV/AIDS in Guangdong.
17 The present findings have implications for reconsidering adjusting the current MMT doses and taking
18 effective measures to facilitate attendance in order to decrease heroin use and ultimately improve the
19 effectiveness among these sub-group MMT clients.

20 **Key words:** Heroin Use; Methadone Maintenance Treatment (MMT); HIV; China

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4 **1 Highlights**

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6 1. This is a long-term consecutive study specifically designed to examine concurrent opioid use
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8 among HIV-positive MMT clients in China.
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11 2. This study focused on heroin use and higher percentages of heroin use among HIV-positive MMT
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13 clients in China.
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16 **6 Limitations**

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18 1. Self-reported data are subject to recall bias or deliberate concealment. Family relationship variable
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20 was a client self-perceived indicator and had no standardized measurement for this dimension so
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22 far.
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26 2. Although we found a high heroin use rate, 18.9% of the registered HIV-positive MMT individuals
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28 were lost for refusal. Therefore, the currently observed rate of heroin use is most likely to be an
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30 underestimation.
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34 3. China is experiencing a significant increase in the use of new drugs, but this study did not consider
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36 it. In addition, we failed to obtain the ART (anti-retroviral treatment) information, and future
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38 studies should be extended to analyze ART as predictor variable to continued heroin use.
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1 Introduction

2 In China, illicit drug use has increased dramatically since the 1980s [1]. There were cumulatively
3 registered 2.95 million drug users by the end of 2014 and 480,000 newly registrations in 2014
4 nationwide [2]. Although China recently is experiencing a significant increase in the use of newtype
5 drugs, heroin still remains the major illicit used drug among drug users [2]. The earliest HIV case was
6 identified among intravenous drug users (IDUs) in Southern Yunnan province in 1989[3]. The early
7 spread of HIV epidemics in China mainly attributed to intravenous drug use (IDU)[4]. As of 2013,
8 437,000 people live with HIV/AIDS in China, including 263,000 people living with HIV and 174,000
9 AIDS patients [5].

10 Globally, methadone maintenance treatment (MMT) is the most widely used pharmacological
11 treatment for opioid dependence. China has operated MMT program as a national strategy to combat
12 the joint threat of drug use and HIV/AIDS since 2004 [6]. For decades, MMT program has achieved its
13 crucial effectiveness not only in reducing heroin use [7] but also in preventing the spread of HIV [8, 9].
14 Meanwhile, studies have shown that MMT is beneficial in reducing drug-related criminal activities [10]
15 and drug-related mortality [11]. In addition, for the HIV-positive individuals, MMT could facilitate the
16 adherence to antiretroviral therapy [12, 13]. By the end of April 2015, China has 767 MMT clinics in
17 28 provinces across the nation, serving nearly 190,000 clients [15].

18 However, many clients did not completely abstain from heroin and exhibited continued heroin use
19 while in MMT [16-19]. Continued heroin use could lead to negative MMT treatment outcomes among
20 clients [20]. Heroin addicts still contribute a high mortality even with MMT [21]. Overdosed drug
21 intake remains the most common cause of death among MMT clients [22]. After a period of abstinence
22 via MMT, the heroin tolerance of clients would decrease, thus overdosed intake may become more

1 prevalent [23, 24]. Individuals with HIV/AIDS are a special group among MMT clients. A
2 meta-analysis showed that HIV seropositivity would increase the mortality risk of overdose [25]. In
3 addition, continued heroin use would decrease the retention rate among MMT clients with HIV/AIDS
4 [26]. Therefore, heroin use deserves more attention among MMT clients with HIV/AIDS. To date,
5 limited data are available on heroin use among MMT clients with HIV/AIDS in China. To fill this gap,
6 we applied this study is to examine the heroin use and correlates of higher percentages of heroin use
7 among MMT clients with HIV/AIDS in Guangdong.

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1 **Methods**

2 **Ethics Statement**

3 The Institutional Review Board (IRB) of the School of Public Health (Sun Yat-sen
4 University ,Guangzhou, China) reviewed and approved the study protocol. All study participants were
5 asked to provide written informed consent.

6 **Study Site and Participants**

7 Guangdong, located in the Southern coast of China, is one of the most developed provinces.
8 Meanwhile, Guangdong also is one of the HIV/AIDS and drug epidemic areas because it has
9 cumulative reported 48,718 HIV-positive cases, ranking fifth among provinces in China as of October
10 2014 [27], in addition, it has one-sixth of totally registered drug users in China [28].

11 This study was conducted in 14 MMT clinics located in 9 cities of Guangdong. Between July 2006
12 and December 2013, there were 9,397 entrants; among them, 8,912 (94.8%) received HIV test at entry
13 and 485 (5.2%) refused to be test. Of the remaining 805 MMT clients who tested HIV positive at MMT
14 entry, 81.1% (653 of 805) participated in this study. Participants were eligible if they were (1)
15 diagnosed with opioid dependence according to the International Classification of Diseases (10th
16 Revision); (2) 18 years or older; (3) tested to be HIV-positive; and (4) able to provide informed
17 consent.

18 In this study, “drop-out” was defined as a participant failing to continue MMT for 14 consecutive
19 days [29]. In the accordance with drop-out, the study period could be classified into two categories: one
20 was defined as the duration between enrolment and dropout, the other was defined as the duration
21 between enrolment and the end of the first 12 months.

22 **Measures**

1 ***Self-report Risk Behaviors***

2 At admission, as well as 6th and 12th month respectively, each participant was requested to
3 complete a questionnaire covering demographic characteristics, drug use history including injecting
4 drug and sharing needle/equipment, sexual activity history, and condom use status.

5 A client was regarded as having corresponding risk behaviors during the study period if he/she
6 reported those behaviors either 6th or 12th interview (i.e. drug use behaviors including injecting drug
7 and sharing needle/equipment; and risk sexual activities including, multiple sex partner, inconsistent
8 condom use and sex trade for drugs.).

9 ***Methadone Maintenance Doses and Attendance***

10 In China, to insure MMT security, clients are forbidden to take Methadone outside the clinic. Once
11 enrolled in MMT, the clients must go to the clinic at consultation hours daily to take the prescribed
12 doses of Methadone under the supervision of clinic staff, and the daily doses and date were routinely
13 recorded in the national unified MMT management system. The treatment cost was RMB 10 Yuan
14 (USD: 1.5 Dollar) per day regardless of the client' intake doses and times.

15 Average maintenance dose was obtained via computing the mean of daily prescribed doses.

16 The percentage of MMT attendance was calculated based on proportion of days that a client
17 actually received the doses over the study period.

18 ***Heroin Use during the Study Period***

19 A positive result of urine morphine generally means heroin use by the clients within a few days.

20 Urine-based morphine tests were monthly performed on a random day during the study period.

21 During the study period, a client was recognized as a heroin user as long as any urine morphine
22 test result was positive. The percentage of heroin use was calculated based on the number of positive

1 urine morphine test results and the number of total urine test times during the study period. Based on
2 the urine morphine tests, the clients were currently grouped as “urine morphine (+) (i.e. heroin use)”
3 and “urine morphine (-)(i.e. no heroin use)”. Additionally, the positive percentages were grouped as
4 <40%, 40-80% and >80% based on the data distribution.

5 ***HIV and Urine Morphine Tests***

6 Except for those who were already confirmed as HIV-positive prior this study, each client was
7 invited to receive HIV testing. HIV infection status was screened using an enzyme-linked
8 immunosorbent assay (ELISA) technique (Beijing BGI-GBI Biotech Co., Ltd, Beijing, China). Positive
9 blood specimens for HIV were confirmed using a Western blot assay (Abbott, MP Biomedicals, LLC,
10 Singapore) by the local Centers for Disease Control (CDC). According to related national guidelines,
11 pre- and post- test counseling services were provided.

12 Random urine morphine status was screened using a Morphine Diagnostic Kit (Colloidal Gold)
13 technique (ABON Biopharm Co., Ltd, Hangzhou, China).

14 **Statistical Analysis**

15 Statistical analyses were performed using SPSS 17.0 for Windows (SPSS Inc., Chicago).
16 Categorical variables were described with percentages. Multivariate ordinal logistic regression analysis
17 was conducted to predict higher percentages of heroin use from baseline information including
18 demographic, drug use and multiple sex partners, as well as average maintenance dose and percentages
19 of MMT attendance during the study period among the MMT clients with HIV/AIDS. Any $p < 0.05$ was
20 considered to be statistically significant.

1 Results

2 *Study Participants and Demographic Characteristics*

3 Among the 642 participants (11 clients were not included for refusing to provide urine specimen),
4 138(21.5%) were elder than 40; 600 (93.5%) were males; 636 (99.1%) were ethnic Han (China's
5 predominant ethnic group), 343 (53.4%) were never married; 25.7% just had elementary or lower
6 education; 63.9% were unemployed; only 23.7% had harmonious family relationship; and 61.7%
7 obtained financial sources from their family or friends (Table 1).

8 *Heroin Use and Multiple Sex Partner at Baseline*

9 Table 1 presents baseline information on heroin use. Of the participants, 78.3% had used heroin
10 for more than 10 years; 64.3% participants used heroin at least 3 times daily on average; the vast
11 majority (97.7%) abused powdered heroin and 98.6% ever administered drug by injection. Among the
12 IDUs, 58.1% ever shared intravenous needles. Only 12.5% never met the peer users.

13 Of these participants, 17.4% had had sexual activity with multiple sex partner (Table 1).

14 *Average Maintenance Doses and Attendance*

15 Among all participants, 60.7% had received doses below 60 ml and the average maintenance dose
16 was (57.9 ± 27.1) ml.

17 In addition, 20.1% participants' MMT attendance percentages were less than 20% and only 36.3%
18 were over 80% (Table 1).

19 *Heroin Use during the Study Period*

20 Approximately 98.4% (632/642) participants were defined as heroin users during the study period.
21 Among the 632 urine morphine (+) clients, positive percentages of urine morphine tests that <40%,
22 40%-80% and >80% were 29.0%, 32.6% and 38.4% respectively (Table 2).

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4 1 After adjusted for potential confounding variables listed in the table, multiple ordinal logistic
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6 2 regression analysis indicated that a higher percentage of heroin use was independently associated with
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8 3 age, family relationship, financial sources, average MMT doses and percentage of MMT attendance.
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10 4 Participants who were younger ($OR_{\leq 30}=0.45$, 95%CI: 0.26-0.80; $OR_{31-35}=0.63$, 95%CI: 0.39-1.00;
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12 5 $OR_{36-40}=0.65$, 95%CI: 0.42-1.01), got money from family or friends ($OR=0.71$, 95%CI: 0.51-0.98) and
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14 6 had MMT doses over 60 ml ($OR=0.49$, 95%CI: 0.36-0.68) were more likely to be tested as having
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16 7 lower percentages of heroin use; and those who had harmonious family relationships ($OR=1.46$, 95%CI:
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18 8 1.01-2.12) and poor MMT attendance percentages ($OR_{\leq 20}=4.74$, 95%CI: 3.01-7.47; $OR_{20-}=1.74$, 95%CI:
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20 9 1.16-2.64) were more likely to have higher percentages of heroin use (Table 2).
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26 ***Self-report High Risk Behaviors during the Study Period***

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29 11 Among the clients with urine morphine (+), 68.5% (440 of 642) and 46.3% (297 of 642) completed
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31 12 the 6th and 12th month follow-up interviews respectively. Of the 440 clients completed at least one
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33 13 follow-up interview, 78.3% ever used drugs, 88.2% used intravenous drugs, and 20.7% ever shared
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35 14 intravenous needles; 57.0% were sexual active, 28.7% had sex with multiple sex partners, and 40.2%
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37 15 never used condom during the sexual course. Also, 13.3% traded sex for drugs (Table 3).
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1 Discussion

2 Heroin use among MMT clients has been reported substantially worldwide [17, 18]. HIV-positive
3 drug users are a unique subgroup for playing a “dual bridge” role in HIV transmission. This study is an
4 extension of our previous study [30].

5 Findings from the current analysis revealed an extremely heroin use rate among MMT clients with
6 HIV/AIDS in Guangdong. Approximately 98.4% participants continued use heroin during the study
7 period, which is far exceeding those reported by other researches in China [16-18]. Our results were
8 based on random, long-term and consecutive urine tests, which was blind to clients in case those
9 continued heroin users deliberately avoid the test time. Meanwhile, the rate was higher than that (75%)
10 of general MMT clients reported by our prior study [30]. Given that continued heroin use might lead to
11 adverse health outcomes [22, 25] and high drop-out rate [26] among MMT clients with HIV/AIDS,
12 targeted interventions and control programs are urgently needed for this subgroup.

13 Compared to the young participants, the elders showed greater likelihood of continued heroin use.
14 Many elders had turned from clinical latency stage to AIDS stage and they may experience more pain
15 and psychological symptoms [31, 32]. Studies had shown that depressive symptoms are common
16 among people with HIV infection [33, 34]. However, MMT improvements in depressive symptoms and
17 the physical domain of QOL (quality of life) among HIV-positive heroin users were poorer than in
18 those without HIV infection [35]. Also, most of them had lost the courage and confidence to live on.
19 Culturally, stigma and discrimination towards drug use and HIV/AIDS might seriously impede the
20 MMT attendance [36]. In addition, inappropriate perceptions of MMT should not be neglected [37].

21 Families play important roles in the life of drug users. Drug use and MMT is regarded as a family
22 issue in China [38]. Harmonious family relationship could potentially encourage treatment

1 participation and enhance compliance [30, 36]. A notable finding in our study was that the clients who
2 had harmonious family relationship were more likely to use heroin, which contradicts previous studies
3 [30, 36]. This is probably because the family members in harmonious family relationship have more
4 tolerance towards them, which may subsequently indulged their heroin use behavior. However, this
5 speculation requires further investigation.

6 Generally, high drug fee generally made the drug users can't afford it. In our study, 63.9% were
7 unemployed; for the employed, many only had short-term jobs. This may partly explain the reasons
8 why the clients whose financial sources depend on family or friends were less likely to use heroin.
9 Money from family or friends is meant to support basic life and is far not enough to meet drug
10 expenditure. Furthermore, family or friends' support might potentially supervise and encourage
11 treatment participation and compliance [38].

12 Higher Methadone doses would promote the retention rate in MMT [39]. An appropriate MMT
13 dose is the most effective in suppressing heroin use in treatment [20, 40]. The Methadone dose
14 recommended by US National Institutes of Health was ≥ 60 mg/day [41], and should be higher for
15 HIV-positive individuals [42]. Studies showed an adequate dose of Methadone (e.g., 80- 120 mgs/day)
16 would significantly reduce heroin use among clients within the first two months of treatment and
17 eventually either eliminated or significantly curtailed with time in treatment [43, 44]. We found 60.7%
18 participants' doses were less than 60 mg/day. Compared to those with higher doses, the clients with
19 lower doses were more likely to use heroin. Further researches are needed on appropriate doses of
20 Methadone and whether increasing doses could decrease the rate of continued heroin use.

21 Without exception, treatment effectiveness relies upon sufficient levels of medication adherence.
22 MMT requires long-term or even life-long intake of Methadone at an adequate dose on a daily basis

1 [45]. We found that the lower attendance meant the higher percentage of heroin use. This was
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6 consistent with our prior study [30]. Continued heroin users attended MMT programs irregularly and
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9 the attendance significantly declined with the duration that they retained in treatment program [46].
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12 Poorer attendance seeded continued heroin use. In addition, misconceptions might predict dropout rates
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14 and poor adherence among newly admitted MMT clients [47]. So, future research might need to
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16 develop and/or integrate other necessary interventions to encourage client adherence to the treatment
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19 program.

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21 HIV-positive drug users have been regarded as a “dual risk” subgroup. They transmit HIV via
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24 either sharing needles or having unprotected sexual intercourse with partners. Currently, sexual
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27 transmission is the most prevalent spread pattern of HIV/AIDS in China [5]. Among the participants
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30 who finished at least once interview, 20.7% ever shared needle; 28.7% ever had sex with multiple
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33 partners; 40.2% never used condom and 13.3% had sex for drugs during the study period. Considering
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36 the potential bridge role of those with dual risk behaviors in transmitting HIV to others, research on the
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39 interaction of HIV-positive MMT clients and risk behaviors should be given high priority. Data showed
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42 that changing unsafe drug use behaviors was more effective than changing unsafe sexual behaviors
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45 [19]. In future treatment procedures, physicians and nurses should play an active role in educating
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48 clients about safe sex and encourage clients to use condoms.

49
50 This study is subject to certain limitations. Firstly, self-reported data are subject to recall bias or
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53 deliberate concealment. Family relationship variable was a client self-perceived indicator and had no
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56 standardized measurement for this dimension so far. Secondly, although we found a high heroin use
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59 rate, 18.9% of the registered HIV-positive MMT individuals were lost for refusal. Therefore, the
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62 currently observed rate of heroin use is most likely to be an underestimation. Thirdly, China is

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4 1 experiencing a significant increase in the use of new drugs [2], but this study did not consider it. In
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6 2 addition, we failed to obtain the ART (anti-retroviral treatment) information, and future studies should
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9 3 be extended to analyze ART as predictor variable to continued heroin use.

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11 4 In summary, findings from this study provide important implications for future MMT programs
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14 5 targeting continued heroin use among HIV-positive clients. Concretely, first, continuous and efficient
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16 6 MMT consulting and health education interventions need to be conducted for reducing continued
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18 7 heroin use. Interventions involving family members in supervision of participation and compliance
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21 8 should be reinforced. Second, doses and attendance are crucial components affecting MMT' outcomes,
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24 9 so how to prescribe an appropriate MMT dose and improve sufficient attendance have become issues of
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26 10 great urgency.

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5 of the manuscript.

6 Contributors

7 XL designed the study, performed data analysis and wrote the draft manuscript. XG and PZ
8 performed data analysis. XZ and WC collected the data. LL supervised the study. All authors
9 contributed to the interpretation of the data and approved the final version for submission.

10 Conflict of Interest

11 The authors declare no conflicts of interest.

12 Data Sharing Statement

13 No additional unpublished data are available.

14 Acknowledgements

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17 sharing with us regarding their information.

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1 Tables

2 Table1. Characteristics of the participants (n* =642)

Characteristics	Urine Morphine(-)	Urine Morphine(+)	Total
	(n=10)	(n=632)	(N=642)
	No. (%)	No. (%)	No. (%)
Age at Baseline (years)			
≤30	2(20.0)	113(17.9)	114(17.9)
31-	5(50.0)	186(29.4)	191(29.8)
36-	1(10.0)	197(31.2)	198(30.8)
≥41	2(20.0)	136(21.5)	138(21.5)
Gender			
Male	10(100.0)	590(93.4)	600(93.5)
Female	0(0)	42(6.6)	42(6.5)
Ethnic			
Han	10(100.0)	626(99.1)	636(99.1)
Others	0(0)	6(0.9)	6(0.9)
Marital Status at Baseline			
Never married	4(40.0)	339(53.6)	343(53.4)
Married currently	5(50.0)	222(35.1)	227(35.4)
Others	1(10.0)	71(11.2)	72(11.2)
Education Level			
Elementary or lower	1(10.0)	164(25.9)	165(25.7)
Juniorhigh school	9(90.0)	400(63.3)	409(63.7)
Senior high school or higher	0(0)	68(10.8)	68(10.6)
Employed Status at Baseline			
Unemployed	2(20.0)	408(64.6)	410(63.9)
Employed	8(80.0)	224(35.4)	232(36.1)
Family Relationship at Baseline			
Harmonious	3(30.0)	149(23.6)	152(23.7)
Inharmonious	7(70.0)	483(76.4)	490(76.3)
Mainly Financial Sources at Baseline			
Family or friends	6(60.0)	390(61.7)	396(61.7)
Others	4(40.0)	242(38.3)	246(38.3)
Duration of Drug Abuse (years)			
≤10	3(30.0)	136(21.5)	139(21.7)
11-15	3(30.0)	263 (41.6)	266(41.4)
≥16	4(40.0)	233(36.9)	237(36.9)
Type of Drug Use at Baseline			
Heroin	9(90.0)	618(97.8)	627(97.7)
Others	1(10.0)	14(2.2)	15(2.3)
Intravenous Drug Use at Baseline			
Yes	10(100.0)	623(98.6)	633(98.6)
No	0(0)	9(1.4)	9(1.4)
Shared Needles to Inject Drugs at Baseline			

Yes	4(40.0)	364(58.4)	368(58.1)
No	6(60.0)	259(41.6)	265(41.9)
Average Times of Drug Use per Day at Baseline			
≤2	3(30.0)	226(35.8)	229(35.7)
≥3	7(70.0)	406(64.2)	413(64.3)
Frequency of Meeting with Peer Users at Baseline			
none	0(0)	80(12.7)	80(12.5)
1-4/month	2(20.0)	160(25.3)	162(25.2)
1-6/week	3(30.0)	161(25.5)	164(25.5)
> 1/day	5(50.0)	231(36.6)	236(36.8)
Multiple Sex Partners at Baseline			
Yes	2(20.0)	110(17.4)	111(17.4)
No	8(80.0)	522(82.6)	530(82.6)
Average Maintenance Doses (ml/day)			
≥60	7(70.0)	245(38.8)	252(39.3)
<60	3(30.0)	387(61.2)	390(60.7)
Percentages of MMT Attendance (%)			
<20	2(20.0)	127(20.1)	129(20.1)
20-	0(0)	140(22.2)	140(21.8)
50-	1(10.0)	139(22.0)	140(21.8)
≥80%	7(70.0)	226(35.8)	233(36.3)

*11 clients refuse to provide urine specimen to morphine test.

1 Table2. Correlates of higher percentages of opioid use among urine morphine (+) participants
 2 during the study period (n=632)

Characteristics	<40% (n=183)	40%-80% (n=206)	>80% (n=243)	OR(95%CI) ^{a, b}	<i>p</i> ^b
	No. (%) [*]	No. (%) [*]	No. (%) [*]		
Age (years)					
≤30	36(31.9)	47(41.6)	30(26.5)	0.45(0.26-0.80)	0.006
31-	55(29.6)	56(30.1)	75(40.3)	0.63(0.39-1.00)	0.051
36-	55(27.9)	68(34.5)	74(37.6)	0.65(0.42-1.01)	0.054
≥41	37(27.2)	35(25.7)	64(47.1)	1.00	
Gender					
Male	168(28.5)	197(33.4)	225(38.1)	0.94(0.50-1.75)	0.844
Female	15(35.7)	9(21.4)	18(42.9)	1.00	
Ethnic					
Han	181(28.9)	206(32.9)	239(38.2)	0.24(0.05-1.26)	0.092
Others	2(33.3)	0(0)	4(66.7)	1.00	
Marital Status					
Never married	97(28.6)	117(34.5)	125(36.9)	1.52(0.91-2.55)	0.111
Married Currently	58(26.1)	71(32.0)	93(41.9)	1.47(0.88-2.48)	0.144
Others	28(39.4)	18(25.4)	25(35.2)	1.00	
Education Level					
Elementary or lower	44(26.8)	54(32.9)	66(40.2)	1.03(0.60-1.79)	0.905
Juniorhigh school	117(29.3)	131(32.8)	152(38.0)	1.11(0.67-1.82)	0.686
Senior high school or higher	22(32.4)	21(30.9)	25(36.8)	1.00	
Employment Status at Baseline					
Unemployed	122(29.9)	136(33.3)	150(36.8)	0.90(0.64-1.27)	0.563
Employed	61(27.2)	70(31.3)	93(41.5)	1.00	
Family Relationship at Baseline					
Harmonious	37(24.8)	48(32.2)	64(43.0)	1.46(1.01-2.12)	0.046
Inharmonious	146(30.2)	158(32.7)	179(37.1)	1.00	
Mainly Financial Sources					
Family or friends	121(31.0)	132(33.8)	137(35.1)	0.71(0.51-0.98)	0.038
Others	62(25.6)	74(30.6)	106(43.8)	1.00	
Duration of Drug Abuse (years)					
≤10	35(25.7)	53(39.0)	48(35.3)	0.91(0.58-1.42)	0.665
11-15	81(30.8)	84(31.9)	98(37.3)	0.96(0.67-1.38)	0.845
≥16	67(28.8)	69(29.6)	97(41.6)	1.00	
Average Times of Drug Use per Day					
≤2	53(23.5)	92(40.7)	81(35.8)	0.86(0.62-1.19)	0.364
≥3	130(32.0)	114(28.1)	162(39.9)	1.00	
Shared Needles at Baseline					
Yes	102(27.9)	126(34.5)	137(37.5)	1.14(0.83-1.55)	0.415
No	81(30.3)	80(30.0)	106(39.7)	1.00	
Frequency of Meeting with Peer					

Users at Baseline						
none	25(31.3)	28(35.0)	27(33.8)	0.89(0.54-1.47)	0.645	
1-4/month	44(27.5)	55(34.4)	61(38.1)	1.11(0.75-1.64)	0.595	
1-6/week	46(28.6)	54(33.5)	61(37.9)	1.13(0.76-1.67)	0.547	
> 1/day	68(29.4)	69(29.9)	94(40.7)	1.00		
Multiple Sex Partners at Baseline						
Yes	26(23.6)	37(33.6)	47(42.7)	1.35(0.90-2.03)	0.148	
No	157(30.1)	169(32.4)	196(37.5)	1.00		
Average Maintenance Doses (ml/day)						
≥60	94(38.4)	84(34.3)	67(27.3)	0.49(0.36-0.68)	<0.001	
<60	89(23.0)	122(31.5)	176(45.5)	1.00		
Percentages of MMT Attendance (%)						
<20	7(5.5)	44(34.6)	76(59.8)	4.74(3.01-7.47)	<0.001	
20-	34(24.3)	53(37.9)	53(37.9)	1.74(1.16-2.64)	0.008	
50-	52(37.4)	42(30.2)	45(32.4)	1.24(0.83-1.84)	0.294	
≥80%	90(39.8)	67(29.6)	69(30.5)	1.00		

1 ^aOR: Odds Ratio, CI: Confidence Interval;

2 ^bObtained from multivariate ordinal logistic regression analysis adjusting for potential confounding variables listed
3 in the table;

4 *Proportions were calculated in the row.

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1 Table3. Self-reported risk behaviors among urine morphine (+) participants during the study
 2 period (n=440)

Characteristics	<40%	40%-80%	>80%	Total
	No. (%)	No. (%)	No. (%)	No. (%)
Drug Use (n=440)				
Yes	61(39.4)	111(68.1)	107(87.7)	279(63.4)
No	94(60.6)	52(31.9)	15(12.3)	161(36.6)
Injected Drugs (n=279)				
Yes	48(78.7)	96(86.5)	102(95.3)	246(88.2)
No	13(21.3)	15(13.5)	5(4.7)	33(11.8)
Shared Needles (n=246)				
Yes	7(14.6)	21(21.9)	23(22.5)	51(20.7)
No	41(85.4)	75(78.1)	79(77.5)	195(79.3)
Sex Activity (n=440)				
Yes	76(49.0)	99(60.7)	76(62.3)	251(57.0)
No	79(51.0)	64(39.3)	46(37.3)	189(43.0)
Multiple Sex Partners (n=251)				
Yes	21(27.9)	37(37.4)	14(18.4)	72(28.7)
No	55(72.4)	62(62.6)	62(81.6)	179(71.3)
Condom Use (n=251)				
Yes	47(61.8)	56(56.6)	47(61.8)	150(59.8)
No	29(38.2)	43(43.4)	29(38.2)	101(40.2)
Sex for Drugs (n=180)				
Yes	7(17.5)	14(19.4)	3(4.4)	24(13.3)
No	33(82.5)	58(80.6)	65(95.6)	156(86.7)

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract Line 6, page 2 (b) Provide in the abstract an informative and balanced summary of what was done and what was found Line 3, page 2; line 16-19, page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Line 18-22, page 4; line 1-4, page 5
Objectives	3	State specific objectives, including any prespecified hypotheses Line 4-7, page 5
Methods		
Study design	4	Present key elements of study design early in the paper Line 11-14, page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Line 11-14, page 6; line 18-21, page 6
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Line 14-17, page 6; line 19-20, page 7 <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed ----- <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Line 22, page 6; line 1-22, page 7; line 1-13, page 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Line 22, page 6; line 1-22, page 7; line 1-13, page 8
Bias	9	Describe any efforts to address potential sources of bias Line 7-10, page 8; line 11-13, page 7
Study size	10	Explain how the study size was arrived at Line 11-14, page 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Line 16, page 8; line 21-22, page 7; line 1-4, page 8

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2		
3	Statistical methods	12
4		(a) Describe all statistical methods, including those used to control for confounding
5		Line 16-20, page 8
6		(b) Describe any methods used to examine subgroups and interactions
7		(c) Explain how missing data were addressed
8		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed
9		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was
10		addressed
11		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of
12		sampling strategy
13		(e) Describe any sensitivity analyses

Continued on next page

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Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Line 11-14, page 6
		(b) Give reasons for non-participation at each stage Line 3, page 9; line 11-12, page 10
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Table 1, line 2-7, page 9
		(b) Indicate number of participants with missing data for each variable of interest Table 1-3
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount) Line 18-21, page 6
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time line 20-22, page 9
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Table 2, page 24-25
		(b) Report category boundaries when continuous variables were categorized Table 1, page 22-23; line 20-22, page 9
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Line 10-15, page 10

Discussion

Key results	18	Summarise key results with reference to study objectives Line 5-6, page 11; line 13 page 11; line 1-2, page 12; line 7-8 page 12; line 17-19, page 12; line 1, page 13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Line 18-22, page 13; line 1-3, page 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Line 7-10, page 11; line 14-20, page 11; line 3-5, page 12; line 7-11, page 12; line 2-7, page 13
Generalisability	21	Discuss the generalisability (external validity) of the study results Line 4-10, page 14

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based
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Line 1-5, page 15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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BMJ Open

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



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Manuscripts

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4 1 **Positive Percentages of Urine Morphine Tests among Methadone Maintenance Treatment Clients**
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6 2 **with HIV/AIDS during the First 12 Months after Treatment Initiation in Guangdong Province,**
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9 3 **China**

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1 **Abstract**

2 **Objective:** We aimed to assess the positive percentages of urine morphine tests and correlates among
3 MMT clients with HIV/AIDS in Guangdong, China.

4 **Setting:** Fourteen MMT clinics located in 9 cities of Guangdong were chosen as study sites.

5 **Participants:** In this study, we reviewed retrospectively 642 clients with opioid dependence, HIV
6 seropositive, 18 years or older, providing informed consent and urine sample during the study period.

7 **Primary and secondary outcome measures:** The positive percentages of urine morphine tests were
8 calculated and underlying predictors were estimated.

9 **Results:** There were 38.4% participants with positive percentages of urine morphine tests over 80%
10 during the first 12 months after treatment initiation. Lower percentages of continued heroin use were
11 associated with being young ($OR_{\leq 30}=0.45$, 95%CI:0.26-0.80; $OR_{31-}=0.63$, 95%CI:0.39-1.00;
12 $OR_{36-}=0.65$, 95%CI:0.42-1.01), financial sources depending on family or friends ($OR=0.71$,
13 95%CI:0.51-0.98) and higher maintenance doses ($OR=0.49$, 95%CI:0.36-0.68). Higher percentages of
14 continued heroin use were associated with having harmonious family relationship ($OR=1.46$,
15 95%CI:1.01-2.12) and poorer MMT attendance ($OR_{<20\%}=4.74$, 95%CI:3.01-7.47; $OR_{20\%}=1.74$,
16 95%CI:1.16-2.64).

17 **Conclusions:** High positive percentages of urine morphine tests remain prevalent among MMT clients
18 with HIV/AIDS in Guangdong. The present findings have implications for reconsidering adjusting the
19 current MMT doses and taking effective measures to facilitate attendance in order to decrease heroin
20 use and ultimately improve the effectiveness among these sub-group MMT clients.

21 **Key words:** Heroin Use; Methadone Maintenance Treatment (MMT); HIV; China

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4 **1 Highlights**

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6 1. This is a long-term consecutive study specifically designed to examine concurrent heroin use
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8 among HIV-positive MMT clients in China.
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10 2. This study mainly focused on positive percentages of urine morphine tests among HIV-positive
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12 MMT clients in China.
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16 **6 Limitations**

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18 1. Self-reported data are subject to recall bias or deliberate concealment. Family relationship variable
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20 was a client self-perceived indicator and had no standardized measurement for this dimension so
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22 far.
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26 2. China is experiencing a significant increase in the use of new drugs, but this study did not consider
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28 it. In addition, we failed to obtain the ART (anti-retroviral treatment) information, and future
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30 studies should be extended to analyze ART as predictor variable to continued heroin use.
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34 3. Frequent drop-out always exists among clients in MMT programs. Most of clients would drop out
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36 within a few months which had been widely noticed. For the drop-outs, many of them probably
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38 were tested only once or twice but all these tests were positive, which might over-estimate the
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40 percentages of heroin use. In addition, we only examined the percentages of heroin use during the
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42 first 12 months after receiving MMT due to the limited sample size and high drop-out.
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1 Introduction

2 In China, illicit drug use has increased dramatically since the 1980s [1]. There were cumulatively
3 registered 2.95 million drug users by the end of 2014 and 480,000 newly registrations in 2014
4 nationwide [2]. Although China recently is experiencing a significant increase in the use of new-type
5 drugs, heroin still remains the major illicit used drug among drug users [2]. The earliest HIV case was
6 identified among intravenous drug users (IDUs) in Southern Yunnan province in 1989 [3]. The early
7 spread of HIV epidemics in China mainly attributed to intravenous drug use (IDU) [4]. As of 2013,
8 437,000 people lived with HIV/AIDS in China (including 263,000 people living with HIV and 174,000
9 AIDS patients), accounting for 0.033% of the total population in China; and sentinel surveillance data
10 showed the HIV/AIDS prevalence was 6.3% among IDUs [5].

11 Globally, methadone maintenance treatment (MMT) is the most widely used pharmacological
12 treatment for opioid dependence. China has operated MMT program as a national strategy to combat
13 the joint threat of drug use and HIV/AIDS since 2004 [6]. For decades, MMT program has achieved its
14 crucial effectiveness not only in reducing heroin use [7] but also in preventing the spread of HIV [8, 9].
15 Meanwhile, studies have shown that MMT is beneficial in reducing drug-related criminal activities
16 [10] and drug-related mortality [11]. In addition, for the HIV-positive individuals, MMT could facilitate
17 the adherence to antiretroviral therapy [12]. By the end of April 2015, China has 767 MMT clinics in
18 28 provinces across the nation, serving nearly 190,000 clients [13].

19 However, many clients did not completely abstain from heroin and exhibited continued heroin use
20 while in MMT [14-17]. Continued heroin use could lead to negative MMT treatment outcomes among
21 clients [18]. Heroin addicts still contribute a high mortality even with MMT [19]. Overdosed drug
22 intake remains the most common cause of death among MMT clients [20]. After a period of abstinence

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4 1 via MMT, the heroin tolerance of clients would decrease, thus overdosed intake may become more
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6 2 prevalent [21, 22]. Individuals with HIV/AIDS are a special group among MMT clients. A
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8 3 meta-analysis showed that HIV seropositivity would increase the mortality risk of overdose [23]. In
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10 4 addition, continued heroin use would decrease the retention rate among MMT clients with HIV/AIDS
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12 5 [24]. Therefore, heroin use deserves more attention among MMT clients with HIV/AIDS. To date,
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14 6 limited data are available on heroin use among MMT clients with HIV/AIDS in China [14, 25] and
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16 7 about the higher percentages of heroin use is even less. To fill this gap, we applied this study is to
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18 8 examine the higher percentages of heroin use among MMT clients with HIV/AIDS in Guangdong.
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1 **Methods**

2 **Ethics Statement**

3 The Institutional Review Board (IRB) of the School of Public Health (Sun Yat-sen
4 University ,Guangzhou, China) reviewed and approved the study protocol. All study participants were
5 asked to provide written informed consent.

6 **Study Site and Participants**

7 Guangdong, located in the Southern coast of China, is one of the most developed provinces.
8 Meanwhile, Guangdong also is one of the HIV/AIDS and drug epidemic areas because it has
9 cumulative reported 48,718 HIV-positive cases, ranking fifth among provinces in China as of October
10 2014 [26], in addition, it has one-sixth of totally registered drug users in China [27].

11 This study was conducted in 14 MMT clinics located in 9 cities of Guangdong (According to
12 whether the 1-year retention rate is above or below 50%, the 61 MMT clinics were divided into two
13 groups, and seven clinics were randomly selected from each group [28]). We got permission and
14 authorization to use and retrieve part of data for the selected MMT clinics from the Chinese National
15 MMT Program data system. Between July 2006 and December 2013, there were 9,397 entrants; among
16 them, 8,912 (94.8%) received HIV test at entry and 485 (5.2%) refused to be test. Of the remaining 805
17 MMT clients who tested HIV positive at MMT entry, 81.1% (653 of 805) participated in this study. In
18 this study, participants were eligible if they were (1) diagnosed with opioid dependence according to
19 the International Classification of Diseases (10th Revision); (2) 18 years or older; (3) tested to be
20 HIV-positive at entry; (4) able to provide informed consent; and (5) able to provide urine specimen to
21 morphine test.

22 In this study, “drop-out” was defined as a participant failing to continue MMT for 14 consecutive

1 days [28]. In accordance with high drop-out rates, the study period could be 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.

4 **Measures**

5 ***Self-reported Risk Behaviors***

6 At admission, as well as 6th and 12th month respectively, each participant was requested to complete a questionnaire covering demographic characteristics, drug use history including injecting drug and sharing needle/equipment, sexual activity history, and condom use status.

9 A client was regarded as having corresponding risk behaviors during the study period if he/she reported those behaviors either 6th or 12th interview (i.e. drug use behaviors including injecting drug and sharing needle/equipment; and risk sexual activities including, multiple sex partner, inconsistent condom use and sex trade for drugs.).

13 ***Methadone Maintenance Doses and Attendance***

14 In China, to insure MMT security, clients are forbidden to take Methadone outside the clinic. Once enrolled in MMT, the clients must go to the clinic at consultation hours daily to take the prescribed doses of Methadone under the supervision of clinic staff, and the daily doses and date were routinely recorded in the national unified MMT management system. The treatment cost was RMB 10 Yuan (USD: 1.5 Dollar) per day regardless of the client' intake doses and times.

19 Average maintenance dose was obtained via computing the mean of daily prescribed doses.

20 The percentage of MMT attendance was calculated based on proportion of days that a client actually received the doses over the study period.

22 ***Positive Percentages of Urine Morphine Tests during the Study Period***

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4 1 A positive result of urine morphine test generally means heroin use by the clients within a few
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6 2 days. Urine-based morphine tests were monthly performed on a random day during the study period.
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9 3 The percentage of heroin use was calculated based on the number of positive urine morphine test
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11 4 results and the number of total urine test times during the study period. Based on the urine morphine
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13 5 tests, the clients were currently grouped as “urine morphine (+)” and “urine morphine (-)”. Additionally,
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15 6 the positive percentages were grouped as <40%, 40-80% and >80% based on the data distribution.
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18 19 7 *HIV and Urine Morphine Tests*

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21 8 Except for those who were already confirmed as HIV-positive prior this study, each client was
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23 9 invited to receive HIV testing. HIV infection status was screened using an enzyme-linked
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25 10 immunosorbent assay (ELISA) technique (Beijing BGI-GBI Biotech Co., Ltd, Beijing, China). Positive
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27 11 blood specimens for HIV were confirmed using a Western blot assay (Abbott, MP Biomedicals, LLC,
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29 12 Singapore) by the local Centers for Disease Control (CDC). According to related national guidelines,
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31 13 pre- and post- test counseling services were provided.
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35 14 Random urine morphine status was screened using a Morphine Diagnostic Kit (Colloidal Gold)
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37 15 technique (ABON Biopharm Co., Ltd, Hangzhou, China).
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39 40 41 16 **Statistical Analysis**

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43 17 Statistical analyses were performed using SPSS 17.0 for Windows (SPSS Inc., Chicago).
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45 18 Categorical variables were described with percentages. Multivariate ordinal logistic regression analysis
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47 19 was conducted to predict higher percentages of heroin use from baseline information including
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49 20 demographic, drug use and multiple sex partners, as well as average maintenance dose and percentages
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51 21 of MMT attendance during the study period among the MMT clients with HIV/AIDS. Any $p < 0.05$ was
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53 22 considered to be statistically significant.
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1 Results

2 *Study Participants and Demographic Characteristics*

3 Among the 642 participants, 138(21.5%) were elder than 40; 600 (93.5%) were males; 636 (99.1%)
4 were ethnic Han (China's predominant ethnic group), 343 (53.4%) were never married; 25.7% just had
5 elementary or lower education; 63.9% were unemployed; only 23.7% had harmonious family
6 relationship; and 61.7% obtained financial sources from their family or friends (Table 1).

7 *Heroin Use and Multiple Sex Partner at Baseline*

8 Table 1 presents baseline information on heroin use. Of the participants, 78.3% had used heroin
9 for more than 10 years; 64.3% participants used heroin at least 3 times daily on average; the vast
10 majority (97.7%) abused powdered heroin and 98.6% ever administered drug by injection. Among the
11 IDUs, 58.1% ever shared intravenous needles. Only 12.5% never met the peer users.

12 Of these participants, 17.4% had had sexual activity with multiple sex partner (Table 1).

13 *Average Maintenance Doses and Attendance*

14 Among all participants, 60.7% had received doses below 60 ml and the average maintenance dose
15 was (57.9 ± 27.1) ml.

16 In addition, 20.1% participants' MMT attendance percentages were less than 20% and only 36.3%
17 were over 80% (Table 1).

18 *Positive Percentages of Urine Morphine Tests during the Study Period*

19 The median positive percentage of urine morphine tests was 52.3% for 2006, 47.9% for 2007, 47.0%
20 for 2008, 45.1% for 2009, 44.5% for 2010, 47.1% for 2011, 23.3% for 2012 and 55.4% for 2013,
21 respectively (Table 2). Among the 632 urine morphine (+) clients, positive percentages of urine
22 morphine tests that <40%, 40%-80% and >80% were 29.0%, 32.6% and 38.4% respectively (Table 3).

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4 1 After adjusted for potential confounding variables listed in the table, multiple ordinal logistic
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6 2 regression analysis indicated that a higher percentage of heroin use was independently associated with
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8 3 age, family relationship, financial sources, average MMT doses and percentage of MMT attendance.
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10 4 Participants who were younger ($OR_{\leq 30}=0.45$, 95%CI: 0.26-0.80; $OR_{31-35}=0.63$, 95%CI: 0.39-1.00;
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12 5 $OR_{36-40}=0.65$, 95%CI: 0.42-1.01), got money from family or friends ($OR=0.71$, 95%CI: 0.51-0.98) and
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14 6 had MMT doses over 60 ml ($OR=0.49$, 95%CI: 0.36-0.68) were more likely to be tested as having
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16 7 lower percentages of heroin use; and those who had harmonious family relationships ($OR=1.46$, 95%CI:
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18 8 1.01-2.12) and poor MMT attendance percentages ($OR_{\leq 20}=4.74$, 95%CI: 3.01-7.47; $OR_{20-}=1.74$, 95%CI:
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20 9 1.16-2.64) were more likely to have higher percentages of heroin use (Table 4).
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26 ***Self-reported High Risk Behaviors during the Study Period***

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29 11 Among the clients with urine morphine (+), 69.6% (440 of 632) and 47.0% (297 of 632) completed
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31 12 the 6th and 12th month follow-up interviews respectively. Of the 440 clients completed at least one
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33 13 follow-up interview, 78.3% ever used drugs, 88.2% used intravenous drugs, and 20.7% ever shared
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35 14 intravenous needles; 57.0% were sexual active, 28.7% had sex with multiple sex partners, and 40.2%
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37 15 never used condom during the sexual course. Also, 13.3% traded sex for drugs (Table 5).
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1 Discussion

2 Heroin use among MMT clients has been reported substantially worldwide [15, 16]. HIV-positive
3 drug users are a unique subgroup for playing a “dual bridge” role in HIV transmission. This study is an
4 extension of our previous study [25]. Our results were based on random, long-term and consecutive
5 urine tests, which was blind to clients in case those continued heroin users deliberately avoid the test
6 time.

7 Findings from the current analysis revealed that there were 38.4% participants with positive
8 percentages of urine morphine tests over 80% during the first 12 months after treatment initiation.
9 Given that continued heroin use might lead to adverse health outcomes [20, 23] and high drop-out rate
10 [24] among MMT clients with HIV/AIDS, targeted interventions and control programs are urgently
11 needed for this subgroup.

12 Compared to the young participants, the elders showed greater likelihood of continued heroin use.
13 Many elders had turned from clinical latency stage to AIDS stage and they may experience more pain
14 and psychological symptoms [29, 30]. Studies had shown that depressive symptoms are common
15 among people with HIV infection [31, 32]. However, MMT improvements in depressive symptoms and
16 the physical domain of QOL (quality of life) among HIV-positive heroin users were poorer than in
17 those without HIV infection [33]. Also, most of them had lost the courage and confidence to live on.
18 Culturally, stigma and discrimination towards drug use and HIV/AIDS might seriously impede the
19 MMT attendance [34]. In addition, inappropriate perceptions of MMT should not be neglected [35].

20 Families play important roles in the life of drug users. Drug use and MMT is regarded as a family
21 issue in China [36]. Harmonious family relationship could potentially encourage treatment participation
22 and enhance compliance [25, 34]. A notable finding in our study was that the clients who had

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4 1 harmonious family relationship were more likely to use heroin, which contradicts previous studies [25,
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6 34]. This is probably because the family members in harmonious family relationship have more
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9 3 tolerance towards them, which may subsequently indulge in their heroin use behavior. However, this
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11 4 speculation requires further investigation.

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14 5 Generally, high drug fee generally made the drug users can't afford it. In our study, 63.9% were
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16 6 unemployed; for the employed, many only had short-term jobs. This may partly explain the reasons
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18 7 why the clients whose financial sources depend on family or friends were less likely to use heroin.
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20 8 Money from family or friends is meant to support basic life and is far not enough to meet drug
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22 9 expenditure. Furthermore, family or friends' support might potentially supervise and encourage
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24 10 treatment participation and compliance [36].

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29 11 Higher Methadone doses would promote the retention rate in MMT [37]. An appropriate MMT
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31 12 dose is the most effective in suppressing heroin use in treatment [18, 38]. The Methadone dose
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33 13 recommended by US National Institutes of Health was ≥ 60 mg/day [39], and should be higher for
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35 14 HIV-positive individuals [40]. Studies showed an adequate dose of Methadone (e.g., 80- 120 mgs/day)
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37 15 would significantly reduce heroin use among clients within the first two months of treatment and
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39 16 eventually either eliminated or significantly curtailed with time in treatment [41, 42]. We found 60.7%
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41 17 participants' doses were less than 60 mg/day. Compared to those with higher doses, the clients with
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43 18 lower doses were more likely to use heroin. Further researches are needed on appropriate doses of
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45 19 Methadone and whether increasing doses could decrease the rate of continued heroin use.

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51 20 Without exception, treatment effectiveness relies upon sufficient levels of medication adherence.
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53 21 MMT requires long-term or even life-long intake of Methadone at an adequate dose on a daily basis
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55 22 [43]. We found that the lower attendance meant the higher percentage of heroin use. This was
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4 1 consistent with our prior study [25]. Continued heroin users attended MMT programs irregularly and
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6 2 the attendance significantly declined with the duration that they retained in treatment program [44].
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9 3 Poorer attendance seeded continued heroin use. In addition, misconceptions might predict dropout rates
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11 4 and poor adherence among newly admitted MMT clients [45]. So, future research might need to
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13 5 develop and/or integrate other necessary interventions to encourage client adherence to the treatment
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15 6 program.

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19 7 HIV-positive drug users have been regarded as a “dual risk” subgroup. They transmit HIV via
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21 8 either sharing needles or having unprotected sexual intercourse with partners. Currently, sexual
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23 9 transmission is the most prevalent spread pattern of HIV/AIDS in China [5]. Among the participants
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25 10 who finished at least once interview, 20.7% ever shared needle; 28.7% ever had sex with multiple
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27 11 partners; 40.2% never used condom and 13.3% had sex for drugs during the study period. Considering
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29 12 the potential bridge role of those with dual risk behaviors in transmitting HIV to others, research on the
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31 13 interaction of HIV-positive MMT clients and risk behaviors should be given high priority. Data showed
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33 14 that changing unsafe drug use behaviors was more effective than changing unsafe sexual behaviors [17].
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35 15 In future treatment procedures, physicians and nurses should play an active role in educating clients
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37 16 about safe sex and encourage clients to use condoms.

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44 17 This study is subject to certain limitations. Firstly, self-reported data are subject to recall bias or
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46 18 deliberate concealment. Family relationship variable was a client self-perceived indicator and had no
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48 19 standardized measurement for this dimension so far. Secondly, China is experiencing a significant
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50 20 increase in the use of new drugs [2], but this study did not consider it. In addition, we failed to obtain
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52 21 the ART (anti-retroviral treatment) information, and future studies should be extended to analyze ART
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54 22 as predictor variable to continued heroin use. Thirdly, frequent drop-out always exists among clients in
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1 MMT programs. Most of clients would drop out within a few months which had been widely noticed
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4 [17, 46]. For the drop-outs, many of them probably were tested only once or twice but all these tests
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9 were positive, which might over-estimate the percentages of heroin use. In addition, we only examined
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11 the percentages of heroin use during the first 12 months after receiving MMT, and did not take 12+
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14 months into consideration due to the limited sample size and high drop-out.
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16 In summary, findings from this study provide important implications for future MMT programs
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18 targeting continued heroin use among HIV-positive clients. Concretely, first, continuous and efficient
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20 MMT consulting and health education interventions need to be conducted for reducing continued
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22 heroin use. Interventions involving family members in supervision of participation and compliance
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24 should be reinforced. Second, doses and attendance are crucial components affecting MMT' outcomes,
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28 so how to prescribe an appropriate MMT dose and improve sufficient attendance have become issues of
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5 of the manuscript.

6 **Contributors**

7 XL designed the study, performed data analysis and wrote the draft manuscript. XG and PZ
8 performed data analysis. XZ and WC collected the data. LL supervised the study. All authors
9 contributed to the interpretation of the data and approved the final version for submission.

10 **Conflict of Interest**

11 The authors declare no conflicts of interest.

12 **Data Sharing Statement**

13 No additional unpublished data are available.

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18

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Tables

Table 1. Characteristics of the participants (n=642)

Characteristics	Urine Morphine(-)	Urine Morphine(+)	Total
	(n=10)	(n=632)	(N=642)
	No. (% ^a)	No. (% ^a)	No. (% ^b)
Age at Baseline (years)			
≤30	2(1.7)	113(98.3)	115(17.9)
31-	5(2.6)	186(97.4)	191(29.8)
36-	1(0.5)	197(99.5)	198(30.8)
≥41	2(1.5)	136(98.5)	138(21.5)
Gender			
Male	10(1.7)	590(98.3)	600(93.5)
Female	0(0)	42(100.0)	42(6.5)
Ethnic			
Han	10(1.6)	626(98.4)	636(99.1)
Others	0(0)	6(100.0)	6(0.9)
Marital Status at Baseline			
Never married	4(1.2)	339(98.8)	343(53.4)
Married currently	5(2.2)	222(97.8)	227(35.4)
Others	1(1.4)	71(98.6)	72(11.2)
Education Level			
Elementary or lower	1(0.6)	164(99.4)	165(25.7)
Juniorhigh school	9(2.2)	400(97.8)	409(63.7)
Senior high school or higher	0(0)	68(100.0)	68(10.6)
Employed Status at Baseline			
Unemployed	2(0.5)	408(99.5)	410(63.9)
Employed	8(3.4)	224(96.6)	232(36.1)
Family Relationship at Baseline			
Harmonious	3(2.0)	149(98.0)	152(23.7)
Inharmonious	7(1.4)	483(98.6)	490(76.3)
Mainly Financial Sources at Baseline			
Family or friends	6(1.5)	390(98.5)	396(61.7)
Others	4(1.6)	242(98.4)	246(38.3)
Duration of Drug Abuse (years)			
≤10	3(2.2)	136(97.8)	139(21.7)
11-15	3(1.1)	263 (98.9)	266(41.4)
≥16	4(1.7)	233(98.3)	237(36.9)
Type of Drug Use at Baseline			
Heroin	9(1.4)	618(98.6)	627(97.7)
Others	1(6.7)	14(93.3)	15(2.3)
Intravenous Drug Use at Baseline			
Yes	10(1.6)	623(98.4)	633(98.6)
No	0(0)	9(100.0)	9(1.4)

Shared Needles to Inject Drugs at Baseline			
Yes	4(1.1)	364(98.9)	368(58.1)
No	6(2.2)	259(97.8)	265(41.9)
Average Times of Drug Use per Day at Baseline			
≤2	3(1.3)	226(98.7)	229(35.7)
≥3	7(1.7)	406(98.3)	413(64.3)
Frequency of Meeting with Peer Users at Baseline			
none	0(0)	80(100.0)	80(12.5)
1-4/month	2(1.2)	160(98.8)	162(25.2)
1-6/week	3(1.8)	161(98.2)	164(25.5)
> 1/day	5(2.1)	231(97.9)	236(36.8)
Multiple Sex Partners at Baseline			
Yes	2(1.8)	110(98.2)	111(17.4)
No	8(1.5)	522(98.5)	530(82.6)
Average Maintenance Doses (ml/day)			
≥60	7(2.8)	245(97.2)	252(39.3)
<60	3(0.8)	387(99.2)	390(60.7)
Percentages of MMT Attendance (%)			
<20	2(1.6)	127(98.4)	129(20.1)
20-	0(0)	140(100.0)	140(21.8)
50-	1(0.7)	139(99.3)	140(21.8)
≥80%	7(3.0)	226(97.0)	233(36.3)

^a calculated by row, ^b calculated by column.

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1 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(118/130)	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)

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1 **Table 3** The distribution of positive percentages of urine morphine tests among the urine morphine
2 (+) participants 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

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1 Table4. Correlates of higher positive percentages among urine morphine (+) participants during
 2 the study period (n=632)

Characteristics	<40% (n=183)	40%-80% (n=206)	>80% (n=243)	OR(95%CI) ^{a, b}	<i>p</i> ^b
	No. (%) [*]	No. (%) [*]	No. (%) [*]		
Age (years)					
≤30	36(31.9)	47(41.6)	30(26.5)	0.45(0.26-0.80)	0.006
31-	55(29.6)	56(30.1)	75(40.3)	0.63(0.39-1.00)	0.051
36-	55(27.9)	68(34.5)	74(37.6)	0.65(0.42-1.01)	0.054
≥41	37(27.2)	35(25.7)	64(47.1)	1.00	
Gender					
Male	168(28.5)	197(33.4)	225(38.1)	0.94(0.50-1.75)	0.844
Female	15(35.7)	9(21.4)	18(42.9)	1.00	
Ethnic					
Han	181(28.9)	206(32.9)	239(38.2)	0.24(0.05-1.26)	0.092
Others	2(33.3)	0(0)	4(66.7)	1.00	
Marital Status					
Never married	97(28.6)	117(34.5)	125(36.9)	1.52(0.91-2.55)	0.111
Married Currently	58(26.1)	71(32.0)	93(41.9)	1.47(0.88-2.48)	0.144
Others	28(39.4)	18(25.4)	25(35.2)	1.00	
Education Level					
Elementary or lower	44(26.8)	54(32.9)	66(40.2)	1.03(0.60-1.79)	0.905
Juniorhigh school	117(29.3)	131(32.8)	152(38.0)	1.11(0.67-1.82)	0.686
Senior high school or higher	22(32.4)	21(30.9)	25(36.8)	1.00	
Employment Status at Baseline					
Unemployed	122(29.9)	136(33.3)	150(36.8)	0.90(0.64-1.27)	0.563
Employed	61(27.2)	70(31.3)	93(41.5)	1.00	
Family Relationship at Baseline					
Harmonious	37(24.8)	48(32.2)	64(43.0)	1.46(1.01-2.12)	0.046
Inharmonious	146(30.2)	158(32.7)	179(37.1)	1.00	
Mainly Financial Sources					
Family or friends	121(31.0)	132(33.8)	137(35.1)	0.71(0.51-0.98)	0.038
Others	62(25.6)	74(30.6)	106(43.8)	1.00	
Duration of Drug Abuse (years)					
≤10	35(25.7)	53(39.0)	48(35.3)	0.91(0.58-1.42)	0.665
11-15	81(30.8)	84(31.9)	98(37.3)	0.96(0.67-1.38)	0.845
≥16	67(28.8)	69(29.6)	97(41.6)	1.00	
Average Times of Drug Use per Day					
≤2	53(23.5)	92(40.7)	81(35.8)	0.86(0.62-1.19)	0.364
≥3	130(32.0)	114(28.1)	162(39.9)	1.00	
Shared Needles at Baseline					
Yes	102(27.9)	126(34.5)	137(37.5)	1.14(0.83-1.55)	0.415
No	81(30.3)	80(30.0)	106(39.7)	1.00	
Frequency of Meeting with Peer					

Users at Baseline						
none	25(31.3)	28(35.0)	27(33.8)	0.89(0.54-1.47)	0.645	
1-4/month	44(27.5)	55(34.4)	61(38.1)	1.11(0.75-1.64)	0.595	
1-6/week	46(28.6)	54(33.5)	61(37.9)	1.13(0.76-1.67)	0.547	
> 1/day	68(29.4)	69(29.9)	94(40.7)	1.00		
Multiple Sex Partners at Baseline						
Yes	26(23.6)	37(33.6)	47(42.7)	1.35(0.90-2.03)	0.148	
No	157(30.1)	169(32.4)	196(37.5)	1.00		
Average Maintenance Doses (ml/day)						
≥60	94(38.4)	84(34.3)	67(27.3)	0.49(0.36-0.68)	<0.001	
<60	89(23.0)	122(31.5)	176(45.5)	1.00		
Percentages of MMT Attendance (%)						
<20	7(5.5)	44(34.6)	76(59.8)	4.74(3.01-7.47)	<0.001	
20-	34(24.3)	53(37.9)	53(37.9)	1.74(1.16-2.64)	0.008	
50-	52(37.4)	42(30.2)	45(32.4)	1.24(0.83-1.84)	0.294	
≥80%	90(39.8)	67(29.6)	69(30.5)	1.00		

1 ^aOR: Odds Ratio, CI: Confidence Interval;

2 ^bObtained from multivariate ordinal logistic regression analysis adjusting for potential confounding variables listed
3 in the table;

4 *Proportions were calculated in the row.

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1 Table5. Self-reported risk behaviors among urine morphine (+) participants during the study
 2 period (n=440)

Characteristics	<40%	40%-80%	>80%	Total
	No. (%)	No. (%)	No. (%)	No. (%)
Drug Use (n=440)				
Yes	61(39.4)	111(68.1)	107(87.7)	279(63.4)
No	94(60.6)	52(31.9)	15(12.3)	161(36.6)
Injected Drugs (n=279)				
Yes	48(78.7)	96(86.5)	102(95.3)	246(88.2)
No	13(21.3)	15(13.5)	5(4.7)	33(11.8)
Shared Needles (n=246)				
Yes	7(14.6)	21(21.9)	23(22.5)	51(20.7)
No	41(85.4)	75(78.1)	79(77.5)	195(79.3)
Sex Activity (n=440)				
Yes	76(49.0)	99(60.7)	76(62.3)	251(57.0)
No	79(51.0)	64(39.3)	46(37.3)	189(43.0)
Multiple Sex Partners (n=251)				
Yes	21(27.9)	37(37.4)	14(18.4)	72(28.7)
No	55(72.4)	62(62.6)	62(81.6)	179(71.3)
Condom Use (n=251)				
Yes	47(61.8)	56(56.6)	47(61.8)	150(59.8)
No	29(38.2)	43(43.4)	29(38.2)	101(40.2)
Sex for Drugs (n=180)				
Yes	7(17.5)	14(19.4)	3(4.4)	24(13.3)
No	33(82.5)	58(80.6)	65(95.6)	156(86.7)

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract In the title (b) Provide in the abstract an informative and balanced summary of what was done and what was found Line 7-8,page 2; line 9-16,page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Line 19-22, page 4; line 1-4, page 5
Objectives	3	State specific objectives, including any prespecified hypotheses Line 5-8, page 5
Methods		
Study design	4	Present key elements of study design early in the paper Line 11-15,page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Line 11-21,page 6
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Line 18-21, page 6; line 1-3,page 7 <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed ----- <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable line 4-22,page 7;line 1-15, page 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group line 4-22,page 7;line 1-15, page 8
Bias	9	Describe any efforts to address potential sources of bias Line 14-17,page 7; line 1-2,page 8
Study size	10	Explain how the study size was arrived at Line 15-17, page 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Line 19-21,page 7; line 1-6,page 8

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3	Statistical methods	12
4		(a) Describe all statistical methods, including those used to control for confounding
5		Line 16-22, page 8
6		(b) Describe any methods used to examine subgroups and interactions
7		(c) Explain how missing data were addressed
8		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed
9		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was
10		addressed
11		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of
12		sampling strategy
13		(e) Describe any sensitivity analyses
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Continued on next page

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Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Line 15-17, page 6
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Table 1, line 2-12, page 9
		(b) Indicate number of participants with missing data for each variable of interest Table 1-5
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount) Line 22, page 6; Line 1-3, page 7
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time line 21-22, page 9
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Table 4, page 26-27
		(b) Report category boundaries when continuous variables were categorized Table 1, page 22-23
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Line 10-15, page 10

Discussion

Key results	18	Summarise key results with reference to study objectives Line 7-8, page 11; line 12, page 11; line 1-2, page 12; line 6-7, page 12; line 16-18, page 12; line 22, page 12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Line 17-22, page 13; line 1-5, page 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Line 9-11, page 11; line 13-19, page 11; line 2-4, page 12; line 6-10, page 12; line 1-6, page 13
Generalisability	21	Discuss the generalisability (external validity) of the study results Line 6-12, page 14

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Line 1-5, page 15
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3 *Give information separately for cases and controls in case-control studies and, if applicable, for exposed and
4 unexposed groups in cohort and cross-sectional studies.
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7 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and
8 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely
9 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
10 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is
11 available at www.strobe-statement.org.
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BMJ Open

Positive Percentages of Urine Morphine Tests among Methadone Maintenance Treatment Clients with HIV/AIDS: A 12-Month Follow-up Study in Guangdong Province, China

Journal:	<i>BMJ Open</i>
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Primary Subject Heading:	Addiction
Secondary Subject Heading:	Epidemiology, HIV/AIDS
Keywords:	Heroin Use, Methadone Maintenance Treatment (MMT), HIV, China

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Manuscripts

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4 **1 Positive Percentages of Urine Morphine Tests among Methadone Maintenance Treatment Clients**
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6 **2 with HIV/AIDS: A 12-Month Follow-up Study in Guangdong Province, China**
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9 Xiaofeng Luo^{1,2}, Xiao Gong^{1,2}, Peizhen Zhao³, Xia Zou^{1,2}, Wen Chen^{1,2}, Li Ling^{1,2*}
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39 **Running head:** Heroin use among MMT clients with HIV/AIDS in Guangdong
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44 **Word Count:** 2,833 for main text including sub-headings, 214 for abstract
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4 **Abstract**

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6 **Objective:** We aimed to assess the positive percentages of urine morphine tests and correlates among
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10 methadone maintenance treatment (MMT) clients with HIV/AIDS in Guangdong, China.

11 **Setting:** Fourteen MMT clinics located in 9 cities of Guangdong were chosen as study sites.

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13 **Participants:** In this study, we reviewed 293 clients with opioid dependence, HIV seropositive, 18
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years or older, providing informed consent and having at least 10 records of urine morphine tests
during the study period.

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Primary and secondary outcome measures: The positive percentages of urine morphine tests were
calculated and underlying predictors were estimated.

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Results: About 91.5% participants had used heroin at least once during the study period. Of them,
positive percentages of urine morphine tests that <20%, 20%-60% and >80% were 25.4%, 36.1% and
38.5% respectively. Lower percentages of continued heroin use were associated with being young
(OR_{≤30}=0.31, 95%CI: 0.12-0.78; OR₃₁₊=0.44, 95%CI: 0.20-1.00), and financial sources depending on
family or friends (OR=0.55, 95%CI: 0.32-0.93). Higher percentages of continued heroin use were
associated with being unemployed (OR=1.99, 95%CI: 1.13-3.49) and poorer MMT attendance
(OR_{<20%}=3.60, 95%CI: 1.55-8.33; OR_{20%}=2.80, 95%CI: 1.48-5.33).

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Conclusions: High positive percentages of urine morphine tests remain prevalent among MMT clients
with HIV/AIDS in Guangdong. The present findings have implications for taking effective measures to
facilitate attendance in order to decrease heroin use and ultimately improve the effectiveness among
these sub-group MMT clients.

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Key words: Heroin Use; Methadone Maintenance Treatment (MMT); HIV; China

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4 **1 Strengths and Limitations**
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- 6 1. This is a long-term consecutive study specifically designed to examine concurrent heroin use
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9 2. This study mainly focused on positive percentages of urine morphine tests among HIV-positive
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1. This is a long-term consecutive study specifically designed to examine concurrent heroin use among HIV-positive MMT clients in China.
 2. This study mainly focused on positive percentages of urine morphine tests among HIV-positive MMT clients in China.
 3. Self-reported data are subject to recall bias or deliberate concealment.
 4. China is experiencing a significant increase in the use of new drugs, but this study did not consider it.
 5. We only examined the percentages of heroin use during the first 12 months after receiving MMT due to the limited sample size and high drop-out.

1 Introduction

2 In China, illicit drug use has increased dramatically since the 1980s [1]. There were cumulatively
3 registered 2.95 million drug users by the end of 2014 and 480,000 newly registrations in 2014
4 nationwide [2]. Although China recently is experiencing a significant increase in the use of new-type
5 drugs, heroin still remains the major illicit used drug among drug users [2]. The earliest HIV case was
6 identified among intravenous drug users (IDUs) in Southern Yunnan province in 1989 [3]. The early
7 spread of HIV epidemics in China mainly attributed to intravenous drug use (IDU) [4]. As of 2013,
8 437,000 people lived with HIV/AIDS in China (including 263,000 people living with HIV and 174,000
9 AIDS patients), accounting for 0.033% of the total population in China; and sentinel surveillance data
10 showed the HIV/AIDS prevalence was 6.3% among IDUs [5].

11 Globally, methadone maintenance treatment (MMT) is the most widely used pharmacological
12 treatment for opioid dependence. China has operated MMT program as a national strategy to combat
13 the joint threat of drug use and HIV/AIDS since 2004 [6]. For decades, MMT program has achieved its
14 crucial effectiveness not only in reducing heroin use [7] but also in preventing the spread of HIV [8, 9].
15 Meanwhile, studies have shown that MMT is beneficial in reducing drug-related criminal activities [10]
16 and drug-related mortality [11]. In addition, for the HIV-positive individuals, MMT could facilitate the
17 adherence to antiretroviral therapy [12]. By the end of April 2015, China has 767 MMT clinics in 28
18 provinces across the nation, serving nearly 190,000 clients [13].

19 However, many clients did not completely abstain from heroin and exhibited continued heroin use
20 while in MMT [14-17]. Continued heroin use could lead to negative MMT treatment outcomes among
21 clients [18]. Heroin addicts still contribute a high mortality even with MMT [19]. Overdosed drug
22 intake remains the most common cause of death among MMT clients [20]. After a period of abstinence

1 via MMT, the heroin tolerance of clients would decrease, thus overdosed intake may become more
2 prevalent [21, 22]. Individuals with HIV/AIDS are a special group among MMT clients. A
3 meta-analysis showed that HIV seropositivity would increase the mortality risk of overdose [23]. In
4 addition, continued heroin use would decrease the retention rate among MMT clients with HIV/AIDS
5 [24]. Therefore, heroin use deserves more attention among MMT clients with HIV/AIDS. To date,
6 limited data are available on heroin use among MMT clients with HIV/AIDS in China [14, 25] and
7 about the higher percentages of heroin use is even less. To fill this gap, we applied this study is to
8 examine the higher percentages of heroin use among MMT clients with HIV/AIDS in Guangdong.

9

1 **Methods**

2 **Ethics Statement**

3 The Institutional Review Board (IRB) of the School of Public Health (Sun Yat-sen University,
4 Guangzhou, China) reviewed and approved the study protocol. All study participants were asked to
5 provide written informed consent.

6 **Study Site and Participants**

7 Guangdong, located in the Southern coast of China, is one of the most developed provinces.
8 Meanwhile, Guangdong also is one of the HIV/AIDS and drug epidemic areas because it has
9 cumulative reported 48,718 HIV-positive cases, ranking fifth among provinces in China as of October
10 2014 [26], in addition, it has one-sixth of totally registered drug users in China [27].

11 This study was conducted in 14 MMT clinics located in 9 cities of Guangdong (According to
12 whether the 1-year retention rate is above or below 50%, the 61 MMT clinics were divided into two
13 groups, and seven clinics were randomly selected from each group [28]). We got permission and
14 authorization to use and retrieve part of data for the selected MMT clinics from the Chinese National
15 MMT Program data system. In this study, participants were eligible if they were (1) diagnosed with
16 opioid dependence according to the International Classification of Diseases (10th Revision); (2) 18
17 years or older; (3) tested to be HIV-positive at entry; (4) able to provide informed consent; and (5) had
18 at least 10 records of urine morphine tests.

19 In this study, “drop-out” was defined as a participant failing to continue MMT for 14 consecutive
20 days [28]. Based on whether drop-out happened before 12 months post-MMT initiation, the study
21 period could be classified into two categories: one was defined as the duration between enrollment and
22 dropout, the other was defined as the duration between enrolment and the end of the first 12 months.

1 Measures

2 *Self-reported Risk Behaviors*

3 At admission, as well as 6th and 12th month respectively, each participant was requested to
4 complete a questionnaire covering demographic characteristics, drug use history including injecting
5 drug and sharing needle/equipment, sexual activity history, and condom use status.

6 A client was regarded as having corresponding risk behaviors during the study period if he/she
7 reported those behaviors either 6th or 12th interview (i.e. drug use behaviors including injecting drug
8 and sharing needle/equipment; and risk sexual activities including, multiple sex partner, inconsistent
9 condom use and sex trade for drugs.).

10 *Methadone Maintenance Doses and Attendance*

11 In China, to insure MMT security, clients are forbidden to take Methadone outside the clinic. Once
12 enrolled in MMT, the clients must go to the clinic at consultation hours daily to take the prescribed
13 doses of Methadone under the supervision of clinic staff, and the daily doses and date were routinely
14 recorded in the national unified MMT management system. The treatment cost was RMB 10 Yuan
15 (USD: 1.5 Dollar) per day regardless of the client' intake doses and times.

16 Average maintenance dose was obtained via computing the mean of daily prescribed doses (The
17 doses of the first month were excluded because the first month of methadone maintenance treatment is
18 to give doctor time to adjust appropriate dose for a client. Usually the dose starts from small, 20 mg to
19 40 mg per day, and it will gradually increase slowly to certain amount.).

20 The percentage of MMT attendance was calculated based on proportion of days that a client
21 actually received the doses over the study period.

22 *Positive Percentages of Urine Morphine Tests during the Study Period*

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4 1 A positive result of urine morphine test generally means heroin use by the clients within a few
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6 2 days. Urine-based morphine tests were monthly performed on a random day during the study period.

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9 3 As mentioned above, there exists a MMT dose adjustment stage for a new enrolled client. During
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11 4 the adjustment stage, most clients often use opioid to adjust themselves to methadone maintenance
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13 5 treatment. Therefore, the result of urine morphine test in the first month was excluded from calculation
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15 6 of heroin use and percentages in our study.

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19 7 During the study period, a client was recognized as a heroin user as long as any urine morphine
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21 8 test result was positive.

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24 9 The percentage of heroin use was calculated based on the number of positive urine morphine test
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26 10 results and the number of total urine test times during the study period.

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29 11 Based on the urine morphine tests, the clients were currently grouped as “urine morphine (+)” and
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31 12 “urine morphine (-)”. Additionally, the positive percentages were grouped as <20%, 20-60% and >60%
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33 13 based on the data distribution.

34 35 36 14 ***HIV and Urine Morphine Tests***

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39 15 Except for those who were already confirmed as HIV-positive prior this study, each client was
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41 16 invited to receive HIV testing. HIV infection status was screened using an enzyme-linked
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43 17 immunosorbent assay (ELISA) technique (Beijing BGI-GBI Biotech Co., Ltd, Beijing, China). Positive
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45 18 blood specimens for HIV were confirmed using a Western blot assay (Abbott, MP Biomedicals, LLC,
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47 19 Singapore) by the local Centers for Disease Control (CDC). According to related national guidelines,
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49 20 pre- and post- test counseling services were provided.

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54 21 Random urine morphine status was screened using a Morphine Diagnostic Kit (Colloidal Gold)
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56 22 technique (ABON Biopharm Co., Ltd, Hangzhou, China).

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4 **1 Statistical Analysis**
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6 Statistical analyses were performed using SPSS 17.0 for Windows (SPSS Inc., Chicago).
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9 3 Categorical variables were described with percentages. Multivariate ordinal logistic regression analysis
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11 4 was conducted to predict higher percentages of heroin use from baseline information including
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13 5 demographic, drug use and multiple sex partners, as well as average maintenance dose and percentages
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15 6 of MMT attendance during the study period among the MMT clients with HIV/AIDS. Any $p < 0.05$ was
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17 7 considered to be statistically significant.
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1 Results

2 *Study Participants and Demographic Characteristics*

3 Among the 293 participants, 16.0% were elder than 40; 91.5% were males; 99.3% were ethnic
4 Han (China's predominant ethnic group), 54.3% were never married; 21.8% just had elementary or
5 lower education; 68.9% were unemployed and 64.2% obtained financial sources from their family or
6 friends (Table 1).

7 *Heroin Use and Multiple Sex Partner at Baseline*

8 Table 1 presents baseline information on heroin use. Of the participants, 77.8% had used heroin
9 for more than 10 years; 59.4% participants used heroin at least 3 times daily on average; the vast
10 majority (98.6%) abused powdered heroin and 99.0% ever administered drug by injection. Among the
11 IDUs, 56.6% ever shared intravenous needles. Only 13.7% never met the peer users.

12 Of these participants, 21.5% had had sexual activity with multiple sex partner (Table 1).

13 *Average Maintenance Doses and Attendance*

14 Among all participants, 46.8% had received doses below 60 ml and the average maintenance dose
15 was (67.5 ± 28.7) ml.

16 In addition, 10.6% participants' MMT attendance percentages were less than 20% and only 40.6%
17 were over 80% (Table 1).

18 *Positive Percentages of Urine Morphine Tests during the Study Period*

19 The median positive percentage of urine morphine tests was 48.6% for 2006, 48.7% for 2007, 44.0%
20 for 2008, 41.2% for 2009, 43.3% for 2010, 43.4% for 2011 and 22.5% for 2013, respectively (Table 2).

21 Among the 268 urine morphine (+) clients, positive percentages of urine morphine tests that <20%,
22 20%-60% and >60% were 25.4%, 36.1% and 38.5% respectively (Table 3).

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4 1 After adjusted for potential confounding variables listed in the table, multiple ordinal logistic
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6 2 regression analysis indicated that a higher percentage of heroin use was independently associated with
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9 3 age, employment status, mainly financial sources and percentages of MMT attendance. Participants
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11 4 who were younger ($OR_{\leq 30}=0.31$, 95%CI: 0.2-0.78; $OR_{31-35}=0.44$, 95%CI: 0.20-1.00), and got money
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13 5 from family or friends ($OR=0.55$, 95%CI: 0.32-0.93) were more likely to be tested as having lower
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15 6 percentages of heroin use; and those who were unemployed ($OR=1.99$, 95%CI: 1.13-3.49) and had
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17 7 poor MMT attendance percentages ($OR_{<20}=3.60$, 95%CI: 1.55-8.33; $OR_{20-}=2.80$, 95%CI: 1.48-5.33)
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19 8 were more likely to have higher percentages of heroin use (Table 4).
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24 9 ***Self-reported High Risk Behaviors during the Study Period***

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26 10 Among the clients with urine morphine (+), 99.3% (266 of 268) and 88.1% (236 of 268)
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28 11 completed the 6th and 12th month follow-up interviews respectively. Of the 266 clients completed at
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30 12 least one follow-up interview, 62.8% ever used drugs, 85.0% used intravenous drugs, and 25.4% ever
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32 13 shared intravenous needles; 63.2% were sexual active, 29.2% had sex with multiple sex partners, and
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34 14 43.5% never used condom during the sexual course. Also, 14.5% traded sex for drugs (Table 5).
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1 Discussion

2 Heroin use among MMT clients has been reported substantially worldwide [15, 16]. HIV-positive
3 drug users are a unique subgroup for playing a “dual bridge” role in HIV transmission. This study is an
4 extension of our previous study [25]. Our results were based on random, long-term and consecutive
5 urine tests, which was blind to clients in case those continued heroin users deliberately avoid the test
6 time.

7 Findings from the current analysis revealed that there were 91.5% participants had used heroin at
8 least once during the study period, which was higher than that (75%) of general MMT clients reported
9 by our prior study [25]. Findings also showed that 14.2% almost always used heroin. Given that
10 continued heroin use might lead to adverse health outcomes [20, 23] and high drop-out rate [24] among
11 MMT clients with HIV/AIDS, targeted interventions and control programs are urgently needed for this
12 subgroup.

13 Compared to the young participants, the elders showed greater likelihood of continued heroin use.
14 Many elders had turned from clinical latency stage to AIDS stage and they may experience more pain
15 and psychological symptoms [29, 30]. Studies had shown that depressive symptoms are common
16 among people with HIV infection [31, 32]. However, MMT improvements in depressive symptoms and
17 the physical domain of QOL (quality of life) among HIV-positive heroin users were poorer than in
18 those without HIV infection [33]. Also, most of them had lost the courage and confidence to live on.
19 Culturally, stigma and discrimination towards drug use and HIV/AIDS might seriously impede the
20 MMT attendance [34]. In addition, inappropriate perceptions of MMT should not be neglected [35].

21 Previous research has documented that the clients who were employed were more likely to use
22 heroin during the treatment period [36]. In contrast, we found that the unemployed had more likelihood

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4 1 with concurrent heroin use. This was possibly due to the unemployed (1) lacked social support; (2) had
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6 2 more time to communicate with former drug taking peers. There was a big difference between the
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8 3 employed and the unemployed not only in terms of sociodemographic factors but also the family tie,
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10 4 which in turn influenced concurrent heroin use [25, 37].
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14 5 Generally, high drug fee generally made the drug users can't afford it. In our study, the clients
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16 6 whose financial sources depend on family or friends were less likely to use heroin. Money from family
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18 7 or friends is meant to support basic life and is far not enough to meet drug expenditure. Furthermore,
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20 8 drug use and MMT is regarded as a family issue in China, and family or friends' support might
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22 9 potentially supervise and encourage treatment participation and compliance [25, 37].
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26 10 There has been controversy over whether higher Methadone doses could decrease heroin use
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28 11 among MMT clients. Studies showed an appropriate MMT dose is the most effective in suppressing
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30 12 heroin use in treatment [18, 38]. There were also further research suggesting that an adequate dose of
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32 13 Methadone (e.g., 80-120 mgs/day) would significantly reduce heroin use among clients within the first
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34 14 two months of treatment and eventually either eliminated or significantly curtailed with time in
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36 15 treatment [39, 40]. However, other studies revealed there was no correlation between Methadone doses
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38 16 and heroin use in treatment [41, 42]. The Methadone dose was ≥ 60 mg/day recommended by US
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40 17 National Institutes of Health [43], and should be higher for HIV-positive individuals [44]. We found
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42 18 46.8% participants' doses were less than 60 mg/day. Compared to those with higher doses, we did not
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44 19 find the clients with lower doses were more likely to use heroin. Given the small sample size and
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46 20 short-term observation, further large sample size and stratified dose research are needed.
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54 21 Without exception, treatment effectiveness relies upon sufficient levels of medication adherence.
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56 22 MMT requires long-term or even life-long intake of Methadone at an adequate dose on a daily basis
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1 [45]. We found that the lower attendance meant the higher percentage of heroin use. This was
2 consistent with our prior study [25]. Continued heroin users attended MMT programs irregularly and
3 the attendance significantly declined with the duration that they retained in treatment program [46].
4 Poorer attendance seeded continued heroin use. In addition, misconceptions might predict poor
5 adherence among newly admitted MMT clients [47]. So, future research might need to develop and/or
6 integrate other necessary interventions to encourage client adherence to the treatment program.

7 HIV-positive drug users have been regarded as a “dual risk” subgroup. They transmit HIV via
8 either sharing needles or having unprotected sexual intercourse with partners. Currently, sexual
9 transmission is the most prevalent spread pattern of HIV/AIDS in China [5]. Among the participants
10 who finished at least once interview, 25.4% ever shared needle; 29.2% ever had sex with multiple
11 partners; 43.5% never used condom and 14.5% had sex for drugs during the study period. Considering
12 the potential bridge role of those with dual risk behaviors in transmitting HIV to others, research on the
13 interaction of HIV-positive MMT clients and risk behaviors should be given high priority. Data showed
14 that changing unsafe drug use behaviors was more effective than changing unsafe sexual behaviors [17].
15 In future treatment procedures, physicians and nurses should play an active role in educating clients
16 about safe sex and encourage clients to use condoms.

17 This study is subject to certain limitations. Firstly, self-reported data are subject to recall bias or
18 deliberate concealment. Secondly, China is experiencing a significant increase in the use of new drugs
19 [2], but this study did not consider it. In addition, we failed to obtain the ART (anti-retroviral treatment)
20 information, and future studies should be extended to analyze ART as predictor variable to continued
21 heroin use. Thirdly, we only examined the percentages of heroin use during the first 12 months after
22 receiving MMT, and did not take 12+ months into consideration due to the limited sample size and

1 high drop-out.

2 In summary, findings from this study provide important implications for future MMT programs
3 targeting continued heroin use among HIV-positive clients. Concretely, first, continuous and efficient
4 MMT consulting and health education interventions need to be conducted for reducing continued
5 heroin use. Interventions involving family members in supervision of participation and compliance
6 should be reinforced. Second, attendance are crucial components affecting MMT⁷ outcomes, so how to
7 improve sufficient attendance have become issues of great urgency.

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For peer review only

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6 **Contributors**

7 XL designed the study, performed data analysis and wrote the draft manuscript. XG and PZ
8 performed data analysis. XZ and WC collected the data. LL supervised the study. All authors
9 contributed to the interpretation of the data and approved the final version for submission.

10 **Conflict of Interest**

11 The authors declare no conflicts of interest.

12 **Data Sharing Statement**

13 No additional unpublished data are available.

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18

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1 Tables

2 Table1. Characteristics of the participants (n=293)

Characteristics	Urine Morphine(-)	Urine Morphine(+)	Total
	(n=25)	(n=268)	(N=293)
	No. (% ^a)	No. (% ^a)	No. (% ^b)
Age at Baseline (years)			
≤30	5(7.5)	62(92.5)	67(22.9)
31-	9(10.1)	80(89.9)	89(30.4)
36-	7(7.8)	83(92.2)	90(30.7)
≥41	4(8.5)	43(91.5)	47(16.0)
Gender			
Male	25(9.3)	243(90.7)	268(91.5)
Female	0(0)	25(100.0)	25(8.5)
Ethnic			
Han	25(8.6)	266(91.4)	291(99.3)
Others	0(0)	2(100.0)	2(0.7)
Marital Status at Baseline			
Never married	17(10.7)	142(89.3)	159(54.3)
Married currently	5(5.2)	92(94.8)	97(33.1)
Others	3(8.1)	34(91.9)	37(12.6)
Education Level			
Elementary or lower	1(1.6)	63(98.4)	64(21.8)
Juniorhigh school	18(9.4)	174(90.6)	192(65.5)
Senior high school or higher	6(16.2)	31(83.8)	37(12.6)
Employed Status at Baseline			
Unemployed	16(7.9)	186(92.1)	202(68.9)
Employed	9(9.9)	82(90.1)	91(31.1)
Mainly Financial Sources at Baseline			
Family or friends	19(10.1)	169(89.9)	188(64.2)
Others	6(5.7)	99(94.3)	105(35.8)
Duration of Drug Abuse (years)			
≤10	3(4.6)	62(95.4)	65(22.2)
11-15	12(9.2)	118(90.8)	130(44.4)
≥16	10(10.2)	88(89.8)	98(33.4)
Type of Drug Use at Baseline			
Heroin	25(8.7)	264(91.3)	289(98.6)
Others	0(0)	4(100.0)	4(1.4)
Intravenous Drug Use at Baseline			
Yes	25(8.6)	265(91.4)	290(99.0)
No	0(0)	3(100.0)	3(1.0)
Shared Needles to Inject Drugs at Baseline			
Yes	11(6.7)	153(93.3)	164(56.6)
No	14(11.1)	112(88.9)	126(43.4)
Average Times of Drug Use per Day at Baseline			

≤2	10(8.4)	109(91.6)	119(40.6)
≥3	15(8.6)	159(91.4)	174(59.4)
Multiple Sex Partners at Baseline			
Yes	4(6.3)	59(93.7)	63(21.5)
No	21(9.1)	209(90.9)	230(78.5)
Average Maintenance Doses (ml/day)			
≥60	18(11.5)	138(88.5)	156(53.2)
<60	7(5.1)	130(94.9)	137(46.8)
Percentages of MMT Attendance (%)			
<20	1(3.2)	30(96.8)	31(10.6)
20-	4(6.1)	62(93.9)	66(22.5)
50-	4(5.2)	73(94.8)	77(26.3)
≥80%	16(13.4)	103(86.6)	119(40.6)

^a calculated by row, ^b calculated by column.

1 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)

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1 Table 3 The distribution of positive percentages of urine morphine tests among the urine morphine
2 (+) participants during the study period (n =268)

Positive percentage (%)	Number (n)	Percentage (%)
<10	34	12.7
10-	34	12.7
20-	29	10.8
30-	28	10.4
40-	22	8.2
50-	18	6.7
60-	23	8.6
70-	20	7.5
80-	22	8.2
90-	38	14.2
total	268	100.0

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1 Table4. Correlates of higher positive percentages among urine morphine (+) participants during
 2 the study period (n=268)

Characteristics	<20% (n=68) No. (%)*	20%-60% (n=97) No. (%)*	>60% (n=103) No. (%)*	OR(95%CI) ^{a, b}	<i>p</i> ^b
Age (years)					
≤30	20(32.3)	28(45.2)	14(22.6)	0.31(0.12-0.78)	0.013
31-	22(27.5)	26(32.5)	32(40.0)	0.44(0.20-1.00)	0.051
36-	13(15.7)	33(39.8)	37(44.6)	0.91(0.43-1.93)	0.814
≥41	13(30.2)	10(23.3)	20(46.5)	1.00	
Gender					
Male	60(24.7)	90(37.0)	93(38.3)	0.97(0.42-2.22)	0.944
Female	8(32.0)	7(28.0)	10(40.0)	1.00	
Marital Status					
Never married	36(25.4)	54(38.0)	52(36.6)	2.04(0.92-4.55)	0.080
Married Currently	23(25.0)	29(31.5)	40(43.5)	1.93(0.85-4.40)	0.117
Others	9(26.5)	14(41.2)	11(32.4)	1.00	
Education Level					
Elementary or lower	16(25.4)	24(38.1)	23(36.5)	1.50(0.64-3.50)	0.347
Juniorhigh school	45(25.9)	58(33.3)	71(40.8)	1.48(0.71-3.12)	0.298
Senior high school or higher	7(22.6)	15(48.4)	9(29.0)	1.00	
Employment Status at Baseline					
Unemployed	45(24.2)	64(34.4)	77(41.4)	1.99(1.13-3.49)	0.017
Employed	23(28.0)	33(40.2)	26(31.7)	1.00	
Mainly Financial Sources					
Family or friends	49(29.0)	60(35.5)	60(35.5)	0.55(0.32-0.93)	0.025
Others	19(19.2)	37(37.4)	43(43.4)	1.00	
Duration of Drug Abuse (years)					
≤10	18(29.0)	21(33.9)	23(37.1)	1.04(0.50-2.16)	0.923
11-15	27(22.9)	46(39.0)	45(38.1)	1.38(0.75-2.55)	0.305
≥16	23(26.1)	30(34.1)	35(39.8)	1.00	
Average Times of Drug Use per Day					
≤2	21(19.3)	47(43.1)	41(37.6)	1.03(0.62-1.71)	0.912
≥3	47(29.6)	50(31.4)	62(39.0)	1.00	
Shared Needles at Baseline					
Yes	38(24.8)	59(38.6)	56(36.6)	1.03(0.63-1.69)	0.902
No	30(26.1)	38(33.0)	47(40.9)	1.00	
Multiple Sex Partners at Baseline					
Yes	12 (20.3)	17(28.8)	30(50.8)	1.65(0.89-3.05)	0.113
No	56(26.8)	80(38.3)	73(34.9)	1.00	
Average Maintenance Doses (ml/day)					
≥60	36(26.1)	56(40.6)	46(33.3)	0.92(0.57-1.49)	0.742
<60	32(24.6)	41(31.5)	57(43.8)	1.00	
Percentages of MMT Attendance (%)					

<20	4(13.3)	9(30.0)	17(56.7)	3.60(1.55-8.33)	0.003
20-	10(16.1)	19(30.6)	33(53.2)	2.80(1.48-5.33)	0.002
50-	22(30.1)	32(43.8)	19(26.0)	0.94(0.53-1.67)	0.841
≥80%	32(31.1)	37(35.9)	34(33.0)	1.00	

1 ^a OR: Odds Ratio, CI: Confidence Interval;

2 ^b Obtained from multivariate ordinal logistic regression analysis adjusting for potential confounding variables
 3 listed in the table;

4 *Proportions were calculated in the row.

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1 Table5. Self-reported risk behaviors among urine morphine (+) participants during the study
 2 period (n=266)

Characteristics	<20%	20%-60%	>60%	Total
	No. (% ^a)	No. (% ^a)	No. (% ^a)	No. (% ^b)
Drug Use (n=266)				
Yes	26(15.6)	55(32.9)	86(51.5)	167(62.8)
No	41(41.4)	41(41.4)	17(17.2)	99(37.2)
Injected Drugs (n=167)				
Yes	21(14.8)	44(31.0)	77(54.2)	142(85.0)
No	5(20.0)	11(44.0)	9(36.0)	25(15.0)
Shared Needles (n=142)				
Yes	3(8.3)	11(30.6)	22(61.1)	36(25.4)
No	18(17.0)	33(31.1)	55(51.9)	106(74.6)
Sex Activity (n=266)				
Yes	38(22.6)	66(39.3)	64(38.1)	168(63.2)
No	29(29.6)	30(30.6)	39(39.8)	98(36.8)
Multiple Sex Partners (n=168)				
Yes	7(14.3)	23(46.9)	19(38.8)	49(29.2)
No	31(26.1)	43(36.1)	45(37.8)	119(70.8)
Condom Use (n=168)				
Yes	24(25.3)	37(38.9)	34(35.8)	95(56.5)
No	14(19.2)	29(39.7)	30(41.1)	73(43.5)
Sex for Drugs (n=117)				
Yes	3(17.6)	8(47.1)	6(35.3)	17(14.5)
No	18(18.0)	32(32.0)	50(50.0)	100(85.5)

3 ^a calculated by row, ^b calculated by column.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract In the title (b) Provide in the abstract an informative and balanced summary of what was done and what was found Line 7-8,page 2; line 9-16,page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Line 19-22, page 4; line 1-4, page 5
Objectives	3	State specific objectives, including any prespecified hypotheses Line 5-8, page 5
Methods		
Study design	4	Present key elements of study design early in the paper Line 11-15,page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Line 11-21,page 6
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Line 18-21, page 6; line 1-3,page 7 <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed ----- <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable line 4-22,page 7;line 1-15, page 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group line 4-22,page 7;line 1-15, page 8
Bias	9	Describe any efforts to address potential sources of bias Line 14-17,page 7; line 1-2,page 8
Study size	10	Explain how the study size was arrived at Line 15-17, page 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Line 19-21,page 7; line 1-6,page 8

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3	Statistical methods	12
4		(a) Describe all statistical methods, including those used to control for confounding
5		Line 16-22, page 8
6		(b) Describe any methods used to examine subgroups and interactions
7		(c) Explain how missing data were addressed
8		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed
9		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was
10		addressed
11		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of
12		sampling strategy
13		(e) Describe any sensitivity analyses
14		

Continued on next page

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Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Line 15-17, page 6
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Table 1, line 2-12, page 9
		(b) Indicate number of participants with missing data for each variable of interest Table 1-5
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount) Line 22, page 6; Line 1-3, page 7
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time line 21-22, page 9
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Table 4, page 26-27
		(b) Report category boundaries when continuous variables were categorized Table 1, page 22-23
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Line 10-15, page 10

Discussion

Key results	18	Summarise key results with reference to study objectives Line 7-8, page 11; line 12, page 11; line 1-2, page 12; line 6-7 page 12; line 16-18, page 12; line 22, page 12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Line 17-22, page 13; line 1-5, page 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Line 9-11, page 11; line 13-19, page 11; line 2-4, page 12; line 6-10, page 12; line 1-6, page 13
Generalisability	21	Discuss the generalisability (external validity) of the study results Line 6-12, page 14

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Line 1-5, page 15
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3 *Give information separately for cases and controls in case-control studies and, if applicable, for exposed and
4 unexposed groups in cohort and cross-sectional studies.
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7 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and
8 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely
9 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
10 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is
11 available at www.strobe-statement.org.
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Positive Percentages of Urine Morphine Tests among Methadone Maintenance Treatment Clients with HIV/AIDS: A 12-Month Follow-up Study in Guangdong Province, China

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Keywords:	Heroin Use, Methadone Maintenance Treatment (MMT), HIV, China

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Manuscripts

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4 **1 Positive Percentages of Urine Morphine Tests among Methadone Maintenance Treatment Clients**
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6 **2 with HIV/AIDS: A 12-Month Follow-up Study in Guangdong Province, China**
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39 **Running head:** Heroin use among MMT clients with HIV/AIDS in Guangdong
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4 **Abstract**

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6 **Objective:** We aimed to assess the positive percentages of urine morphine tests and correlates among
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8
9 methadone maintenance treatment (MMT) clients with HIV/AIDS in Guangdong, China.

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11 **Setting:** Fourteen MMT clinics located in 9 cities of Guangdong were chosen as study sites.

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14 **Participants:** In this study, we reviewed 293 clients with opioid dependence, HIV seropositive, 18
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16 years or older, providing informed consent and having at least 10 records of urine morphine tests
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18 during the study period.

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21 **Primary and secondary outcome measures:** The positive percentages of urine morphine tests were
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24 calculated and underlying predictors were estimated.

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27 **Results:** The highest positive percentage (95.9%) was observed in the first month. After excluding the
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29 highest percentage in the first month, the average positive percentage was 40.9% for month 2 to month
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31 12. Positive percentages of urine morphine tests that <20%, 20%-60% and >80% were 25.4%, 36.1%
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33 and 38.5% respectively. Lower percentages of continued heroin use were associated with being young
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35 (OR_{≤30}=0.31, 95%CI: 0.12-0.78; OR₃₁₊=0.44, 95%CI: 0.20-1.00), and financial sources depending on
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37 family or friends (OR=0.55, 95%CI: 0.32-0.93). Higher percentages of continued heroin use were
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39 associated with being unemployed (OR=1.99, 95%CI: 1.13-3.49) and poorer MMT attendance
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41 (OR_{<20%}=3.60, 95%CI: 1.55-8.33; OR_{20%}=2.80, 95%CI: 1.48-5.33).
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47 **Conclusions:** High positive percentages of urine morphine tests remain prevalent among MMT clients
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49 with HIV/AIDS in Guangdong. The present findings have implications for taking effective measures to
50
51 facilitate attendance in order to decrease heroin use and ultimately improve the effectiveness among
52
53 these sub-group MMT clients.
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57 **Key words:** Heroin Use; Methadone Maintenance Treatment (MMT); HIV; China
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4 **1 Strengths and Limitations**
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- 6 1. This is a long-term consecutive study specifically designed to examine concurrent heroin use
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8 among HIV-positive MMT clients in China.
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11 2. This study mainly focused on positive percentages of urine morphine tests among HIV-positive
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13 MMT clients in China.
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16 3. Self-reported data are subject to recall bias or deliberate concealment.
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19 4. China is experiencing a significant increase in the use of new drugs, but this study did not consider
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21 it.
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24 5. We only examined the percentages of heroin use during the first 12 months after receiving MMT
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26 due to the limited sample size and high drop-out.
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1 Introduction

2 In China, illicit drug use has increased dramatically since the 1980s [1]. There were cumulatively
3 registered 2.95 million drug users by the end of 2014 and 480,000 newly registrations in 2014
4 nationwide [2]. Although China recently is experiencing a significant increase in the use of new-type
5 drugs, heroin still remains the major illicit used drug among drug users [2]. The earliest HIV case was
6 identified among intravenous drug users (IDUs) in Southern Yunnan province in 1989 [3]. The early
7 spread of HIV epidemics in China mainly attributed to intravenous drug use (IDU) [4]. As of 2013,
8 437,000 people lived with HIV/AIDS in China (including 263,000 people living with HIV and 174,000
9 AIDS patients), accounting for 0.033% of the total population in China; and sentinel surveillance data
10 showed the HIV/AIDS prevalence was 6.3% among IDUs [5].

11 Globally, methadone maintenance treatment (MMT) is the most widely used pharmacological
12 treatment for opioid dependence. China has operated MMT program as a national strategy to combat
13 the joint threat of drug use and HIV/AIDS since 2004 [6]. For decades, MMT program has achieved its
14 crucial effectiveness not only in reducing heroin use [7] but also in preventing the spread of HIV [8, 9].
15 Meanwhile, studies have shown that MMT is beneficial in reducing drug-related criminal activities [10]
16 and drug-related mortality [11]. In addition, for the HIV-positive individuals, MMT could facilitate the
17 adherence to antiretroviral therapy [12]. By the end of April 2015, China has 767 MMT clinics in 28
18 provinces across the nation, serving nearly 190,000 clients [13].

19 However, many clients did not completely abstain from heroin and exhibited continued heroin use
20 while in MMT [14-17]. Continued heroin use could lead to negative MMT treatment outcomes among
21 clients [18]. Heroin addicts still contribute a high mortality even with MMT [19]. Overdosed drug
22 intake remains the most common cause of death among MMT clients [20]. After a period of abstinence

1 via MMT, the heroin tolerance of clients would decrease, thus overdosed intake may become more
2 prevalent [21, 22]. Individuals with HIV/AIDS are a special group among MMT clients. A
3 meta-analysis showed that HIV seropositivity would increase the mortality risk of overdose [23]. In
4 addition, continued heroin use would decrease the retention rate among MMT clients with HIV/AIDS
5 [24]. Therefore, heroin use deserves more attention among MMT clients with HIV/AIDS. To date,
6 limited data are available on heroin use among MMT clients with HIV/AIDS in China [14, 25] and
7 about the higher percentages of heroin use is even less. To fill this gap, we applied this study is to
8 examine the higher percentages of heroin use among MMT clients with HIV/AIDS in Guangdong.
9

1 **Methods**

2 **Ethics Statement**

3 The Institutional Review Board (IRB) of the School of Public Health (Sun Yat-sen University,
4 Guangzhou, China) reviewed and approved the study protocol. All study participants were asked to
5 provide written informed consent.

6 **Study Site and Participants**

7 Guangdong, located in the Southern coast of China, is one of the most developed provinces.
8 Meanwhile, Guangdong also is one of the HIV/AIDS and drug epidemic areas because it has
9 cumulative reported 48,718 HIV-positive cases, ranking fifth among provinces in China as of October
10 2014 [26], in addition, it has one-sixth of totally registered drug users in China [27].

11 This study was conducted in 14 MMT clinics located in 9 cities of Guangdong (According to
12 whether the 1-year retention rate is above or below 50%, the 61 MMT clinics were divided into two
13 groups, and seven clinics were randomly selected from each group [28]). We got permission and
14 authorization to use and retrieve part of data for the selected MMT clinics from the Chinese National
15 MMT Program data system. In this study, participants were eligible if they were (1) diagnosed with
16 opioid dependence according to the International Classification of Diseases (10th Revision); (2) 18
17 years or older; (3) tested to be HIV-positive at entry; (4) able to provide informed consent; and (5) had
18 at least 10 records of urine morphine tests.

19 In this study, “drop-out” was defined as a participant failing to continue MMT for 14 consecutive
20 days [28]. Based on whether drop-out happened before 12 months post-MMT initiation, the study
21 period could be classified into two categories: one was defined as the duration between enrollment and
22 dropout, the other was defined as the duration between enrolment and the end of the first 12 months.

1 **Measures**

2 ***Self-reported Risk Behaviors***

3 At admission, as well as 6th and 12th month respectively, each participant was requested to
4 complete a questionnaire covering demographic characteristics, drug use history including injecting
5 drug and sharing needle/equipment, sexual activity history, and condom use status.

6 A client was regarded as having corresponding risk behaviors during the study period if he/she
7 reported those behaviors either 6th or 12th interview (i.e. drug use behaviors including injecting drug
8 and sharing needle/equipment; and risk sexual activities including, multiple sex partner, inconsistent
9 condom use and sex trade for drugs.).

10 ***Methadone Maintenance Doses and Attendance***

11 In China, to insure MMT security, clients are forbidden to take Methadone outside the clinic. Once
12 enrolled in MMT, the clients must go to the clinic at consultation hours daily to take the prescribed
13 doses of Methadone under the supervision of clinic staff, and the daily doses and date were routinely
14 recorded in the national unified MMT management system. The treatment cost was RMB 10 Yuan
15 (USD: 1.5 Dollar) per day regardless of the client' intake doses and times.

16 Average maintenance dose was obtained via computing the mean of daily prescribed doses (The
17 doses of the first month were excluded because the first month of methadone maintenance treatment is
18 to give doctor time to adjust appropriate dose for a client. Usually the dose starts from small, 20 mg to
19 40 mg per day, and it will gradually increase slowly to certain amount.).

20 The percentage of MMT attendance was calculated based on proportion of days that a client
21 actually received the doses over the study period.

22 ***Positive Percentages of Urine Morphine Tests during the Study Period***

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4 1 A positive result of urine morphine test generally means heroin use by the clients within a few
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6 2 days. Urine-based morphine tests were monthly performed on a random day during the study period.

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9 3 As mentioned above, there exists a MMT dose adjustment stage for a new enrolled client. During
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11 4 the adjustment stage, most clients often use opioid to adjust themselves to methadone maintenance
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13 5 treatment. Therefore, the result of urine morphine test in the first month was excluded from calculation
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15 6 of heroin use and percentages in our study.

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19 7 A client was recognized as a heroin user as long as any urine morphine test result was positive
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21 8 within 12 months.

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24 9 The percentage of heroin use was calculated based on the number of positive urine morphine test
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26 10 results and the number of total urine test times within 12 months.

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29 11 Based on the urine morphine tests, the clients were currently grouped as “urine morphine (+)” and
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31 12 “urine morphine (-)”. Additionally, the positive percentages were grouped as <20%, 20-60% and >60%
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33 13 based on the data distribution.

34 35 36 14 ***HIV and Urine Morphine Tests***

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39 15 Except for those who were already confirmed as HIV-positive prior this study, each client was
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41 16 invited to receive HIV testing. HIV infection status was screened using an enzyme-linked
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43 17 immunosorbent assay (ELISA) technique (Beijing BGI-GBI Biotech Co., Ltd, Beijing, China). Positive
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45 18 blood specimens for HIV were confirmed using a Western blot assay (Abbott, MP Biomedicals, LLC,
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47 19 Singapore) by the local Centers for Disease Control (CDC). According to related national guidelines,
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49 20 pre- and post- test counseling services were provided.

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54 21 Random urine morphine status was screened using a Morphine Diagnostic Kit (Colloidal Gold)
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56 22 technique (ABON Biopharm Co., Ltd, Hangzhou, China).

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4 **1 Statistical Analysis**
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6 Statistical analyses were performed using SPSS 17.0 for Windows (SPSS Inc., Chicago).
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9 3 Categorical variables were described with percentages. Multivariate ordinal logistic regression analysis

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11 4 was conducted to predict higher percentages of heroin use from baseline information including

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13 5 demographic, drug use and multiple sex partners, as well as average maintenance dose and percentages

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15 6 of MMT attendance during the study period among the MMT clients with HIV/AIDS. Any $p < 0.05$ was

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17 7 considered to be statistically significant.
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1 Results

2 *Study Participants and Demographic Characteristics*

3 Among the 293 participants, 16.0% were elder than 40; 91.5% were males; 99.3% were ethnic
4 Han (China's predominant ethnic group), 54.3% were never married; 21.8% just had elementary or
5 lower education; 68.9% were unemployed and 64.2% obtained financial sources from their family or
6 friends (Table 1).

7 *Heroin Use and Multiple Sex Partner at Baseline*

8 Table 1 presents baseline information on heroin use. Of the participants, 77.8% had used heroin
9 for more than 10 years; 59.4% participants used heroin at least 3 times daily on average; the vast
10 majority (98.6%) abused powdered heroin and 99.0% ever administered drug by injection. Among the
11 IDUs, 56.6% ever shared intravenous needles. Only 13.7% never met the peer users.

12 Of these participants, 21.5% had had sexual activity with multiple sex partner (Table 1).

13 *Average Maintenance Doses and Attendance*

14 Among all participants, 46.8% had received doses below 60 ml and the average maintenance dose
15 was (67.5 ± 28.7) ml.

16 In addition, 10.6% participants' MMT attendance percentages were less than 20% and only 40.6%
17 were over 80% (Table 1).

18 *Positive Percentages of Urine Morphine Tests during the Study Period*

19 Between 2006 and 2012, there were 3471 urine morphine tests performed and 1580 were positive
20 (45.5%). The highest positive percentage was observed in the first month (95.9%), then it remained as
21 high as between 39.3% and 53.6% for month 2 to month 12. After excluding the highest percentage in
22 the first month, the average positive percentage was 40.9% for month 2 to month 12. The median

1 positive percentage of urine morphine tests was 48.6% for 2006, 48.7% for 2007, 44.0% for 2008, 41.2%
2 for 2009, 43.3% for 2010, 43.4% for 2011 and 22.5% for 2013, respectively (Table 2). Among the 268
3 urine morphine (+) clients, positive percentages of urine morphine tests that <20%, 20%-60% and >60%
4 were 25.4%, 36.1% and 38.5% respectively (Table 3).

5 After adjusted for potential confounding variables listed in the table, multiple ordinal logistic
6 regression analysis indicated that a higher percentage of heroin use was independently associated with
7 age, employment status, mainly financial sources and percentages of MMT attendance. Participants
8 who were younger ($OR_{\leq 30}=0.31$, 95%CI: 0.2-0.78; $OR_{31-35}=0.44$, 95%CI: 0.20-1.00), and got money
9 from family or friends ($OR=0.55$, 95%CI: 0.32-0.93) were more likely to be tested as having lower
10 percentages of heroin use; and those who were unemployed ($OR=1.99$, 95%CI: 1.13-3.49) and had
11 poor MMT attendance percentages ($OR_{<20}=3.60$, 95%CI: 1.55-8.33; $OR_{20-}=2.80$, 95%CI: 1.48-5.33)
12 were more likely to have higher percentages of heroin use (Table 4).

13 ***Self-reported High Risk Behaviors during the Study Period***

14 Among the clients with urine morphine (+), 99.3% (266 of 268) and 88.1% (236 of 268)
15 completed the 6th and 12th month follow-up interviews respectively. Of the 266 clients completed at
16 least one follow-up interview, 62.8% ever used drugs, 85.0% used intravenous drugs, and 25.4% ever
17 shared intravenous needles; 63.2% were sexual active, 29.2% had sex with multiple sex partners, and
18 43.5% never used condom during the sexual course. Also, 14.5% traded sex for drugs (Table 5).

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1 Discussion

2 Heroin use among MMT clients has been reported substantially worldwide [15, 16]. HIV-positive
3 drug users are a unique subgroup for playing a “dual bridge” role in HIV transmission. This study is an
4 extension of our previous study [25]. Our results were based on random, long-term and consecutive
5 urine tests, which was blind to clients in case those continued heroin users deliberately avoid the test
6 time.

7 Findings from the current analysis revealed that there were 91.5% participants had used heroin at
8 least once during the study period, which was higher than that (75%) of general MMT clients reported
9 by our prior study [25]. Findings also showed that 14.2% almost always used heroin. Given that
10 continued heroin use might lead to adverse health outcomes [20, 23] and high drop-out rate [24] among
11 MMT clients with HIV/AIDS, targeted interventions and control programs are urgently needed for this
12 subgroup.

13 Compared to the young participants, the elders showed greater likelihood of continued heroin use.
14 Many elders had turned from clinical latency stage to AIDS stage and they may experience more pain
15 and psychological symptoms [29, 30]. Studies had shown that depressive symptoms are common
16 among people with HIV infection [31, 32]. However, MMT improvements in depressive symptoms and
17 the physical domain of QOL (quality of life) among HIV-positive heroin users were poorer than in
18 those without HIV infection [33]. Also, most of them had lost the courage and confidence to live on.
19 Culturally, stigma and discrimination towards drug use and HIV/AIDS might seriously impede the
20 MMT attendance [34]. In addition, inappropriate perceptions of MMT should not be neglected [35].

21 Previous research has documented that the clients who were employed were more likely to use
22 heroin during the treatment period [36]. In contrast, we found that the unemployed had more likelihood

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4 1 with concurrent heroin use. This was possibly due to the unemployed (1) lacked social support; (2) had
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6 2 more time to communicate with former drug taking peers. There was a big difference between the
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8 3 employed and the unemployed not only in terms of sociodemographic factors but also the family tie,
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10 4 which in turn influenced concurrent heroin use [25, 37].
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14 5 Generally, high drug fee generally made the drug users can't afford it. In our study, the clients
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16 6 whose financial sources depend on family or friends were less likely to use heroin. Money from family
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18 7 or friends is meant to support basic life and is far not enough to meet drug expenditure. Furthermore,
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20 8 drug use and MMT is regarded as a family issue in China, and family or friends' support might
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22 9 potentially supervise and encourage treatment participation and compliance [25, 37].
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26 10 There has been controversy over whether higher Methadone doses could decrease heroin use
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28 11 among MMT clients. Studies showed an appropriate MMT dose is the most effective in suppressing
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30 12 heroin use in treatment [18, 38]. There were also further research suggesting that an adequate dose of
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32 13 Methadone (e.g., 80-120 mgs/day) would significantly reduce heroin use among clients within the first
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34 14 two months of treatment and eventually either eliminated or significantly curtailed with time in
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36 15 treatment [39, 40]. However, other studies revealed there was no correlation between Methadone doses
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38 16 and heroin use in treatment [41, 42]. The Methadone dose was ≥ 60 mg/day recommended by US
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40 17 National Institutes of Health [43], and should be higher for HIV-positive individuals [44]. We found
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42 18 46.8% participants' doses were less than 60 mg/day. Compared to those with higher doses, we did not
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44 19 find the clients with lower doses were more likely to use heroin. Given the small sample size and
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46 20 short-term observation, further large sample size and stratified dose research are needed.
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54 21 Without exception, treatment effectiveness relies upon sufficient levels of medication adherence.
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56 22 MMT requires long-term or even life-long intake of Methadone at an adequate dose on a daily basis
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1 [45]. We found that the lower attendance meant the higher percentage of heroin use. This was
2 consistent with our prior study [25]. Continued heroin users attended MMT programs irregularly and
3 the attendance significantly declined with the duration that they retained in treatment program [46].
4 Poorer attendance seeded continued heroin use. In addition, misconceptions might predict poor
5 adherence among newly admitted MMT clients [47]. So, future research might need to develop and/or
6 integrate other necessary interventions to encourage client adherence to the treatment program.

7 HIV-positive drug users have been regarded as a “dual risk” subgroup. They transmit HIV via
8 either sharing needles or having unprotected sexual intercourse with partners. Currently, sexual
9 transmission is the most prevalent spread pattern of HIV/AIDS in China [5]. Among the participants
10 who finished at least once interview, 25.4% ever shared needle; 29.2% ever had sex with multiple
11 partners; 43.5% never used condom and 14.5% had sex for drugs during the study period. Considering
12 the potential bridge role of those with dual risk behaviors in transmitting HIV to others, research on the
13 interaction of HIV-positive MMT clients and risk behaviors should be given high priority. Data showed
14 that changing unsafe drug use behaviors was more effective than changing unsafe sexual behaviors [17].
15 In future treatment procedures, physicians and nurses should play an active role in educating clients
16 about safe sex and encourage clients to use condoms.

17 This study is subject to certain limitations. Firstly, self-reported data are subject to recall bias or
18 deliberate concealment. Secondly, China is experiencing a significant increase in the use of new drugs
19 [2], but this study did not consider it. In addition, we failed to obtain the ART (anti-retroviral treatment)
20 information, and future studies should be extended to analyze ART as predictor variable to continued
21 heroin use. Thirdly, we only examined the percentages of heroin use during the first 12 months after
22 receiving MMT, and did not take 12+ months into consideration due to the limited sample size and

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4 1 high drop-out.
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6 2 In summary, findings from this study provide important implications for future MMT programs
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8 3 targeting continued heroin use among HIV-positive clients. Concretely, first, continuous and efficient
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10 4 MMT consulting and health education interventions need to be conducted for reducing continued
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12 5 heroin use. Interventions involving family members in supervision of participation and compliance
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14 6 should be reinforced. Second, attendance are crucial components affecting MMT⁷ outcomes, so how to
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16 7 improve sufficient attendance have become issues of great urgency.
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6 **Contributors**

7 XL designed the study, performed data analysis and wrote the draft manuscript. XG and PZ
8 performed data analysis. XZ and WC collected the data. LL supervised the study. All authors
9 contributed to the interpretation of the data and approved the final version for submission.

10 **Conflict of Interest**

11 The authors declare no conflicts of interest.

12 **Data Sharing Statement**

13 No additional unpublished data are available.

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18

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1 Tables

2 Table1. Characteristics of the participants (n=293)

Characteristics	Urine Morphine(-)	Urine Morphine(+)	Total
	(n=25)	(n=268)	(N=293)
	No. (% ^a)	No. (% ^a)	No. (% ^b)
Age at Baseline (years)			
≤30	5(7.5)	62(92.5)	67(22.9)
31-	9(10.1)	80(89.9)	89(30.4)
36-	7(7.8)	83(92.2)	90(30.7)
≥41	4(8.5)	43(91.5)	47(16.0)
Gender			
Male	25(9.3)	243(90.7)	268(91.5)
Female	0(0)	25(100.0)	25(8.5)
Ethnic			
Han	25(8.6)	266(91.4)	291(99.3)
Others	0(0)	2(100.0)	2(0.7)
Marital Status at Baseline			
Never married	17(10.7)	142(89.3)	159(54.3)
Married currently	5(5.2)	92(94.8)	97(33.1)
Others	3(8.1)	34(91.9)	37(12.6)
Education Level			
Elementary or lower	1(1.6)	63(98.4)	64(21.8)
Juniorhigh school	18(9.4)	174(90.6)	192(65.5)
Senior high school or higher	6(16.2)	31(83.8)	37(12.6)
Employed Status at Baseline			
Unemployed	16(7.9)	186(92.1)	202(68.9)
Employed	9(9.9)	82(90.1)	91(31.1)
Mainly Financial Sources at Baseline			
Family or friends	19(10.1)	169(89.9)	188(64.2)
Others	6(5.7)	99(94.3)	105(35.8)
Duration of Drug Abuse (years)			
≤10	3(4.6)	62(95.4)	65(22.2)
11-15	12(9.2)	118(90.8)	130(44.4)
≥16	10(10.2)	88(89.8)	98(33.4)
Type of Drug Use at Baseline			
Heroin	25(8.7)	264(91.3)	289(98.6)
Others	0(0)	4(100.0)	4(1.4)
Intravenous Drug Use at Baseline			
Yes	25(8.6)	265(91.4)	290(99.0)
No	0(0)	3(100.0)	3(1.0)
Shared Needles to Inject Drugs at Baseline			
Yes	11(6.7)	153(93.3)	164(56.6)
No	14(11.1)	112(88.9)	126(43.4)
Average Times of Drug Use per Day at Baseline			

≤2	10(8.4)	109(91.6)	119(40.6)
≥3	15(8.6)	159(91.4)	174(59.4)
Multiple Sex Partners at Baseline			
Yes	4(6.3)	59(93.7)	63(21.5)
No	21(9.1)	209(90.9)	230(78.5)
Average Maintenance Doses (ml/day)			
≥60	18(11.5)	138(88.5)	156(53.2)
<60	7(5.1)	130(94.9)	137(46.8)
Percentages of MMT Attendance (%)			
<20	1(3.2)	30(96.8)	31(10.6)
20-	4(6.1)	62(93.9)	66(22.5)
50-	4(5.2)	73(94.8)	77(26.3)
≥80%	16(13.4)	103(86.6)	119(40.6)

^a calculated by row, ^b calculated by column.

1 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)

2

1 Table 3 The distribution of positive percentages of urine morphine tests among the urine morphine
2 (+) participants during the study period (n =268)

Positive percentage (%)	Number (n)	Percentage (%)
<10	34	12.7
10-	34	12.7
20-	29	10.8
30-	28	10.4
40-	22	8.2
50-	18	6.7
60-	23	8.6
70-	20	7.5
80-	22	8.2
90-	38	14.2
total	268	100.0

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1 Table4. Correlates of higher positive percentages among urine morphine (+) participants during
 2 the study period (n=268)

Characteristics	<20% (n=68) No. (%)*	20%-60% (n=97) No. (%)*	>60% (n=103) No. (%)*	OR(95%CI) ^{a, b}	<i>p</i> ^b
Age (years)					
≤30	20(32.3)	28(45.2)	14(22.6)	0.31(0.12-0.78)	0.013
31-	22(27.5)	26(32.5)	32(40.0)	0.44(0.20-1.00)	0.051
36-	13(15.7)	33(39.8)	37(44.6)	0.91(0.43-1.93)	0.814
≥41	13(30.2)	10(23.3)	20(46.5)	1.00	
Gender					
Male	60(24.7)	90(37.0)	93(38.3)	0.97(0.42-2.22)	0.944
Female	8(32.0)	7(28.0)	10(40.0)	1.00	
Marital Status					
Never married	36(25.4)	54(38.0)	52(36.6)	2.04(0.92-4.55)	0.080
Married Currently	23(25.0)	29(31.5)	40(43.5)	1.93(0.85-4.40)	0.117
Others	9(26.5)	14(41.2)	11(32.4)	1.00	
Education Level					
Elementary or lower	16(25.4)	24(38.1)	23(36.5)	1.50(0.64-3.50)	0.347
Juniorhigh school	45(25.9)	58(33.3)	71(40.8)	1.48(0.71-3.12)	0.298
Senior high school or higher	7(22.6)	15(48.4)	9(29.0)	1.00	
Employment Status at Baseline					
Unemployed	45(24.2)	64(34.4)	77(41.4)	1.99(1.13-3.49)	0.017
Employed	23(28.0)	33(40.2)	26(31.7)	1.00	
Mainly Financial Sources					
Family or friends	49(29.0)	60(35.5)	60(35.5)	0.55(0.32-0.93)	0.025
Others	19(19.2)	37(37.4)	43(43.4)	1.00	
Duration of Drug Abuse (years)					
≤10	18(29.0)	21(33.9)	23(37.1)	1.04(0.50-2.16)	0.923
11-15	27(22.9)	46(39.0)	45(38.1)	1.38(0.75-2.55)	0.305
≥16	23(26.1)	30(34.1)	35(39.8)	1.00	
Average Times of Drug Use per Day					
≤2	21(19.3)	47(43.1)	41(37.6)	1.03(0.62-1.71)	0.912
≥3	47(29.6)	50(31.4)	62(39.0)	1.00	
Shared Needles at Baseline					
Yes	38(24.8)	59(38.6)	56(36.6)	1.03(0.63-1.69)	0.902
No	30(26.1)	38(33.0)	47(40.9)	1.00	
Multiple Sex Partners at Baseline					
Yes	12 (20.3)	17(28.8)	30(50.8)	1.65(0.89-3.05)	0.113
No	56(26.8)	80(38.3)	73(34.9)	1.00	
Average Maintenance Doses (ml/day)					
≥60	36(26.1)	56(40.6)	46(33.3)	0.92(0.57-1.49)	0.742
<60	32(24.6)	41(31.5)	57(43.8)	1.00	
Percentages of MMT Attendance (%)					

<20	4(13.3)	9(30.0)	17(56.7)	3.60(1.55-8.33)	0.003
20-	10(16.1)	19(30.6)	33(53.2)	2.80(1.48-5.33)	0.002
50-	22(30.1)	32(43.8)	19(26.0)	0.94(0.53-1.67)	0.841
≥80%	32(31.1)	37(35.9)	34(33.0)	1.00	

1 ^a OR: Odds Ratio, CI: Confidence Interval;

2 ^b Obtained from multivariate ordinal logistic regression analysis adjusting for potential confounding variables
 3 listed in the table;

4 *Proportions were calculated in the row.

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1 Table5. Self-reported risk behaviors among urine morphine (+) participants during the study
 2 period (n=266)

Characteristics	<20%	20%-60%	>60%	Total
	No. (% ^a)	No. (% ^a)	No. (% ^a)	No. (% ^b)
Drug Use (n=266)				
Yes	26(15.6)	55(32.9)	86(51.5)	167(62.8)
No	41(41.4)	41(41.4)	17(17.2)	99(37.2)
Injected Drugs (n=167)				
Yes	21(14.8)	44(31.0)	77(54.2)	142(85.0)
No	5(20.0)	11(44.0)	9(36.0)	25(15.0)
Shared Needles (n=142)				
Yes	3(8.3)	11(30.6)	22(61.1)	36(25.4)
No	18(17.0)	33(31.1)	55(51.9)	106(74.6)
Sex Activity (n=266)				
Yes	38(22.6)	66(39.3)	64(38.1)	168(63.2)
No	29(29.6)	30(30.6)	39(39.8)	98(36.8)
Multiple Sex Partners (n=168)				
Yes	7(14.3)	23(46.9)	19(38.8)	49(29.2)
No	31(26.1)	43(36.1)	45(37.8)	119(70.8)
Condom Use (n=168)				
Yes	24(25.3)	37(38.9)	34(35.8)	95(56.5)
No	14(19.2)	29(39.7)	30(41.1)	73(43.5)
Sex for Drugs (n=117)				
Yes	3(17.6)	8(47.1)	6(35.3)	17(14.5)
No	18(18.0)	32(32.0)	50(50.0)	100(85.5)

3 ^a calculated by row, ^b calculated by column.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract In the title (b) Provide in the abstract an informative and balanced summary of what was done and what was found Line 7-8,page 2; line 9-16,page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Line 19-22, page 4; line 1-4, page 5
Objectives	3	State specific objectives, including any prespecified hypotheses Line 5-8, page 5
Methods		
Study design	4	Present key elements of study design early in the paper Line 11-15,page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Line 11-21,page 6
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Line 18-21, page 6; line 1-3,page 7 <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed ----- <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable line 4-22,page 7;line 1-15, page 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group line 4-22,page 7;line 1-15, page 8
Bias	9	Describe any efforts to address potential sources of bias Line 14-17,page 7; line 1-2,page 8
Study size	10	Explain how the study size was arrived at Line 15-17, page 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Line 19-21,page 7; line 1-6,page 8

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3	Statistical methods	12
4		(a) Describe all statistical methods, including those used to control for confounding
5		Line 16-22, page 8
6		(b) Describe any methods used to examine subgroups and interactions
7		(c) Explain how missing data were addressed
8		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed
9		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was
10		addressed
11		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of
12		sampling strategy
13		(e) Describe any sensitivity analyses
14		

Continued on next page

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Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Line 15-17, page 6
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Table 1, line 2-12, page 9
		(b) Indicate number of participants with missing data for each variable of interest Table 1-5
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount) Line 22, page 6; Line 1-3, page 7
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time line 21-22, page 9
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Table 4, page 26-27
		(b) Report category boundaries when continuous variables were categorized Table 1, page 22-23
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Line 10-15, page 10

Discussion

Key results	18	Summarise key results with reference to study objectives Line 7-8, page 11; line 12, page 11; line 1-2, page 12; line 6-7 page 12; line 16-18, page 12; line 22, page 12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Line 17-22, page 13; line 1-5, page 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Line 9-11, page 11; line 13-19, page 11; line 2-4, page 12; line 6-10, page 12; line 1-6, page 13
Generalisability	21	Discuss the generalisability (external validity) of the study results Line 6-12, page 14

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Line 1-5, page 15
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3 *Give information separately for cases and controls in case-control studies and, if applicable, for exposed and
4 unexposed groups in cohort and cross-sectional studies.
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7 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and
8 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely
9 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
10 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is
11 available at www.strobe-statement.org.
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