

BMJ Open Trends and factors in human immunodeficiency virus and/or hepatitis C virus testing and infection among injection drug users newly entering methadone maintenance treatment in Guangdong Province, China 2006-2013: a consecutive cross sectional study

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ABSTRACT

Objectives To assess trends and related factors in HIV and/or hepatitis C virus (HCV) antibody testing and infection among injection drug users (IDUs) newly entering methadone maintenance treatment (MMT) in Guangdong Province, China.

Method Consecutive cross sectional surveys were conducted in 14 MMT clinics from July 2006 to December 2013 in Guangdong Province, China. IDUs were excluded if they were re-enrolled or referred from other MMT clinics. Trend tests were used to examine HIV and/or HCV testing and infection, sociodemographic characteristics, drug use related behaviours and the past 3 month sexual behaviours on enrolment. Multivariate logistic regression was used to identify correlates of HIV and/or HCV testing and infection.

Results 7539 IDUs with an average age of 35.6±6.2 years were newly enrolled with a history of injection for an average of 11.8±4.9 years. The average frequency of injection before enrolment had been increasing. HIV, HCV and HIV/HCV dual testing increased from 2006 to 2013 ($p_{\text{trend}} < 0.001$). However, all three types of infections remained stable ($p_{\text{trend}} > 0.05$) until reaching a peak in 2011, excluding the first year. Associating with fellow drug users 1–4 times during the past month, injecting for 15+ years and having multiple sexual partners during the past 3 months predicted higher percentages for HIV and/or HCV testing ($p < 0.05$), while those injecting 4+ times per day in the past month and those who had ever shared needles were less likely to take both tests ($p < 0.05$). Having multiple sexual partners, a longer duration of injection drug use and sharing needles or sharing more frequently were major risk factors for HIV, HCV and HIV/HCV co-infection ($p < 0.05$).

Conclusions The prevalence of HIV and HCV were high and quite stable among new IDU entrants in MMT. Publicising MMT, routine screening, and behavioural and structural interventions is needed.

INTRODUCTION

Globally, injection drug users (IDUs) account for approximately 41.4% of people with drug

Strengths and limitations of this study

- This is a long term consecutive study with a large sample size.
- Compared with previous research, it is the first study focusing on injection drug users newly entering Chinese methadone maintenance treatment programmes.
- Self-reported sensitive data were subjected to recall and social desirability bias.

use disorders.¹ This subgroup represents one of the most at risk populations for HIV or hepatitis C virus (HCV) infection, while also suffering from a variety of chronic and acute drug related morbidities and mortality.² The estimated global prevalence of HIV and HCV among IDUs is as high as 14% and 67%,^{1 3} respectively, and IDUs account for more than half of the 2.3 million HIV/HCV co-infected people worldwide.⁴ In China, there were 2.17 million IDUs in 2011.⁵ The substantial numbers of IDUs has been a major driver in the ever growing HIV and HCV cases, representing a much worse epidemic compared with other high risk populations (eg, men who have sex with men, female sex workers).^{6 7} National estimates suggest that HIV prevalence was 9.1% in 2011,⁶ and HCV prevalence was 65.0% in 2012 among Chinese IDUs.⁷

Correcting relevant risk behaviours among IDUs is a major method for preventing HIV and HCV infections. Studies have shown that a longer history of injection, unsafe sexual behaviours and sharing needles/syringes

are major risk factors for the spread of HIV and HCV infection among IDUs.^{8,9} The methadone maintenance treatment (MMT) programme, a community based treatment, was initiated in 2004 and officially launched in 2006 in China, and has been shown to be an effective strategy to curtail drug use, HCV/HIV incidence and injection related risk behaviours.^{10,11} By 2015, there were 767 MMT clinics in 28 provinces in China, serving about 190 000 clients.¹² Understanding trends in HIV and HCV infections and related factors among new IDU entrants into MMT would provide evidence supporting the intervention for this key population and guidance for improving the MMT programme. A study has shown that the national prevalence of HCV among drug users on initial enrolment in the MMT programme decreased from 66.8% in 2005 to 45.9% in 2012,¹³ but few studies have reported the trends for HIV and HCV infections and correlated risk factors among IDUs on MMT entry. Even fewer studies have explored the risk factors related with HIV/HCV co-infection among new IDU entrants into MMT in China.

Routine antibody screening for HIV and HCV is a crucial prevention tool for curtailing the spread of these viruses. It is likely that IDUs who are diagnosed HIV positive might facilitate their timely initiation of antiretroviral therapy (ART) and lower the likelihood of AIDS related morbidity and mortality.^{14,15} HIV testing is also associated with a lower frequency of risky behaviours,¹¹ and evidence has indicated that MMT could promote initiation of ART among IDUs.¹⁶ The WHO highlights that testing interventions are associated with an increased HCV treatment rate and might reduce mortality in the long term. In spite of the fact that HIV and HCV antibody testing are recommended for all IDUs on enrolment into MMT, only 75.7% and 78.4% of new entrants ever receive HIV and HCV testing, respectively.¹⁷ Nonetheless, the trends for HIV and HCV testing as well as correlated factors among new IDU entrants into MMT are not clear.

Guangdong Province is located in southern China and has the largest number of registered drug users (457 000), accounting for one-sixth of the total 2 760 000 registered drug users in China.¹⁸ By January 2016, 63 MMT clinics had been established in Guangdong,¹⁹ serving approximately 9.3% of all IDUs in the Chinese national MMT programmes.²⁰ The issues of HIV/HCV infection, seroconversion and testing uptake have been analysed using Guangdong MMT data,^{10,21,22} but previous studies mainly focused on general MMT entrants rather than on new IDU entrants.

In the present study, we assessed: the trends in HIV and HCV antibody testing; the trends for HIV, HCV and HIV/HCV co-infections; and the correlates of both testing and infection among new IDU entrants to MMT in Guangdong Province from 2006 to 2013.

METHODS

Study design and participants

This is a secondary data analysis conducted among 14 MMT clinics located in nine cities in Guangdong

Province, China. The study sample comprised IDUs newly enrolled in MMT from July 2006 to December 2013. Participants were eligible if they were: (1) willing to provide written informed consent; (2) were classified as current 'injecting' or 'mixed' (injection and non-injection) drug users; (3) were diagnosed with opioid dependence according to the Chinese Classification of Mental Disorders, version III, criteria; and (4) were >18 years of age. Participants were excluded if they were re-enrolled or referred from other MMT clinics in Guangdong Province. The study protocol was reviewed and approved by the institutional review board of the School of Public Health, Sun Yat-sen University, Guangzhou, China (No 2013–26).

Data collection

An interviewer administered survey was conducted among participants on enrolment into the MMT programme to collect data on their sociodemographic characteristics (gender, age, ethnicity, marital status, educational level, occupation, relationship with families and association with fellows drug users in the past month), drug use related behaviours (duration of injection, injection times per day in the past month, ever shared needles and times of sharing needles in the past month) and past 3 month sexual behaviours (including number of sexual partners). This information was further entered into the National Unified MMT Management System. Thus all relevant data for our current analysis were abstracted from the system. According to current guidelines, all new MMT clients should be tested for HIV and HCV at enrolment. In our study, on enrolment and every 6 months after MMT enrolment, each participant was tested for HIV-1/2 and HCV, excluding those already confirmed. HIV antibodies were screened using the immunocolloidal golden method (Aibo Biotech Company, China) in the MMT clinics, with positive results confirmed by the local Centre for Disease Prevention and Control using western blot and two positive enzyme linked immunosorbent assays (ELISAs) (ELISA-1, Beijing BGI-GBI Biotech, Co Ltd, China; ELISA-2, fourth generation ELISA, BioMerieux by, The Netherlands). HCV antibodies were tested using ELISA (Aibo Biotech Company). In this study, we limited the screening period to within the first 6 months after IDUs were enrolled into the MMT programme. We only assessed the trends in HIV infection, HCV infection, HIV/HCV co-infection and related issues among those who had received HIV testing, HCV testing and HIV/HCV dual testing.

Statistical analysis

First, we used frequency distributions and percentages to describe the sociodemographic and behavioural characteristics of the participants by year of enrolment (2006–2013). We used χ^2 trend tests to examine whether the distribution of sociodemographic factors, risky behaviours, HIV and/or HCV testing, and HIV and/or HCV infection changed significantly over time.

Then, bivariate and multivariate logistic regression analyses were conducted to individually assess factors that were associated with HIV testing (tested vs not tested), HCV testing (tested vs not tested) or HIV/HCV dual testing (tested for both vs tested for one and not tested). We also used the same techniques to assess correlates with HIV infection (HIV positive vs HIV negative), HCV infection (HCV positive vs HCV negative) and HIV/HCV co-infection (co-infected vs not co-infected). To build the multivariate regression model, variables significant ($p < 0.05$) in the bivariate model were initially selected to be entered, followed by a stepwise forward selection procedure to only retain variables with a p value < 0.05 to generate the final multivariate model. Data were analysed using SAS V.9.4.

RESULTS

Demographic and behavioural characteristics

A total of 7539 new IDU entrants were enrolled in the study. The average age was 35.9 ± 6.2 years (range 18–59) and the average duration of being an IDU was 11.8 ± 4.9 years. In general, most of these participants were men (93.2%), Han Chinese (99.2%), unmarried (56.4%), junior high school educated (65.0%), unemployed (61.9%), reporting harmonious relationships with their families (92.8%) and had associated with fellows drug uses at least once during the past month (88.8%). About 27.9% injected four or more times per day during the past month, 22.8% had ever shared needles, 7.2% shared needles during the past month and 8.8% had multiple

sexual partners in the past 3 months. The proportion of those who were < 30 years old, Han Chinese and had ever shared needles decreased over time ($p_{\text{trend}} < 0.01$) while the proportion of those with an educational level of primary school or above, an injection history of 15 or more years or who had associated with fellow drug uses more than once per day had increased ($p_{\text{trend}} < 0.001$). The average duration of injection drug use increased from 11.0 ± 3.8 years to 14.5 ± 5.7 years (see online supplementary table 1).

HIV/HCV antibody testing for new IDU entrants

Among the participants, 91.9% (6871/7539, 95% CI 90.4–91.7%), 86.9% (6557/7539, 95% CI 86.2–87.8%) and 80.9% (6099/7539, 95% CI 80.0–81.8%) received HIV, HCV and both HIV/HCV antibody testing within 6 months after enrolment, respectively. The overall trends for HIV, HCV and both HIV/HCV antibody testing from 2006 to 2013 are shown in figure 1. Our data suggest that the percentages of the three types of tests increased significantly during the study period ($p_{\text{trend}} < 0.001$). Except for the first and fourth years (2006 and 2009), there was no significant difference between HIV and HCV antibody testing rates ($p > 0.05$).

HIV and/or HCV testing based on different sociodemographic and behavioural characteristics are shown in the online supplementary table 2. After adjusting for potential confounding variables, multivariate logistic regression analyses suggested that injection four or more times per day in the past month was associated with a

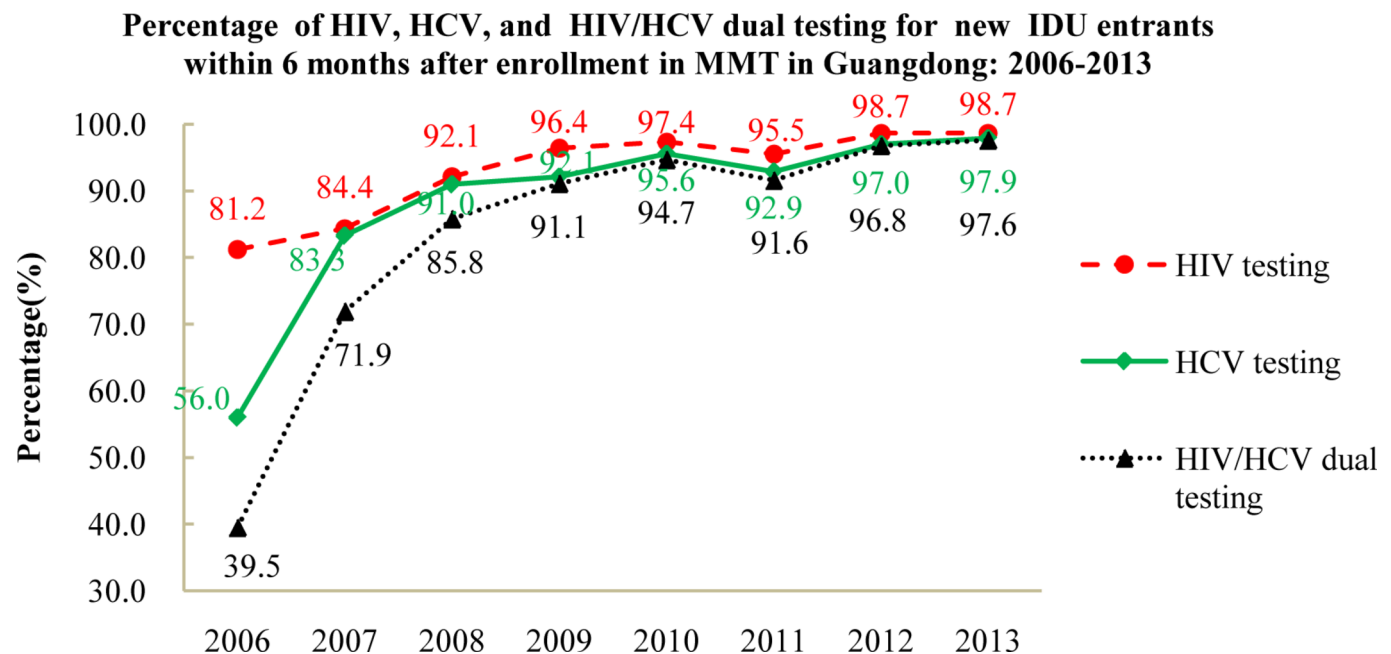


Figure 1 Percentage of HIV, hepatitis C virus (HCV) and HIV/HCV dual testing for new injection drug user entrants within 6 months after enrolment in methadone maintenance treatment (MMT) in Guangdong, 2006–2013. The red broken line represents the percentage of HIV testing, which increased from 81.2% in 2006 to 98.7% in 2013 ($\chi^2_{\text{trend}} = 266.94$, $p_{\text{trend}} < 0.001$). The green solid line represents the percentage of HCV testing, which increased from 56.0% in 2006 to 97.9% in 2013 ($\chi^2_{\text{trend}} = 462.68$, $p_{\text{trend}} < 0.001$). The black dotted line represents the percentage of combined HIV/HCV testing, which increased from 39.2% in 2006 to 97.6% in 2013 ($\chi^2_{\text{trend}} = 834.49$, $p_{\text{trend}} < 0.001$).

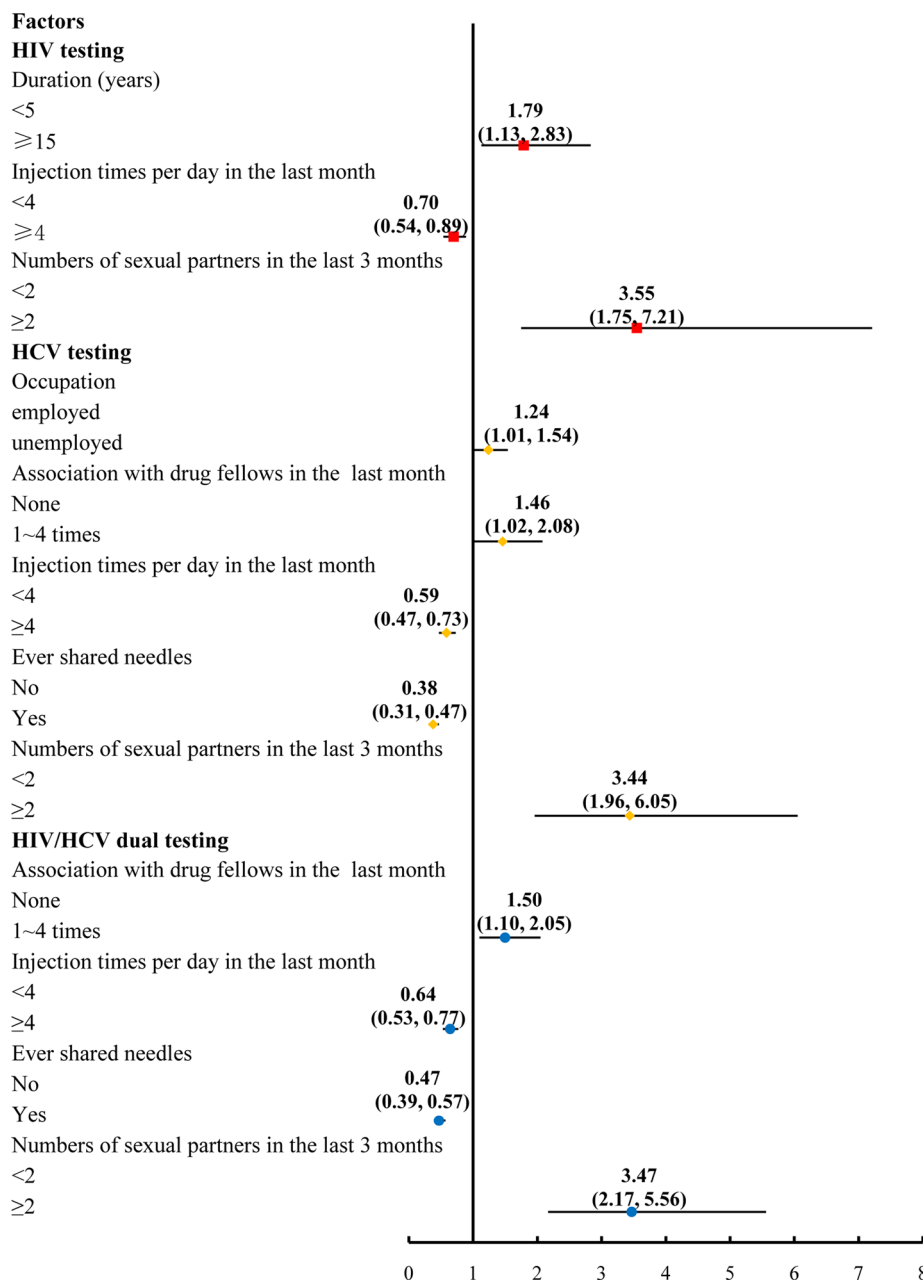


Figure 2 Correlates with HIV, hepatitis C virus (HCV) and HIV/HCV dual testing for new injection drug user entrants within 6 months after enrolment in methadone maintenance treatment, based on multiple logistic regression.

lower likelihood of testing for HIV (adjusted OR (aOR) 0.70, 95% CI 0.54 to 0.89), HCV (aOR 0.59, 95% CI 0.47 to 0.73) and dual testing (aOR 0.64, 95% CI 0.53 to 0.77), while having multiple sexual partners during the past 3 months was associated with a higher likelihood of HIV testing (aOR 3.55, 95% CI 1.75 to 7.21), HCV testing (aOR 3.44, 95% CI 1.96 to 6.05) and dual testing (aOR 3.47, 95% CI 2.17 to 5.56). Meanwhile, we found injection for 15 or more years also had a higher likelihood of undergoing HIV testing (AOR 1.79, 95% CI 1.13 to 2.83), while associating with fellow drug users for 1–4 times during the past month and ever sharing needles had a lower likelihood of HCV testing and dual testing (figure 2).

HIV and/or HCV infection for new IDU entrants

The overall trends for HIV infection, HCV infection and HIV/HCV co-infection from 2006 to 2013 are shown in figure 3. Among participants receiving testing for HIV and/or HCV, 10.6% (728/6871, 95% CI 9.9–11.3%) were HIV infected, 80.5% (5281/6557, 95% CI 79.5%–81.5%) were HCV infected and 5.0% (302/6099, 95% CI 4.5–5.5%) were HIV/HCV co-infected. Among those being tested for HIV and HCV, 67.0% of HIV infected IDUs were co-infected with HCV.

The prevalence of HIV infection was 34.1% in 2006 but sharply decreased to 7.1% in the following year ($\chi^2=260.08$, $p<0.001$) and then remained stable ($\chi^2_{\text{trend}}=0.19$, $p_{\text{trend}}=0.667$) until an increase to 11.5% in

Prevalence of HIV infection, HCV infection, HIV/HCV co-infection for new IDU entrants in MMT in Guangdong: 2006-2013

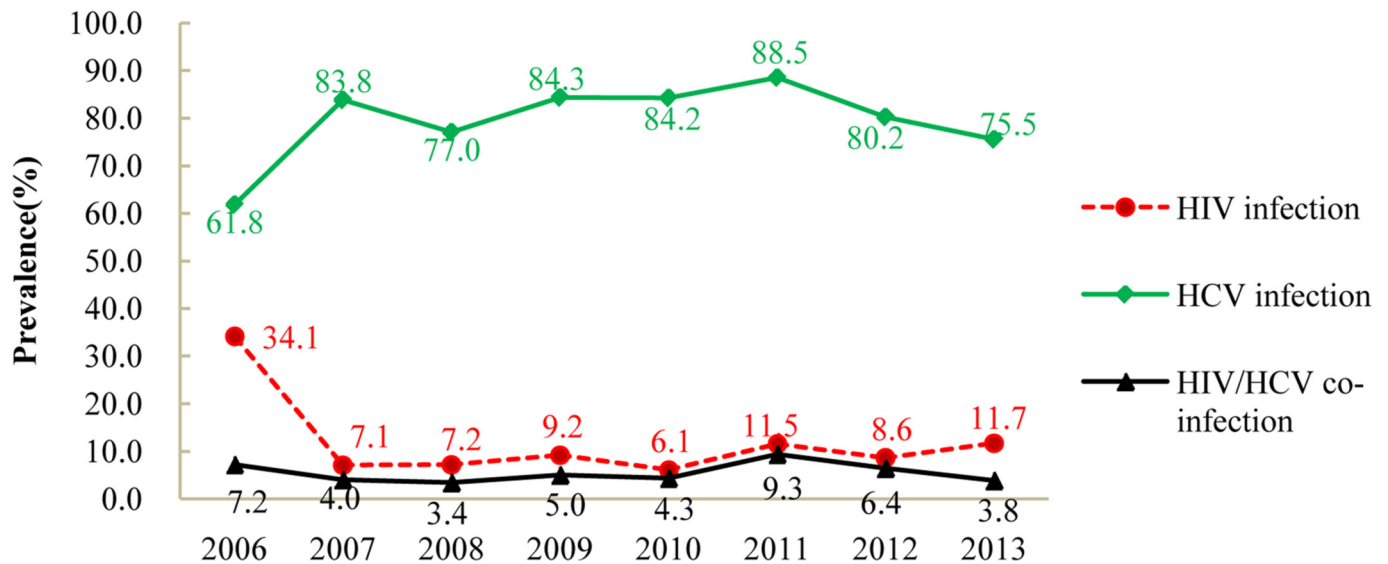


Figure 3 Prevalence of HIV infection, hepatitis C virus (HCV) infection and HIV/HCV co-infection for new injection drug user entrants in methadone maintenance treatment in Guangdong, 2006–2013. The red broken line represents the prevalence of HIV infection, the green solid line represents the prevalence of HCV infection and the black solid line represents the prevalence of HIV/HCV co-infection.

2011, a peak for HIV infection, and remained steady during the last 3 years of the study ($\chi^2_{\text{trend}}=0.04$, $p=0.879$). The prevalence of HCV infection was 61.8% in 2006 and sharply increased to 83.8% in the next year ($\chi^2=98.61$, $p<0.001$), then stabilised ($\chi^2_{\text{trend}}=0.49$, $p_{\text{trend}}=0.484$) until reaching the zenith of 88.5% in 2011, then sharply decreased to 75.5% in 2013 ($\chi^2_{\text{trend}}=30.57$, $p_{\text{trend}}<0.001$). The prevalence of HIV/HCV co-infection was 7.2% in 2006 and decreased to 4.0% in 2007 ($\chi^2=5.67$, $p=0.017$), then stabilised ($\chi^2_{\text{trend}}=0.64$, $p_{\text{trend}}=0.424$) until a leap to 9.3% in 2011, but then decreased to 3.8% in the last year of the study ($\chi^2_{\text{trend}}=11.50$, $p_{\text{trend}}<0.001$; see figure 3).

HIV and/or HCV infection based on different socio-demographic and behavioural characteristics are shown in the online supplementary table 3. After adjusting for potential confounding variables, for HIV infection, participants with a longer duration of injecting (eg, 10–14 years: aOR 2.28, 95% CI 1.45 to 3.57), ever sharing needles (aOR 6.28, 95% CI 5.24 to 7.53) and having multiple sex partners during the past 3 months (aOR 3.91, 95% CI 3.12–4.90) had higher odds, while those with a higher educational level (eg, senior high school or above: aOR 0.53, 95% CI 0.38 to 0.74) had lower odds (figure 4A). For HCV infection, those who were older (eg, ≥ 45 years old: aOR 1.45, 95% CI 1.06 to 1.97), unmarried (eg, single: aOR 1.33, 95% CI 1.15 to 1.53), having non-harmonious relationships with their families (aOR 1.41, 95% CI 1.05 to 1.89), associating with fellow drug users during the past month 1–6 times per day (aOR 1.59, 95% CI 1.25 to 2.02), having a longer duration of injection (eg, ≥ 15 years: aOR: 2.55, 95% CI 1.99 to 3.46), injecting four or more times per day in the past 30 days

(aOR 1.36, 95% CI 1.16 to 1.60), sharing needles more than four times in the past month (aOR 1.30, 95% CI 1.11 to 1.52) and having multiple sex partners during the past 3 months (aOR 1.58, 95% CI 1.21 to 2.05) were more likely to be HCV infected (figure 4B). For HIV/HCV co-infection, those with a longer duration of injection (eg, 10–14 years: aOR 2.23, 95% CI 1.19 to 4.17), injecting four or more times per day in the past 30 days (aOR 1.43, 95% CI 1.09 to 1.86), ever sharing needles (aOR 4.33, 95% CI 3.37 to 5.55) and having multiple sex partners during the past 3 months (aOR 7.65, 95% CI 5.90 to 9.92) had a higher likelihood of co-infection, while those with a higher educational level (eg, senior high school or above: aOR 0.64, 95% CI 0.41 to 0.99) were less likely to be co-infected (figure 4C).

DISCUSSION

This is the first study to report the trend in HIV/HCV testing and infections among new IDU entrants into MMT programmes. In our study, 91.9% (95% CI 90.4% to 91.7%) and 86.9% (95% CI 86.2% to 87.8%) of IDUs received HIV and HCV testing within 6 months after programme entry, which was a higher rate than that among general drug users.^{13 17} However, only 80.9% (95% CI 80.0% to 81.8%) received both HIV and HCV testing. During the first few years of our study, especially in 2006, the percentage of HIV testing was higher than HCV testing, which may be related to the varying government initiated intervention emphasis on HIV and HCV in China. The Chinese MMT programme was originally started with the purpose of curbing the epidemic of HIV

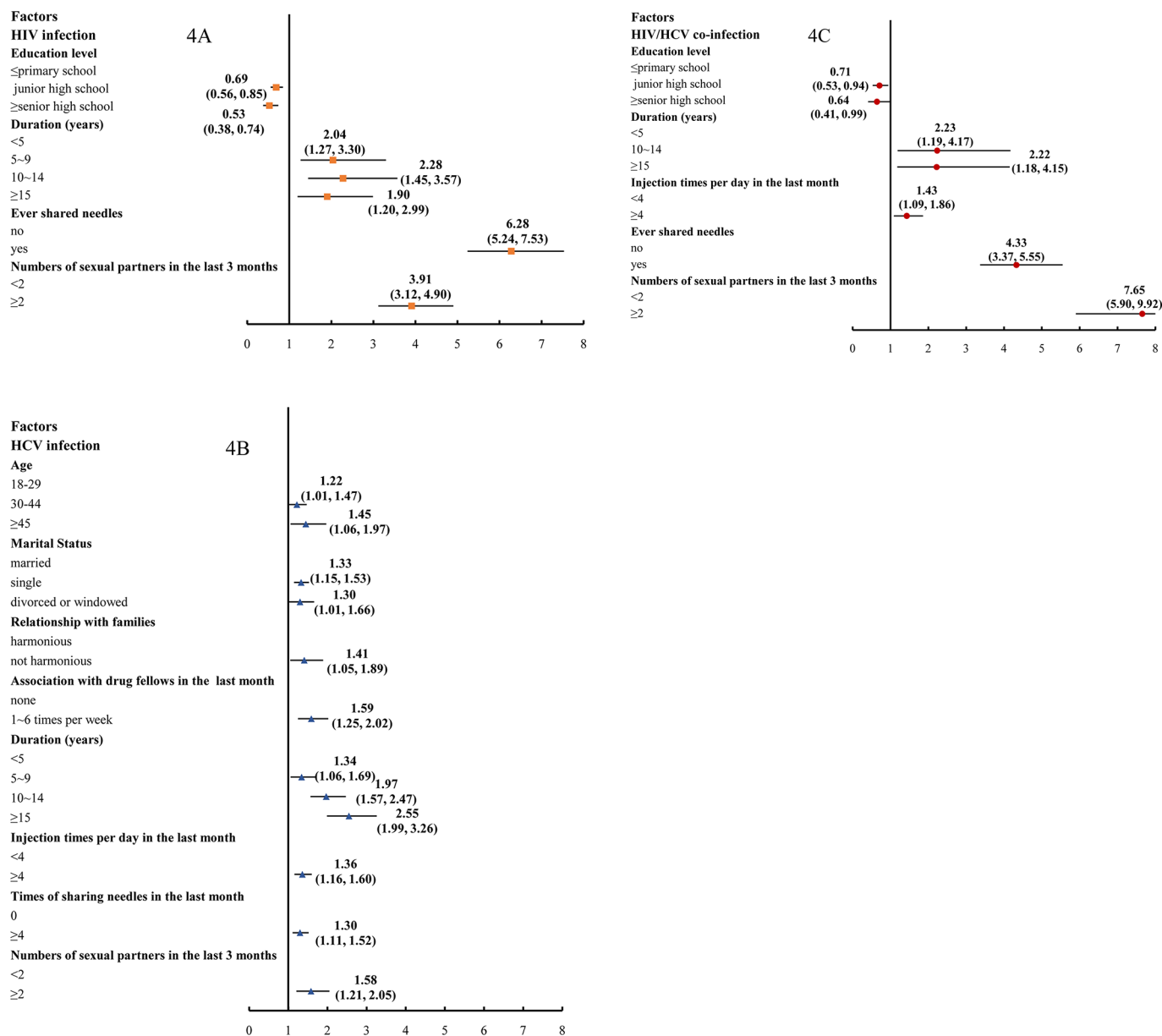


Figure 4 Factors associated with HIV infection, HCV infection, HIV/HCV co-infection for new injection drug user (IDU) entrants in methadone maintenance treatment (MMT), based on multiple logistic regression.

and has already made substantial achievements in the past decade.²⁰

Our estimated overall prevalence of HIV and HCV infection among new IDU entrants in MMT in Guangdong Province was 10.6% (95% CI 9.9% to 11.3%) and 80.5% (95% CI 79.5% to 81.5%), respectively. The prevalence of HIV infection was similar to the national prevalence among IDUs in China (9.1%, 95% CI 8.0% to 10.5%),⁶ while the prevalence of HCV infection was higher than the national estimates (71.7%, 95% CI 71.5% to 71.9%).¹³ In our study, we found a much higher prevalence of HIV infection than that among the general population and non-IDUs^{23 24}; more than half of HIV infected participants were HCV co-infected. In general, the HIV/HCV co-infection rate among new IDU entrants in MMT in Guangdong Province was low (5.0%,

95% CI 4.5% to 5.5%) and similar to the national prevalence among all drug users in MMT (4.6%, 95% CI 2.9% to 7.2%).²³ We speculate that there are two reasons for our observed higher prevalence in this study. On the one hand, the testing rate for both HIV and HCV was relatively low, and those undetected tended to have a history of sharing needles and a higher frequency of injecting, which may result in underestimation of infection. On the other hand, this may correlate with the different nature of transmission dynamics between HIV and HCV. Most HCV infections are likely to occur within the first few years of injecting, compared with HIV infection.²⁵ In the long term, significantly higher rates of co-infection may be found in IDUs if they do not receive any treatment. Thus, in this respect, earlier intervention for IDUs is beneficial for prevention and control of HIV/HCV.

In our study, despite the low testing rate for HIV in 2006, the HIV infection was high (34.1%). One explanation could be that during the first years of MMT in China, HIV infected IDUs would have been more likely to participate in the programme with the aim of controlling disease progression. After excluding the first year (2006), the rates for HIV, HCV and HIV/HCV co-infection were fairly stable until 2011, which was a peak for the three types of infection. This may correlate with a national policy on drug control. In 2011, China issued their newest drug regulations, making strict and specific instructions for drug addicts to participate in community based treatment.²⁶ It states, "For drug addicts, country and municipal public security organs can order them to receive community rehabilitation, issue the order to drug addicts and their family members, and notify their street office of domicile or residence". This may have resulted in higher enrolment rates for those previously undetected HIV/HCV infected IDUs. Further research on the impact of the regulations on MMT enrolment rates is needed. In any event, it went a long way towards prevention and control of HIV/HCV infection for the Chinese MMT programme.

There are two major approaches to curbing HIV and HCV infection: prevention of new infections (primary prevention) and management of current infections (secondary prevention). Correcting related risk factors is a key element for primary prevention. We found having multiple sexual partners, a longer duration of injecting and sharing needles or sharing more frequently were major risk factors for HIV, HCV and HIV/HCV co-infection, similar to the results from other studies,^{13 27 28} suggesting some measures, such as promotion of safe sex education and use of sterile needles and syringes, should be strengthened. Although MMT clinics provide condoms to clients, the percentage of condom use was reported to be relatively low (38–52%).²⁹ We only investigated 'condom use in the last sex act' but more than 30% of subjects (those having more than one sexual partners) did not reply. Moreover, some studies have shown that condom use in the last sex act was not related to HIV/HCV infection.²¹ Therefore, we did not use data on condom use, but we found that 8.8% of IDUs had had multiple sexual partners during the past 3 months, and there was no downward trend for the percentage during the study period. In addition, we found the average age for IDUs among new entrants was 35.6±6.2 years, but with an average injecting duration or 11.8±4.9 years, this means that most entrants began abusing drugs at <25 years of age. The average duration of injection and the proportion of those injecting for more than 15 years increased steadily. Thus expanding publicity about MMT, especially among young IDUs, and calling for IDUs to enrol in MMT earlier are immediately needed. Unlike other investigations,³⁰ we found being female was not a risk factor for infections among IDUs. In previous studies, a high proportion of females who injected drugs (FWID) were reported to be involved in commercial sex work in China and likely to inject and share needles more frequently.^{21 31 32} However, FWID often suffer stigma

and had lower participation in MMT, needle and syringe programmes, and other harm reduction programmes.^{30 33} In our study, FWID accounted for only 6.8% of the participants, and thus the low enrolment rate for FWID into MMT could underestimate the prevalence of infections among FWID. Further study is needed to test this speculation. Moreover, some studies have also indicated that even though HIV prevalence was significantly higher among FWID, the effect size was extremely modest,³⁰ suggesting that equal emphasis should be given to women and men who inject drugs.

Routine screening for and treatment of HIV/HCV are key elements for secondary prevention. We found that some high risk subgroups, such as those ever sharing needles and having a higher frequency of injection, had a lower testing rate. Our findings suggest that such key groups should be strengthened in future MMT practice and interventions. ART could reduce HIV related mortality and morbidity, and it has been reported that expanding ART to target IDUs was much more cost effective than targeting non-IDUs, and would avert more than 40 000 new HIV infections.³⁴ However, HIV infected IDUs are less likely than non-IDUs to receive ART. It was estimated that only about 25% of IDU patients received ART in China.³⁵ Furthermore, despite the fact that antiviral therapy for HCV infection can also reduce the prevalence of HCV in IDUs,³⁶ it is most cost effective when the prevalence is <60%.³⁷ Furthermore, HCV therapy is almost invalid among those patients co-infected with HIV.^{38 39} Therefore, the primary prevention of new infections of HIV/HCV is essential, and routine screening as well as behavioural and structural interventions are needed.

The study has several limitations. First, the study participants we chose were not all IDUs but only those enrolled in MMT in Guangdong Province for the first time who had received at least HIV/HCV antibody testing within 6 months after their enrolment. According to our study, HCV/HIV testing rates were significantly different among those with different high risk behavioural characters, which may limit the generalisability of our findings. Second, the nature of the secondary data analysis in this study may limit our ability to ascertain other informative drug injecting related and sexual behaviours, and the self-reported sensitive data were subjected to social desirability bias. Third, since the report relied on consecutive cross sectional surveys, temporal or causal relationships between characteristics and infection could not be firmly established.

HIV and HCV testing rates increased from 2006 to 2013 among new entrants in MMT in Guangdong Province, China. HCV prevalence was high, and most HIV infected were co-infected with HCV among the IDUs studied. The average duration of injecting before enrolments in MMT was relatively high. Publicity about MMT and health education should be strengthened. Routine antibody screening, condom programmes and sterile needle exchanges should be integrated with the MMT programme to control and prevent HIV and HCV infection.

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Contributors Li Ling coordinated the study and wrote the protocol. Xia Zou and Wen Chen collected the data, and Yin Liu led the data analysis and wrote the first draft. Yu Liu, Xia Zou and Wen Chen helped develop the manuscript. All authors have read and approved the final article.

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Competing interests The views in this paper are the sole responsibilities of the authors; none of the funding agencies influenced the design, conduct or conclusions of the study.

Patient consent obtained.

Ethics approval The study was approved by the institutional review board of the School of Public Health, Sun Yat-sen University, Guangzhou, China.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional unpublished data are available.

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