

Re-entry and related predictors among HIV-infected clients receiving methadone maintenance treatment in Guangdong province, China

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Summary

This study examined the re-entry characteristics and related predictors among HIV-infected methadone maintenance treatment (MMT) clients in Guangdong, China. Data on HIV-infected MMT clients was obtained from the clinic MMT registration system in Guangdong. Of the 653 participants, only 9.0% remained in the MMT program until the end of the study. For the drop-outs, 70.0% returned to MMT at least once by the end of the study. Re-entry was independently associated with marital status ($OR_{\text{never married}} = 2.24$, 95% CI: 1.02-4.93; $OR_{\text{married currently}} = 2.34$, 95% CI: 1.05-5.22), being unemployed ($OR = 1.92$, 95% CI: 1.12-3.27), lower positive percentages of urine tests ($OR_{<40\%} = 4.08$, 95% CI: 2.21-7.54; $OR_{40\%-80\%} = 2.52$, 95% CI: 1.39-4.56), higher maintenance doses ($OR = 3.78$, 95% CI: 2.21-7.54) and poorer MMT attendance percentages ($OR_{<20\%} = 282.02$, 95% CI: 62.75-1268.11; $OR_{20-49\%} = 20.75$, 95% CI: 10.52-40.93; $OR_{50-79\%} = 6.07$, 95% CI: 3.44-10.73). A higher re-entry frequency was independently associated with lower education level ($OR_{\text{junior high school}} = 0.49$, 95% CI: 0.26-0.93), average drug use times less than twice ($OR = 0.64$, 95% CI: 0.41-1.00), lower positive percentages of urine tests ($OR = 0.39$, 95% CI: 0.22-0.70) and poorer percentages of MMT attendance ($OR_{<20\%} = 7.24$, 95% CI: 2.99-17.55; $OR_{20-49\%} = 14.30$, 95% CI: 5.94-34.42; $OR_{50-79\%} = 6.15$, 95% CI: 2.55-14.85). Re-entry and repeated re-entry were prevalent among HIV-infected MMT clients in Guangdong, underscoring the urgent needs of tailored interventions and health education programs for this population.

Keywords: Re-entry, methadone maintenance treatment (MMT), HIV, China

1. Introduction

Opioid dependence is a worldwide health problem that leads to enormous economic, personal and public health consequences (1). The World Health Organization (WHO) statistics show that an estimated 69,000 people die from opioid overdose each year; an estimated 15 million people suffer from opioid dependence, yet only 10% of them are receiving effective treatments (2).

Methadone is a safe, low-cost, convenient and effective substitute treatment drug for opioid dependence (3). Decades of experience have demonstrated that methadone maintenance treatment (MMT) is currently the most effective intervention measure for controlling opioid use and its related HIV transmission among opioid users (4-6). Meanwhile, MMT could improve stability for society (7) and help drug users recover their physical and social functions (8-10).

China has the largest number of intravenous drug users (IDUs) in the world (11), and it is well recognized that the national epidemic of HIV originated and spread rapidly in this group by sharing needles (11). In response, the Chinese government introduced MMT in 2004 to control the rapid spread of both heroin use and HIV transmission (12,13). From 2006, MMT was quickly expanded from its original 8 clinics in 2004 to

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767 clinics covering 28 Chinese provinces as of April 2015 (14,15). In the past decade, MMT has effectively reduced heroin use (14,16,17) and curbed the spread of HIV/AIDS among heroin addicts (17-19). According to official statistics, HIV incidence among clients has decreased from 0.95% in 2006 to 0.12% in 2014 since the implementation of the MMT program (15). As estimated, 15,000 new HIV infections among opioid addicts were prevented; consumption of heroin was reduced by 100 tons; and 65 billion Yuan (RMB) in heroin trade were avoided (15).

Nonetheless, MMT in China faces many challenges, such as low coverage (14) and high drop-out rates (20). So far, retention has proven to be a valuable indicator of MMT effectiveness (21). High drop-out means many clients terminated the treatment before obtaining therapeutic benefits. However, repeated drop-out and re-entry remains prevalent among clients in MMT programs, often for multiple episodes (22,23). With the expansion of the MMT program and the increase of treatment accessibility, this phenomenon appears to have increased (23). HIV-infected drug users have been regarded as a "dual risk" subgroup (24). They transmit HIV via either sharing needles or having unprotected sex with partners. A study has demonstrated that MMT not only decreased the frequency of drug use but also improved the health-related quality of life among HIV-infected opioid addicts (25). Therefore, it becomes particularly important to strengthen MMT retention in this subgroup. Given that there are limited resources for drug treatment programs in China, it is imperative to know the re-entry characteristics of HIV-infected attendees to maximize the impact of MMT and tailor it to effectively target the population. Therefore, we used the data from 14 clinics in Guangdong to evaluate the re-entry and correlates among HIV-infected MMT clients.

2. Materials and Methods

2.1. Ethics approval

This study was approved by the Institutional Review Board (IRB) of the School of Public Health of Sun Yat-sen University, Guangzhou, China (No: 2013-26).

2.2. Study site and participants

Fourteen MMT clinics located in 9 cities of Guangdong Province were chosen as the study site for this study. From July 2006 to December 2013, all registered HIV-infected MMT clients in the unified MMT management system who met the Chinese Classification of Mental Disorders version 3 criteria for opioid dependence (26), were 18 years old or above, tested to be HIV-infected and able to provide written informed consent were included in this study.

2.3. Study procedure

At admission, a structured interview was developed to assess demographic characteristics, drug use history and sexual activity history. An interview was conducted by local clinic staff that had been trained in administration of the interview schedule. In China, to help insure security, clients were asked to attend the clinic daily once they have been enrolled in the program to take their methadone doses under the supervision of clinic staff, and the data on doses and date were routinely collected and stored in the national unified MMT management system. Urine morphine tests were performed on a random day each month. Participants were provided with no incentives.

In China, each client has a unique MMT ID based on personal ID regardless of the re-entry times. The study period was defined as the duration between the first and the last methadone uptake date.

2.4. Measures

2.4.1. Methadone maintenance doses and attendance

The average daily maintenance dose during the study period was calculated according to the following formula:

The average daily maintenance dose = total intake doses/total number of days taking methadone.

The percentage of MMT attendance during the study period was calculated according to the following formula:

The percentage of MMT attendance = (total actual number of days taking methadone/total expected number of days taking methadone) × 100%.

2.4.2. Positive percentages of urine morphine tests

The percentage of urine morphine tests during the study period was calculated according to the following formula:

The percentage of urine morphine tests = (total number of positive urine morphine test results/total number of testing times) × 100%.

According to the positive percentage distribution, it was classified as < 40%, 40-80% and > 80%.

2.4.3. Re-entry during the study period

In this study, "drop-out" was defined as a participant failing to continue MMT for 14 consecutive days (21,22), and the drop-outs included "loss-to-follow-up" and "re-entry". Those drop-outs who did not return by the end of the study were classified into the "loss-to-follow-up" group, while those who returned at least once by the end of the study were classified into the "re-entry" group.

For the "re-entry" group, the re-entry frequency was calculated based on the returned times over the study period, and it was classified as low (< once/year), moderate (1-2 times/year) and frequent (> twice/year) based on the distribution.

2.4.4. HIV and urine morphine tests

Anti-HIV antibody was screened using an enzyme-linked immunosorbent assay (ELISA) technique (Beijing BGI-GBI BiotechCo., Ltd, Beijing, China). Any samples that screened HIV positive were confirmed using a Western blot assay (Abbott, MP Biomedicals, LLC, Singapore) by the local CDC (Centers for Disease Control).

Urine morphine was screened using a Morphine Diagnostic Kit (Colloidal Gold) technique (ABON Biopharm Co., Ltd, Hangzhou, China).

2.5. Statistical analysis

All analyses were performed in SPSS version 17.0 for Windows (SPSS Inc., Chicago). Categorical variables were presented with percentages. Binary logistic regression analyses (including univariate and multivariate analyses) were performed to explore correlates of re-entry; and multivariate ordinal logistic regression analysis was conducted to explore correlates of higher frequency of re-entry. The criterion for statistical significance was $p < 0.05$.

3. Results

3.1. Study participants and demographic characteristics

Totally, there were 805 registered HIV-infected MMT clients between Jul. 2006 and Dec. 2013 in the unified MMT management system. Among them, 81.1% (653 of 805) were eligible for this study.

Among the 653 participants, 22.1% were older than 40; 93.4% were males; 99.1% were ethnic Han, 53.1% were never married; 63.4% had received junior high school education; 64.2% were unemployed; only 23.7% had a harmonious family relationship; and 61.7% relied on their family or friends (Table 1).

3.2. Multiple sex partners at baseline

Among all participants, 17.3% had had sexual activity with multiple sex partners (Table 1).

3.3. Heroin use

Table 1 presents detailed information about opioid use at baseline among the study participants. Among the participants, only 21.4% had used drugs less than 10 years; 64.8% participants used drugs on average at

least 3 times per day; 97.7% abused heroin, and 98.6% abused drugs by injection. Among the IDUs, 58.7% shared intravenous needles to inject drugs. Only 12.4% reported never meeting drug users.

As Table 1 summarizes, the positive percentage of urine morphine results that < 0%, 40-80% and > 80% were 29.0%, 32.6% and 38.4% respectively during the study period.

3.4. Average maintenance dose and attendance

Of the participants, only 39.4% received doses of more than 60 mg/day. Also, 20.1% participants' attendance rates were less than 20%, and only 35.8% over 80% (Table 1).

3.5. Re-entry during the study period

Only 9.0% (59 of 653) participants remained in the MMT during the study period. For the 594 drop-outs, 70.0% (416 of 594) returned to MMT at least once by the end of the study (Table 1). Of the 416 participants who experienced re-entries, the re-entry frequencies of < 1, 1- and 2- times/year were 51.9%, 22.6% and 9.4% respectively; and 5.3% returned to MMT ≥ 5 times/year (Table 2). The distribution of re-entry frequency at different entry years and institutions are listed in Table 3.

After controlling for potential confounding variables, multivariate binary logistic regression analysis indicated that re-entry was independently associated with marital status, being unemployed, lower positive proportion of urine tests, higher maintenance doses and poorer percentages of MMT attendance (Table 4).

Multivariate ordinal logistic regression analysis indicated that after controlling for potential confounding variables among the re-entries, a higher re-entry frequency was independently associated with lower education level, average drug use times less than twice, lower positive proportion of urine tests and poorer MMT attendance percentages (Table 5).

4. Discussion

Although MMT re-entry of general clients has previously been reported in China (22), to our knowledge, this is the first study to reveal the re-entry and re-entry frequency characteristics among HIV-infected MMT clients. In the present analyses, we observed a high re-entry rate (70.0%) among HIV-infected drug users, which was similar to that (two-thirds) reported by Bell and colleagues (23). However, this was lower than the rate of 81.2% in whole MMT clients in our previous study (22). This may be due to the fact that the HIV-infected clients (1) have much higher mortality than general clients (27); and (2) have higher continued heroin use rate than general clients (according to our previous studies, the rates were 75% for all clients

Table 1. Characteristics of the participants

Characteristics	Retain (n = 59) No. (%)	Re-entry (n = 416) No. (%)	Non-re-entry (n = 178) No. (%)	Total (n = 653) No. (%)
Age (years)				
≤ 30	8 (13.6)	83 (20.0)	24 (13.5)	115 (17.6)
31-35	13 (22.0)	127 (30.5)	53 (29.8)	193 (29.6)
36-40	15 (25.4)	133 (32.0)	53 (29.8)	201 (30.8)
≥ 41	23 (39.0)	73 (17.5)	48 (27.0)	144 (22.1)
Gender				
Male	54 (91.5)	388 (93.3)	168 (94.4)	610 (93.4)
Female	5 (8.5)	28 (6.7)	10 (5.6)	43 (6.6)
Ethnic				
Han	59 (100.0)	412 (99.0)	176 (98.9)	647 (99.1)
Others	0 (0)	4 (1.0)	2 (1.1)	6 (0.9)
Marital Status				
Single	32 (54.2)	230 (55.3)	85 (47.8)	347 (53.1)
Married Currently	18 (30.5)	146 (35.1)	67 (37.6)	231 (35.4)
Others	9 (15.3)	40 (9.6)	26 (14.6)	75 (11.5)
Education Level				
Elementary or lower	11 (18.6)	110 (26.4)	49 (27.5)	170 (26.0)
Junior high school	39 (66.1)	261 (62.7)	114 (64.0)	414 (63.4)
Senior high school or higher	9 (15.3)	45 (10.8)	15 (8.4)	69 (10.6)
Employed Status at Baseline				
Unemployed	39 (66.1)	273 (65.6)	107 (60.1)	419 (64.2)
Employed	20 (33.9)	143 (34.4)	71 (39.9)	234 (35.8)
Family Relationship at Baseline				
Harmonious	12 (20.3)	94 (22.6)	49 (27.5)	155 (23.7)
Inharmonious	47 (79.7)	322 (77.4)	129 (72.5)	498 (76.3)
Mainly Financial Sources at Baseline				
Family and Friends	35 (59.3)	263 (63.2)	105 (59.0)	403 (61.7)
Others	24 (40.7)	153 (36.8)	73 (41.0)	250 (38.3)
Duration of Drug Abuse (years)				
≤ 10	9 (15.3)	88 (21.2)	43 (24.2)	140 (21.4)
11-15	21 (35.6)	179 (43.0)	68 (38.2)	268 (41.0)
≥ 16	29 (49.2)	149 (35.8)	67 (37.6)	245 (37.5)
Type of Drug Use at Baseline				
Heroin	57 (96.6)	408 (98.1)	173 (97.2)	638 (97.7)
Others	2 (3.4)	8 (1.9)	5 (2.8)	15 (2.3)
Drug administration method at Baseline				
Inhaled only	2 (3.4)	18 (4.3)	15 (8.4)	35 (5.4)
Injected only	54 (91.5)	387 (93.0)	159 (89.3)	600 (91.9)
Mixed (injected and inhaled)	3 (5.1)	11 (2.6)	4 (2.2)	18 (2.8)
Injected Drugs at Baseline				
Yes	58 (98.3)	413 (99.3)	173 (97.2)	644 (98.6)
No	1 (1.7)	3 (0.7)	5 (2.8)	9 (1.4)
Shared Needles to Inject Drugs at Baseline				
Yes	29 (50.0)	248 (60.0)	101 (58.4)	378 (58.7)
No	29 (50.0)	165 (40.0)	72 (41.6)	266 (41.3)
Average Times of Drug Use per Day at Baseline				
≤ 2	15 (25.4)	154 (37.0)	61 (34.3)	230 (35.2)
≥ 3	44 (74.6)	262 (63.0)	117 (65.7)	423 (64.8)
Frequency of Meeting with Peer Users at Baseline				
none	14 (23.7)	46 (11.1)	21 (11.8)	81 (12.4)
1-4/month	11 (18.6)	100 (24.0)	51 (28.7)	162 (24.8)
1-6/week	20 (33.9)	100 (24.0)	47 (26.4)	167 (25.6)
> 1/day	14 (23.7)	170 (40.9)	59 (33.1)	243 (37.2)
Multiple Sex Partners at Baseline				
Yes	5 (8.5)	79 (19.0)	29 (16.3)	113 (17.3)
No	54 (91.5)	337 (81.0)	149 (83.7)	540 (82.7)
Positive Proportion of Urine Tests* (%)				
< 40	32 (58.2)	111 (27.1)	40 (23.8)	183 (29.0)
40-80	13 (23.6)	146 (35.7)	47 (28.0)	206 (32.6)
> 80	10 (18.2)	152 (37.2)	81 (48.2)	243 (38.4)
Average Maintenance Dose (ml/day)				
≥ 60	37 (62.7)	176 (42.3)	44 (24.7)	257 (39.4)
< 60	22 (37.3)	240 (57.7)	134 (75.3)	396 (60.6)
Percentages of MMT Attendance (%)				
< 20	0 (0)	129 (31.0)	2 (1.1)	131 (20.1)
20-	0 (0)	121 (29.1)	20 (11.2)	141 (21.6)
50-	5 (8.5)	101 (24.3)	41 (23.0)	147 (22.5)
≥ 80%	54 (91.5)	65 (15.6)	115 (64.6)	234 (35.8)

*: 21 participants had no urine test results.

Table 2. Re-entry frequency among the re-entries during study period (n = 416)

Frequency (times/year)	Number (n)	Percentage (%)
< 1	216	51.9
1-	94	22.6
2-	39	9.4
3-	28	6.7
4-	17	4.1
≥ 5	22	5.3

Table 3. Re-entry frequency at the different entrant year and institution (n = 416)

Variables	< 1 (n = 216) No. (%) ^a	1- (n = 94) No. (%) ^a	2- (n = 39) No. (%) ^a	3- (n = 28) No. (%) ^a	4- (n = 17) No. (%) ^a	≥ 5 (n = 22) No. (%) ^a	Total (n = 416) No. (%) ^b
Year							
2006	31 (64.6)	14 (29.2)	2 (4.2)	0 (0)	1 (2.1)	0 (0)	48 (11.5)
2007	64 (65.3)	16 (16.3)	10 (10.2)	3 (3.1)	1 (1.0)	4 (4.1)	98 (23.6)
2008	44 (53.7)	19 (23.2)	6 (7.3)	7 (8.)	2 (2.4)	4 (4.9)	82 (19.7)
2009	29 (54.7)	11 (20.8)	4 (7.5)	4 (7.5)	2 (3.8)	3 (5.7)	53 (12.7)
2010	11 (34.4)	11 (34.4)	2 (6.3)	2 (6.3)	2 (6.3)	4 (12.5)	32 (7.7)
2011	25 (44.6)	16 (28.9)	7 (12.5)	4 (7.1)	2 (3.6)	2 (3.6)	56 (13.5)
2012	11 (35.5)	6 (19.4)	4 (12.9)	2 (6.5)	6 (19.4)	2 (6.5)	31 (7.5)
2013	1 (6.3)	1 (6.3)	4 (25.0)	6 (37.5)	1 (6.3)	3 (18.8)	16 (3.8)
Institution							
No. 1	17 (60.7)	5 (17.9)	3 (10.7)	0 (0)	0 (0)	3 (10.7)	28 (6.7)
No. 2	2 (40.0)	2 (40.0)	0 (0)	0 (0)	0 (0)	1 (20.0)	5 (1.2)
No. 3	2 (20.0)	5 (50.0)	0 (0)	2 (20.0)	1 (10.0)	0 (0)	10 (2.4)
No. 4	4 (40.0)	1 (10.0)	2 (20.0)	1 (10.0)	1 (10.0)	1 (10.0)	10 (2.4)
No. 5	18 (62.1)	3 (10.3)	1 (3.4)	2 (6.9)	3 (10.3)	2 (6.9)	29 (7.0)
No. 6	12 (40.0)	12 (40.0)	1 (3.3)	2 (6.7)	0 (0)	3 (10.0)	30 (7.2)
No. 7	35 (48.6)	19 (26.4)	8 (11.1)	3 (4.2)	4 (5.6)	3 (4.2)	72 (17.3)
No. 8	30 (63.8)	6 (12.8)	4 (8.5)	2 (4.3)	1 (2.1)	4 (8.5)	47 (11.3)
No. 9	16 (57.1)	8 (28.6)	1 (3.6)	2 (7.1)	1 (3.6)	0 (0)	28 (6.7)
No. 10	6 (54.5)	3 (27.3)	0 (0)	1 (9.1)	1 (9.1)	0 (0)	11 (2.6)
No. 11	29 (46.8)	14 (22.6)	8 (12.9)	7 (11.3)	2 (3.2)	2 (3.2)	62 (14.9)
No. 12	12 (52.2)	6 (26.1)	4 (17.4)	0 (0)	1 (4.3)	0 (0)	23 (5.5)
No. 13	10 (45.5)	4 (18.2)	3 (13.6)	3 (13.6)	0 (0)	2 (9.1)	22 (5.3)
No. 14	23 (59.0)	6 (15.4)	4 (10.3)	3 (7.7)	2 (5.1)	1 (2.6)	39 (9.4)

^acalculated by row, ^bcalculated by column.

(28) and 98.4% for HIV-infected clients (unpublished) during the first 12 months after treatment initiation), and subsequent more likelihood of being incarcerated. Of course, the reasons for not re-entry become the next step, which needs to be solved urgently. In addition, we also found the re-entry frequency exceeded once per year among 48.1% clients. Given that repeated drop-out and re-entry could not reach the expected treatment targets, tailored intervention measures are urgently needed for the study population.

China has made impressive progress in the MMT program since 2004. The agencies that were tasked with the program's expansion have been confronted with many challenges (14). The major concern is retention. We found that marital status was associated with re-entry in our study. For many clients, marriage provides the primary form of social support. In China, those who were never married always lived with their parents and other members. The study suggested that being married and having a close relationship with a spouse were associated with better treatment outcomes over time (29). Therefore,

family members and/or spouse potentially played a crucial role in encouraging re-entry (30). It is widely recognized that drug-abuse will cause a huge loss of both life and wealth. For the HIV-infected MMT clients, most of them had lost work capacity and had prolonged unemployment. Economic pressures might force them into re-entry MMT. Literature has demonstrated that a poor knowledge level often contributes to the misconceptions about MMT, which could be potential factors causing drop-out (31). Our study found that clients with lower education levels were associated with lower re-entry frequency. This probably is because those misconceptions lead to immature drop-outs and re-entries (31). Hence, interventions strengthening accurate MMT information propagation should be greatly warranted.

Positive morphine urine results generally indicate heroin use by the clients within the last 2-3 days (32). Heroin use would decrease the retention rate among HIV-infected MMT clients (33). Concurrent heroin use was extremely prevalent among HIV-infected MMT clients, and our 12 month follow-up study has

Table 4. Correlates of re-entry among the drop-outs (n = 577)

Variables	Univariate		Multivariate	
	OR (95% CI) ^a	p	OR (95% CI)	p
Age (years)				
≤ 30	2.27 (1.27-4.07)	0.006	1.20 (0.49-2.94)	0.693
31-35	1.58 (0.97-2.56)	0.066	0.82 (0.40-1.68)	0.587
36-40	1.65 (1.020-2.68)	0.042	0.96 (0.49-1.88)	0.900
≥ 41	1.00		1.00	
Gender				
Male	0.83 (0.39-1.74)	0.825	1.03 (0.40-2.68)	0.955
Female	1.00		1.00	
Marital Status				
Single	1.76 (1.01-3.06)	0.045	2.24 (1.02-4.93)	0.045
Married Currently	1.42 (0.80-2.51)	0.233	2.34 (1.05-5.22)	0.038
Others	1.00		1.00	
Education Level				
Elementary or lower	0.75 (0.38-1.47)	0.399	0.89 (0.34-2.33)	0.814
Junior high school	0.76 (0.41-1.43)	0.396	0.82 (0.34-2.00)	0.667
Senior high school or higher	1.00		1.00	
Employed Status at Baseline				
Unemployed	1.27 (0.88-1.82)	0.200	1.92 (1.12-3.27)	0.017
Employed	1.00		1.00	
Family Relationship at Baseline				
Harmonious	0.77 (0.52-1.15)	0.198	0.93 (0.53-1.63)	0.794
Inharmonious	1.00		1.00	
Mainly Financial Sources at Baseline				
Family and Friends	1.20 (0.84-1.71)	0.331	0.97 (0.58-1.63)	0.914
Others	1.00		1.00	
Duration of Drug Abuse (years)				
≤ 10	0.92 (0.58-1.47)	0.920	0.74 (0.36-1.50)	0.401
11-15	1.18 (0.79-1.77)	0.410	1.14 (0.64-2.01)	0.658
≥ 16	1.00		1.00	
Shared Needles at Baseline				
Yes	1.13(0.79-1.61)	0.515	1.09 (0.65-1.84)	0.723
No	1.00		1.00	
Average Times of Drug Use per Day at Baseline				
≤ 2	1.13(0.78-1.63)	0.523	1.09 (0.65-1.84)	0.732
≥ 3	1.00		1.00	
Frequency of Meeting with Peer Users at Baseline				
none	0.76 (0.42-1.38)	0.367	0.96 (0.43-2.12)	0.915
1-4/month	0.68 (0.43-1.07)	0.093	0.83 (0.46-1.53)	0.557
1-6/week	0.74 (0.47-1.17)	0.192	0.74 (0.39-1.36)	0.344
> 1/day	1.00		1.00	
Multiple Sex Partners at Baseline				
Yes	1.20(0.76-1.92)	0.435	1.30 (0.68-2.48)	0.430
No	1.00		1.00	
Positive Percentages of Urine Tests (%)				
< 40	1.48 (0.94-2.32)	0.089	4.08 (2.21-7.54)	< 0.001
40-80	1.66 (1.08-2.53)	0.020	2.52 (1.39-4.56)	0.002
> 80	1.00		1.00	
Average Maintenance Dose (ml/day)				
≥ 60	2.23 (1.51-3.31)	< 0.001	3.78 (2.21-7.54)	< 0.001
< 60	1.00		1.00	
Percentages of MMT Attendance (%)				
< 20	114.12 (27.33-476.54)	< 0.001	282.08 (62.75-1268.11)	< 0.001
20-49	10.70 (6.10-18.78)	< 0.001	20.75 (10.52-40.93)	< 0.001
50-79	4.36 (2.71-7.00)	< 0.001	6.07 (3.44-10.73)	< 0.001
≥ 80%	1.00		1.00	

Note. ^aOR: Odds Ratio, CI: Confidence Interval, obtained from binary logistic regression analysis.

shown the concurrent heroin use rate reached 98.4% (unpublished data). We found that clients with lower positive percentages of urine morphine tests have more likelihood to return to the MMT, yet have a lower frequency of re-entry. These components should be

considered: *i*) after a period of treatment, addictive syndrome was clearly alleviated, so many clients might consider themselves recuperated enough to leave the program (34). However, not long after leaving MMT, they would experience the abstinence symptoms again

Table 5. Correlates of higher frequency of re-entry among the re-entries (n = 416)

Variables	low No. (%) [*]	moderate No. (%) [*]	frequent No. (%) [*]	OR (95% CI) ^{a,b}	p ^b
Age (years)					
≤ 30	51 (61.4)	17 (20.5)	15 (18.1)	0.63 (0.29-1.37)	0.246
31-35	63 (49.6)	30 (23.6)	34 (26.8)	0.82 (0.43-1.56)	0.547
36-40	68 (51.1)	30 (22.6)	35 (26.3)	0.83 (0.45-1.52)	0.540
≥ 41	34 (46.6)	17 (23.3)	22 (30.1)	1.00	
Gender					
Male	202 (52.1)	89 (22.9)	97 (25.0)	0.80 (0.35-1.84)	0.598
Female	14 (50.0)	5 (17.9)	9 (32.1)	1.00	
Marital Status					
Single	126 (54.8)	48 (20.9)	56 (24.3)	0.90 (0.43-1.88)	0.781
Married Currently	74 (50.7)	32 (21.9)	40 (27.4)	0.81 (0.39-1.69)	0.569
Others	16 (40.0)	14 (35.0)	10 (25.0)	1.00	
Education Level					
Elementary or lower	53 (48.2)	28 (25.5)	29 (26.4)	0.55 (0.27-1.13)	0.104
Junior high school	144 (55.2)	55 (21.1)	62 (23.8)	0.49 (0.26-0.93)	0.030
Senior high school or higher	19 (42.2)	11 (24.4)	15 (33.3)	1.00	
Employed Status at Baseline					
Unemployed	147 (53.8)	60 (22.0)	66 (24.2)	0.71 (0.45-1.11)	0.134
Employed	69 (48.3)	34 (23.8)	40 (28.0)	1.00	
Family Relationship at Baseline					
Harmonious	51 (54.3)	21 (22.3)	22 (23.4)	0.86 (0.52-1.42)	0.558
Inharmonious	165 (51.2)	73 (22.7)	84 (26.1)	1.00	
Mainly Financial Sources at Baseline					
Family and Friends	138 (52.5)	61 (23.2)	64 (24.3)	0.84 (0.55-1.29)	0.433
Others	78 (51.0)	33 (21.6)	42 (27.5)	1.00	
Duration of Drug Abuse (years)					
≤ 10	50 (56.8)	17 (19.3)	21 (23.9)	0.72 (0.39-1.32)	0.288
11-15	98 (54.7)	39 (21.8)	42 (23.5)	0.73 (0.46-1.17)	0.196
≥ 16	68 (45.6)	38 (25.5)	43 (28.9)	1.00	
Shared Needles Drugs at Baseline					
Yes	120 (48.4)	65 (26.2)	63 (25.4)	1.37 (0.89-2.09)	0.149
No	96 (57.1)	29 (17.3)	43 (25.6)	1.00	
Average Times of Drug Use per Day at Baseline					
≤ 2	89 (57.8)	34 (22.1)	31 (20.1)	0.64 (0.41-1.00)	0.050
≥ 3	127 (48.5)	60 (22.9)	75 (28.6)	1.00	
Frequency of Meeting with Peer Users at Baseline					
none	23 (50.0)	8 (17.4)	15 (32.6)	1.40 (0.70-2.79)	0.344
1-4/month	55 (55.0)	20 (20.0)	25 (25.0)	0.90 (0.53-1.51)	0.685
1-6/week	48 (48.0)	30 (30.0)	22 (22.0)	1.28 (0.76-2.16)	0.358
> 1/day	90 (52.9)	36 (21.2)	44 (25.9)	1.00	
Multiple Sex Partners at Baseline					
Yes	46 (58.2)	15 (19.0)	18 (22.8)	0.70 (0.41-1.20)	0.194
No	170 (50.4)	79 (23.4)	88 (26.1)	1.00	
Positive Percentages of Urine Tests (%)					
< 40	73 (65.8)	24 (21.6)	14 (12.6)	0.39 (0.22-0.70)	0.001
40-80	80 (54.8)	32 (21.9)	34 (23.3)	0.65 (0.40-1.05)	0.078
> 80	61 (40.1)	38 (25.0)	53 (34.9)	1.00	
Average Maintenance Dose (ml/day)					
≥ 60	96 (54.5)	41 (23.3)	39 (22.2)	0.92 (0.60-1.40)	0.684
< 60	120 (50.0)	53 (22.1)	67 (27.9)	1.00	
Percentages of MMT Attendance (%)					
< 20	59 (45.7)	27 (20.9)	43 (33.3)	7.24 (2.99-17.55)	<0.001
20-49	47 (38.8)	29 (24.0)	45 (37.2)	14.30 (5.94-34.42)	<0.001
50-79	53 (52.5)	30 (29.7)	18 (17.8)	6.15 (2.55-14.85)	<0.001
≥ 80%	57 (87.7)	8 (12.3)	0 (0)	1.00	

Note. ^a OR: Odds Ratio, CI: Confidence Interval; ^b Obtained from multivariate ordinal logistic regression analysis adjusting for potential confounding variables listed in the table; * Proportions were calculated in the row.

and had to return to MMT; *ii*) the clients with lower positive percentages of urine morphine tests had a stronger desire to abstain from drug use, and if they had drug desire, they would prefer to receive MMT; *iii*) the clients with higher positive percentages of urine morphine tests might have a poorer desire to

abstain from drug use, which subjected them to drug expenditure concerns, and therefore they exhibited repeated drop-out and re-entry.

Doses have already been well documented to be a crucial component of MMT retention in varied settings (20,35-37). Higher doses of MMT are associated with

longer retention (37-39). The prescribed dose should be able to prevent withdrawal, block craving and discourage patients from reverting to heroin use (20). Our study revealed that clients (1) with higher maintenance doses or (2) with higher frequency of drug use at baseline had more likelihood to return to the MMT program. We speculated that those two group clients depended more seriously on heroin use, but given their low affordability for the drug fees, the clients had to return to the MMT program to alleviate the cravings. The US National Institutes of Health has recommended methadone doses should be not less than 60 mg/day (40). However, both staff and clients have a preference for lower doses in China (41). Concurrent heroin use was a common phenomenon among MMT clients (28,42), especially among HIV-infected clients (our unpublished data has shown the concurrent opioid use rate for 12 months was 98.4%), which could directly lead to drop-out (33). A study demonstrated that clients needed higher doses when they continued to use drugs during MMT (43). Also some scholars hold that HIV-infected clients probably require a higher methadone dose (27). However, further research is needed to provide solid evidence.

A daily MMT dose could relieve the drug craving for only 24-36 hours (44). If clients do not sufficiently adhere to the MMT, the effectiveness of the MMT program would be greatly compromised. We found that poorer attendance was associated with both re-entry and higher frequency of re-entry. The literature suggested that MMT-related misconceptions were very prevalent among newly recruited MMT clients in China, which eventually led to poor compliance and drop-outs (31,45). The primary reasons could be *i*) the clients regard MMT as a transient program for drug detoxification, and most of them did not want to remain on treatment once their addictive reactions are alleviated. However, once they leave MMT, they experience the abstinence symptoms again and cannot afford heroin, and they had to return to MMT (22); *ii*) many clients did not intend to terminate the service completely, since they want to switch back and forth freely between heroin use and MMT depending on the affordability for drug fees.

The present study has limitations. First, like most other studies involving high-risk behavior measures, recall bias and deliberate concealment are inevitable. Second, we could not obtain the reasons for not re-entry among those who have been lost to follow-up. Third, the enrolment period of this study lasted for seven years, demographic characteristics, risk behaviors and treatment performance may vary temporally. Fourth, the data of this study was extracted from the Chinese National MMT Program data system. Characteristics related to the participant's HIV infection and antiretroviral treatment status (*e.g.*, CD4 counts, HIV viral load, comorbidities, biochemical testing results particularly liver functions given a substantial proportion of drug users could be co-infected with HCV) might play an important role in re-

entry to MMT. Yet, that information was registered and managed by other special institutions, and we failed to obtain them in this study.

Despite these limitations, this study identified some important implications for future harm reduction programs targeting re-entry among HIV-infected MMT clients in Guangdong. Study results underscore the importance of *i*) providing continuous and efficient MMT consulting and health education interventions to HIV-infected clients as a strategy to address re-entry; also, the study showed that even health professionals had misconceptions about MMT (46). Clinic staff plays a critical role in retaining the participants in treatment, so it is necessary to provide on-going staff training to improve the quality of their services, increase their understanding of drug addiction and enhance their professionalism; and *ii*) strengthening and/or improving supervision measures to potentially improve MMT attendance. In addition, the effectiveness of higher-dose MMT vs. the standard dose deserves further research investigation.

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References

1. World Health Organization. Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. Geneva, 2009.
2. World Health Organization. Information sheet on opioid overdose. Geneva 2014.
3. Gambashidze N, Sikharulidze Z, Piralishvili G, Gvakharia N. Evaluation of pilot methadone maintenance therapy in Georgia (Caucasus). *Georgian Med News*. 2008;25-30.
4. Gowing LR, Farrell M, Bornemann R, Sullivan LE, Ali RL. Brief report: Methadone treatment of injecting opioid users for prevention of HIV infection. *J Gen Intern Med*. 2006; 21:193-5.
5. Michels II, Stover H, Gerlach R. Substitution treatment for opioid addicts in Germany. *Harm Reduct J*. 2007; 4:5.
6. MacArthur GJ, Minozzi S, Martin N, Vickerman P, Deren S, Bruneau J, Degenhardt L, Hickman M. Opiate substitution treatment and HIV transmission in people who inject drugs: Systematic review and meta-analysis. *BMJ*. 2012; 345:e5945-e5945.
7. Nguyen TTM, Nguyen LT, Pham MD, Vu HH, Mulvey KP. Methadone maintenance therapy in Vietnam: An overview and scaling-up plan. *Adv Prev Med*. 2012;

- 2012:1-5.
8. Xiao L, Wu Z, Luo W, Wei X. Quality of Life of Outpatients in Methadone Maintenance Treatment Clinics. *J Acquir Immune Defic Syndr.* 2010; 53:S116-S120.
 9. Chou YC, Shih SF, Tsai WD, Li CS, Xu K, Lee TS. Improvement of quality of life in methadone treatment patients in northern Taiwan: A follow-up study. *BMC Psychiatry.* 2013; 13:190.
 10. Sun HM, Li XY, Chow EPF, Li T, Xian Y, Lu YH, Tian T, Zhuang X, Zhang L. Methadone maintenance treatment programme reduces criminal activity and improves social well-being of drug users in China: A systematic review and meta-analysis. *BMJ Open.* 2015; 5:e005997-e005997.
 11. Mathers BM, Degenhardt L, Phillips B, Wiessing L, Hickman M, Strathdee SA, Wodak A, Panda S, Tyndall M, Toufik A, Mattick RP. Global epidemiology of injecting drug use and HIV among people who inject drugs: A systematic review. *Lancet.* 2008; 372:1733-45.
 12. Sullivan SG, Wu Z. Rapid scale up of harm reduction in China. *Int J Drug Policy.* 2007; 18:118-128.
 13. Wu Z, Rou K, Cui H. The HIV/AIDS epidemic in China: History, current strategies and future challenges. *AIDS Educ Prev.* 2004; 16:7-17.
 14. Yin W, Hao Y, Sun X, Gong X, Li F, Li J, Rou K, Sullivan SG, Wang C, Cao X, Luo W, Wu Z. Scaling up the national methadone maintenance treatment program in China: Achievements and challenges. *Int J Epidemiol.* 2010; 39:ii29-ii37.
 15. The National Health and Family Planning Commission of the People's Republic of China. The national health and family planning commission published online. <http://www.nhfpc.gov.cn/zhuz/zxfb1/201506/f2bd445f5ec04085adb9b84d995cb22b.shtml> (accessed June 26, 2015). (in Chinese)
 16. Zhang L, Chow EP, Zhuang X, Liang Y, Wang Y, Tang C, Ling L, Tucker JD, Wilson DP. Methadone maintenance treatment participant retention and behavioural effectiveness in China: A systematic review and meta-analysis. *PLoS One.* 2013; 8:e68906.
 17. Pang L, Hao Y, Mi G, Wang C, Luo W, Rou K, Li J, Wu Z. Effectiveness of first eight methadone maintenance treatment clinics in China. *AIDS.* 2007; 21 Suppl 8:S103-7.
 18. Zou X, Ling L, Zhang L. Trends and risk factors for HIV, HCV and syphilis seroconversion among drug users in a methadone maintenance treatment programme in China: A 7-year retrospective cohort study. *BMJ Open.* 2015; 5:e008162.
 19. Dai J, Zhao L, Liang Y. Policy implementation of methadone maintenance treatment and HIV infection: Evidence from Hubei province, China. *Subst Abuse Treat Prev Policy.* 2013; 8:38.
 20. Zhou K, Zhuang G. Retention in methadone maintenance treatment in mainland China, 2004-2012: A literature review. *Addict Behav.* 2014; 39:22-29.
 21. Lin C, Hung C, Peng C, Chao E, Lee TS. Factors associated with methadone treatment duration: A Cox regression analysis. *PLoS One.* 2015; 10:e0123687.
 22. Zhang L, Zou X, Zhang D, Li X, Zhao P, Ling L. Investigation of repeat client drop-out and re-enrolment cycles in fourteen methadone maintenance treatment clinics in Guangdong, China. *PLoS One.* 2015; 10:e0139942.
 23. Bell J, Burrell T, Indig D, Gilmour S. Cycling in and out of treatment; participation in methadone treatment in NSW, 1990–2002. *Drug Alcohol Depen.* 2006; 81:55-61.
 24. Liu H, Grusky O, Li X, Ma E. Drug users: A potentially important bridge population in the transmission of sexually transmitted diseases, including AIDS, in China. *Sex Transm Dis.* 2006; 33:111-117.
 25. Tran BX, Ohinmaa A, Duong AT, Do NT, Nguyen LT, Nguyen QC, Mills S, Jacobs P, Houston S. Changes in drug use are associated with health-related quality of life improvements among methadone maintenance patients with HIV/AIDS. *Qual Life Res.* 2012; 21:613-623.
 26. National Working Group on Community-based Methadone Maintenance Treatment for Opium Dependents, National Training Center for Methadone Maintenance Treatment. Clinical guidelines of methadone maintenance treatment. 2005.
 27. Liu E, Rou K, McGoogan JM, Pang L, Cao X, Wang C, Luo W, Sullivan SG, Montaner JSG, Bulterys M, Detels R, Wu Z. Factors associated with mortality of HIV-positive clients receiving methadone maintenance treatment in China. *J Infect Dis.* 2013; 208:442-453.
 28. Luo X, Zhao P, Gong X, Zhang L, Tang W, Zou X, Chen W, Ling L. Concurrent heroin use and correlates among methadone maintenance treatment clients: A 12-month follow-up study in Guangdong Province, China. *Int J Environ Res Public Health.* 2016; 13:305.
 29. Heinz AJ, Wu J, Witkiewitz K, Epstein DH, Preston KL. Marriage and relationship closeness as predictors of cocaine and heroin use. *Addict Behav.* 2009; 34:258-263.
 30. Liu H, Li J, Lu Z, Liu W, Zhang Z. Does Chinese culture influence psychosocial factors for heroin use among young adolescents in China? A cross-sectional study. *BMC Public Health.* 2010; 10:563.
 31. Xu H, Gu J, Lau JTF, Zhong Y, Fan L, Zhao Y, Hao C, He W, Ling W. Misconceptions toward methadone maintenance treatment (MMT) and associated factors among new MMT users in Guangzhou, China. *Addict Behav.* 2012; 37:657-662.
 32. Couper FJ, Logan BK. Drug and human performance fact sheets. <https://one.nhtsa.gov/people/injury/research/job185drugs/index.htm> (accessed April, 2014).
 33. Jiang H, Cao X, Wang C, Luo W, Li J, Rou K, Zhang B, Fang Y, Li C. Study on the adherence and related determinants among HIV-positive clients under methadone maintenance treatment in Dali, Yunnan province from 2005 to 2013. *Chin J Epidemiol (in Chinese).* 2014; 35:255-258.
 34. Gu J, Xu H, Lau JTF, Hao Y, Zhong Y, Fan L, Zhao Y, Hao C, Ling W. Misconceptions predict dropout and poor adherence prospectively among newly admitted first-time methadone maintenance treatment clients in Guangzhou, China. *Addiction.* 2012; 107:1641-1649.
 35. Wickersham JA, Zahari MM, Azar MM, Kamarulzaman A, Altice FL. Methadone dose at the time of release from prison significantly influences retention in treatment: Implications from a pilot study of HIV-infected prisoners transitioning to the community in Malaysia. *Drug Alcohol Depen.* 2013; 132:378-382.
 36. Yang F, Lin P, Li Y, He Q, Long Q, Fu X, Luo Y. Predictors of retention in community-based methadone maintenance treatment program in Pearl River Delta, China. *Harm Reduct J.* 2013; 10:3.
 37. Bao YP, Liu ZM, Epstein DH, Du C, Shi J, Lu L. A meta-analysis of retention in methadone maintenance by dose and dosing strategy. *Am J Drug Alcohol Abuse.* 2009;

- 35:28-33.
38. Amato L, Davoli M, Perucci CA, Ferri M, Faggiano F, Mattick RP. An overview of systematic reviews of the effectiveness of opiate maintenance therapies: Available evidence to inform clinical practice and research. *J Subst Abuse Treat.* 2005; 28:321-9.
 39. Strain EC, Bigelow GE, Liebson IA, Stitzer ML. Moderate- vs high-dose methadone in the treatment of opioid dependence: A randomized trial. *JAMA.* 1999; 281:1000-5.
 40. NIH Consensus Conference. Effective medical treatment of opiate addiction. National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction. *JAMA.* 1998; 280:1936-43.
 41. Lin C, Wu Z, Detels R. Family support, quality of life and concurrent substance use among methadone maintenance therapy clients in China. *Public Health.* 2011; 125:269-274.
 42. Wang R, Ding Y, Bai H, Duan S, Ye R, Yang Y, Wang J, Tang R, Gao M, He N. Illicit heroin and methamphetamine use among methadone maintenance treatment patients in Dehong Prefecture of Yunnan Province, China. *PLoS One.* 2015; 10:e0133431.
 43. Fareed A, Casarella J, Amar R, Vayalapalli S, Drexler K. Methadone maintenance dosing guideline for opioid dependence, a literature review. *J Addict Dis.* 2010; 29:1-14.
 44. Joseph H, Stancliff S, Langrod J. Methadone maintenance treatment (MMT): A review of historical and clinical issues. *Mt Sinai J Med.* 2000; 67:347-364.
 45. Gossop M, Stewart D, Marsden J. Treatment process components and heroin use outcome among methadone patients. *Drug Alcohol Depen.* 2003; 71:93-102.
 46. Leavitt SB. Methadone dosing & safety in the treatment of opioid addiction. *Funct Ecol.* 2001; 15:696-699.

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