

BMJ Open 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

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ABSTRACT

Objective: This study explores the trends and associated factors of HIV, hepatitis C virus (HCV) and syphilis seroconversion among Chinese methadone maintenance treatment (MMT) clients over a follow-up period of up to 7 years.

Design: Drug users from 14 MMT clinics in Guangdong Province were recruited during 2006–2014. Participants were seronegative with at least one HIV, HCV or syphilis infection at baseline and had completed at least one follow-up test during the study period. We estimated HIV, HCV and syphilis seroconversion rates in follow-up years and identified the underlying predictors using a multivariate Cox regression model.

Results: Among 9240 participants, the overall HIV seroconversion rate was 0.20 (0.13 to 0.28)/100 person-years (pys), 20.54 (18.62 to 22.46)/100 pys for HCV and 0.77 (0.62 to 0.93)/100 pys for syphilis, over the study period. HIV seroconversion rate showed a moderate but non-significant annual decline of 13.34% (–42.48% to 30.56%) (χ^2 trend test; $p=0.369$), whereas the decline of HCV seroconversion was 16.12% (5.53% to 25.52%) per annum ($p<0.001$). Syphilis seroconversion rate remained stable ($p=0.540$). Urine results positive for opioid predicted HIV seroconversion ($\geq 60\%$ vs $<60\%$; HR=3.40, 1.07 to 10.85), being unmarried (HR=1.59, 1.15 to 2.20), injection drug use in the past 30 days (HR=2.17, 1.42 to 3.32), having sexual intercourse in the past 3 months (HR=1.74, 1.22 to 2.47) and higher daily dosage of methadone (≥ 60 mL vs <60 mL; HR=1.40, 1.01 to 1.94) predicted HCV seroconversion. Being female (HR=3.56, 2.25 to 5.64) and infected with HCV at baseline (HR=2.40, 1.38 to 8.36) were associated with subsequent syphilis seroconversion.

Conclusions: MMT in China has demonstrated moderate-to-good effectiveness in reducing HIV and HCV incidence but not syphilis infection among participating drug users.

INTRODUCTION

The rapid spread of blood-borne and sexually transmitted infections represents a major

Strengths and limitations of this study

- This study tested 4536, 1077 and 3910 samples for HIV, hepatitis C virus (HCV) and syphilis, respectively, and identified 27, 440 and 98 person-times seroconversions, respectively. However, national data with a larger sample size are needed.
- The participants in this cohort study were followed for 7 years, thus we were able to explore the trends of HIV, HCV and syphilis seroconversion rate by follow-up years.
- This study identified significant treatment-related factors that predicted HIV (positive rate for urine tests) and HCV (average dosage) seroconversions.

public health concern in many parts of the world. In particular, the transmission of HIV, hepatitis C virus (HCV) and syphilis infections has contributed to high levels of disease burden and mortality worldwide. Sharing of injection equipment for illicit drug use has fuelled the transmission of HIV and HCV in many developing country settings.^{1–3} Syphilis infection is commonly reported among drug users as illicit drug use also facilitates risky sexual behaviour.⁴ Opioid substitution therapy (OST) has been widely accepted as an effective harm reduction strategy for drug users. Accumulating evidence has shown that OST can effectively reduce risky drug-use behaviours⁵ and hence the risk of acquiring HIV and HCV among drug users.

Methadone maintenance treatment (MMT), a key component of OST, was initiated in China during 2004. As of 2013, 761 MMT clinics have cumulatively been established nationwide, linking over 2.47 million opioid drug users to the programme in China.⁶ The programme has shown to be effective in reducing risk behaviour among participating

Chinese drug users.⁷ We established our study sites in Guangdong Province, an open and economically developed southern Chinese province with 370 000 registered drug users. HIV, HCV and syphilis prevalence among drug users in Guangdong were reportedly as high as 6.3%, 78.7% and 12.6%, respectively. MMT in Guangdong was initiated in 2005. By the end of 2013, 60 MMT clinics had been established and cumulatively 30 410 drug users had received MMT.

Previous studies have shown lower HIV and HCV incidence rates among MMT clients than among the community of drug users.⁸⁻⁹ Participants who have remained in MMT longer have also demonstrated lower risk in acquiring HIV, HCV and syphilis infections.¹⁰⁻¹¹ Numerous studies have reported the prevalence of HIV, HCV and syphilis in various subgroups of MMT clients and at different treatment stages.¹⁰⁻¹³ By linking infection status to clients' demographic, biological, behavioural and treatment-related indicators, these studies have provided important insights into the contributing factors of these infections at a certain time.¹⁴⁻¹⁶ However, infection prevalence is a good indication of disease burden but not of the trend of disease progression. Similarly, factors associated with disease prevalence explain the potential causes of infections at one fixed time but may not reflect the potential changes in risk factors due to treatment. Built on the previous findings, this study further explores the trends of HIV, HCV and syphilis seroconversion among MMT clients during the course of treatment, and identifies associated factors of new infections based on a retrospective cohort approach.

METHODS

Study sites and participants

Our study was conducted in 14 MMT clinics located in nine cities in Guangdong Province, China. This retrospective cohort study recruited 9412 MMT clients between July 2006 and March 2014. Participants were eligible if they were: (1) diagnosed with opioid dependence according to the International Classification of Diseases, 10th Revision, (2) aged 20 years or above and (3) local residents who settled in the catchment areas of the clinics. Written informed consent was obtained at treatment enrolment. We excluded participants who were (1) not tested for HIV, HCV and syphilis, (2) seropositive for HIV, HCV or syphilis at enrolment in their respective cohorts; however, clients infected with a different infection (eg, HCV) were allowed to enrol into other cohorts (eg, HIV and syphilis cohorts) and (3) those who did not complete at least one follow-up test. Three retrospective cohorts were created at baseline with regard to the negative infection status of HIV, HCV and syphilis, respectively (figure 1).

Data collection

Data were routinely collected and stored in the national unified MMT management system. At enrolment,

demographic information was collected. Drug use-related behaviours and sexual behaviours were surveyed at both enrolment and subsequent half-yearly follow-ups. Blood samples of clients were also collected to assess HIV, hepatitis C and syphilis status at enrolment and follow-ups. Urine-opiate tests were performed at a random day each month. Methadone was dispensed to patients daily. All information was entered into the MMT management system by clinic staff. For this study, data of 14 studied clinics were extracted from the MMT management system, with personally identifiable information being removed.

Laboratory tests

Blood specimens were tested for HIV-1/2, HCV and syphilis. The presence of HIV antibodies was screened using a colloidal gold method (Aibo Biotech Company, China) in the MMT clinics. Positive blood specimens were sent to the provincial Center for Disease Control and Prevention for confirmatory tests. HIV infection was determined by two positive ELISAs (ELISA-1, Beijing BGI-GBI Biotech Company, Ltd, China; ELISA-2, the 4th generation ELISA, bioMerieux bv, The Netherlands) and western blot (Abbott, MP Biomedicals, LLC, Singapore). HCV testing was carried out using ELISAs (Aibo Biotech Company, China). Toluidine red unheated serum test (TRUST, Rongsheng Biotech Company, China) was performed on all serum samples. Confirmation of positive results was made with a *Treponema pallidum* particle agglutination (TPPA, Lizhu Reagent Company, China) test.

MMT clients who were diagnosed with HIV, HCV and syphilis were notified and referred to designated public hospitals for further treatment.

Statistical analysis

The rate of positive urine tests is defined as the proportion of urine samples tested positive for opioids among the total urine samples submitted. Average MMT dosage is calculated by dividing the total dosage consumed by an individual by the number of days of attendance. Two-sample Student t test, Mann-Whitney test and χ^2 test were used for normally distributed continuous data, non-parametric data and frequencies, respectively.

The event of interest in this study was HIV, HCV and syphilis seroconversion during the course of MMT. For syphilis, an occasion of seroconversion was considered as a case with regard to the curability of the disease. The duration of follow-up was determined as the time between the date of MMT enrolment and the date of seroconversion, or the end of study. The date of seroconversion was approximated as the midpoint between the last negative and the first positive test for all infections. Seroconversion rate with 95% CIs was calculated as numbers of events over person-years, and its temporal trend significance was determined with a Joinpoint regression model.¹⁷ Univariate and multivariate Cox proportional hazard regression analyses were conducted to

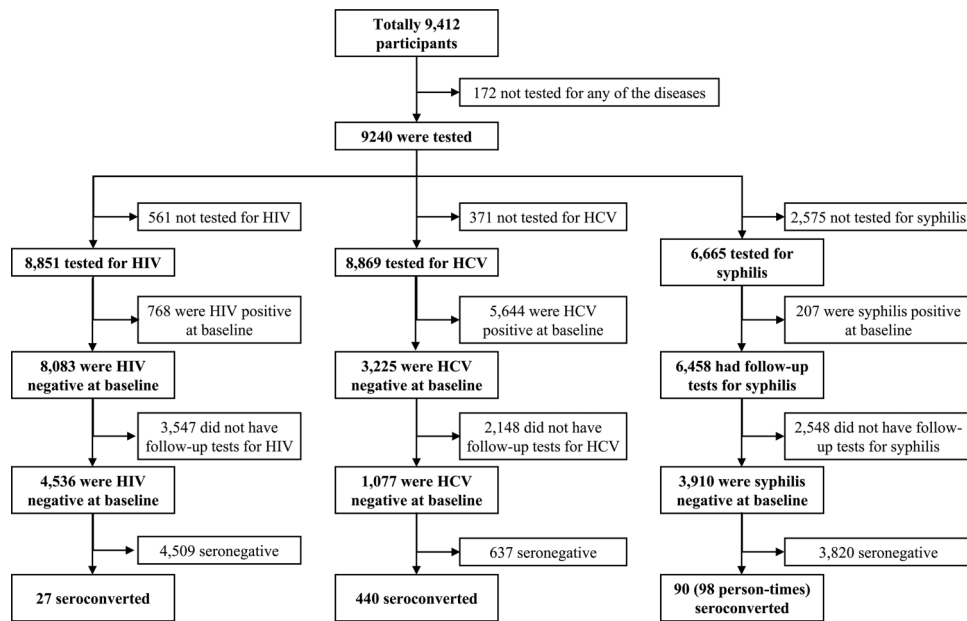


Figure 1 Eligibility and screening procedures for study participants (HCV, hepatitis C virus).

identify predictors of HIV, HCV and syphilis seroconversion. Variables with a bivariate p value <0.20 were included in subsequent multivariate regression. The last behavioural record before seroconversion or end point of the study was used for the regression analysis. Multivariate Cox regression analyses were adjusted for sociodemographic and behavioural variables. Regression models were built using stepwise techniques. The p value <0.05 was considered as statistically significant. Statistical analyses were performed using SAS V.9.2 and Joinpoint V.3.4.

RESULTS

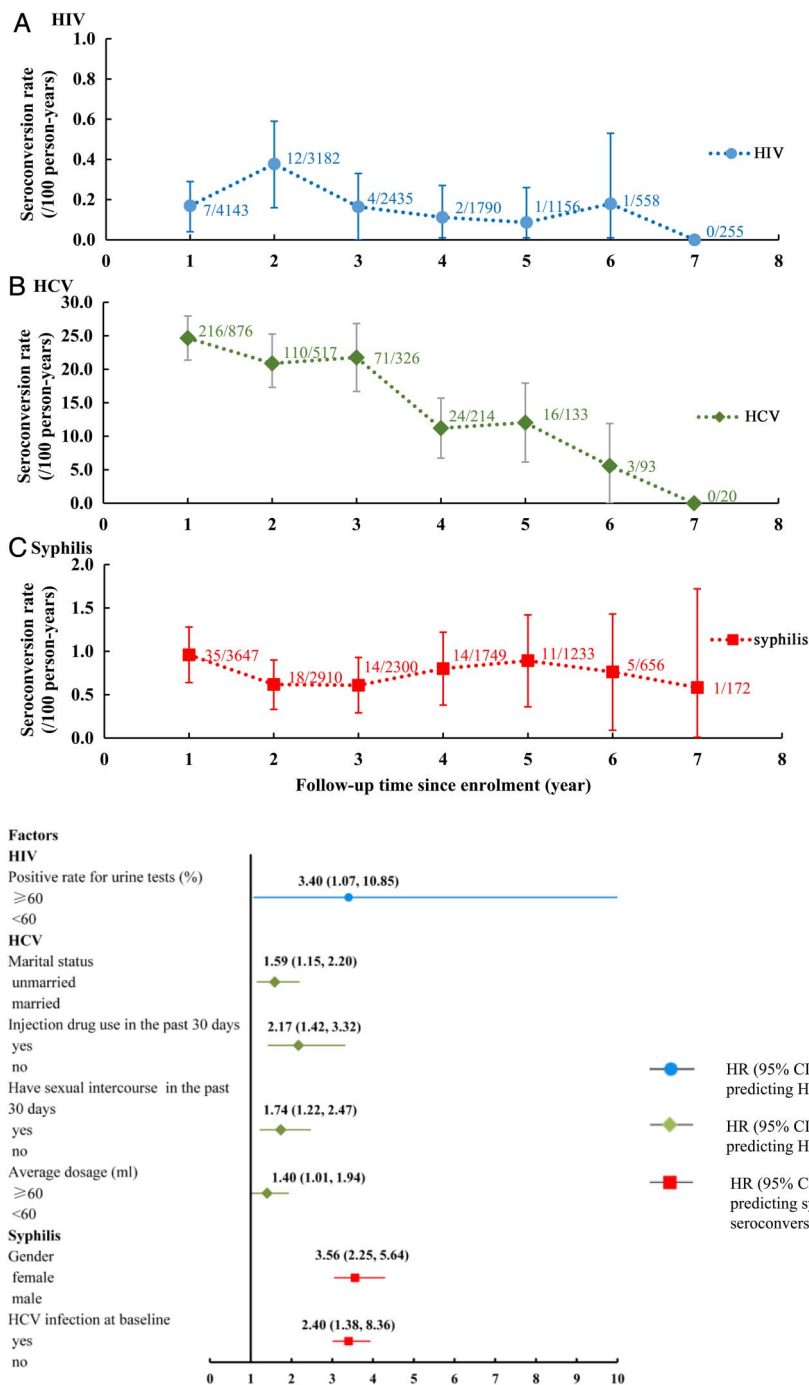
Among the 9412 enrolled MMT clients, 9240 had at least one test for either HIV, HCV or syphilis infections at enrolment and were recruited. Most of the participants included were 30 years or older (82.12%), male (92.50%) and unemployed (59.39%); about half were unmarried (53.92%); and the majority had low education level (junior high or below: 84.10%). The prevalence of HIV, HCV and syphilis at baseline was 8.68% (768/8851), 75.78% (6721/8869) and 3.11% (207/6665), respectively (see online supplementary table S1). Co-infections of HIV/HCV, HIV/syphilis and HCV/syphilis were found among 5.31% (452/8512), 0.06% (4/6667) and 2.37% (156/6582) study participants, respectively, and 0.12% (8/6667) were reportedly infected with all three diseases (see online supplementary figure S1). We identified 4536, 1077 and 3910 individuals who were HIV, HCV and syphilis seronegative at enrolment, respectively, with at least one follow-up test record. Of these, 27, 440 and 98 HIV, HCV and syphilis incidence cases with total follow-up durations of 13 360 person-years (pys), 2142 pys and 12 727 pys, respectively were reported during the study period (figure 1). In contrast, 3547, 2148 and 2548

HIV, HCV and syphilis-negative participants dropped-out of MMT after the first visit, respectively. Compared with participants included in the analyses, those who dropped out were more likely to be male, less educated, employed, HIV positive but HCV negative and with a shorter history of drug use and less sexual activity in the past 3 months (see online supplementary table S1).

Among the seronegative participants at baseline, follow-up rates at each visit were 51.26%, 39.37%, 30.12%, 22.15%, 14.30%, 6.90%, 3.15% for HIV; 81.33%, 48.00%, 30.27%, 19.87%, 12.35%, 8.64%, 1.86% for HCV; and 93.27%, 74.42%, 58.82%, 44.73%, 31.53%, 16.78%, 4.40% for syphilis, respectively. The overall seroconversion rate of HIV, HCV and syphilis was 0.20 (0.13 to 0.28)/100 pys, 20.54 (18.62 to 22.46)/100 pys, and 0.77 (0.62 to 0.93)/100 pys over the course of MMT, respectively. HIV seroconversion rate declined from 0.17/100 pys at baseline to 0/100 pys among those who remained in treatment after 7 years, corresponding to a moderate but non-significant annual decline of 13.34% (-42.48% to 30.56%) (Joinpoint regression model; $p=0.369$). In comparison, HCV seroconversion rate declined from 24.66/100 pys to 0/100 pys over the same follow-up period, corresponding to a significant annual reduction of 16.12% (5.53% to 25.52%, $p<0.001$). Seroconversion rate of syphilis infection (0.77/100 pys) remained stable over the course of treatment ($p=0.540$) (figure 2A).

A positive rate for urine tests was found to be the only predictor for HIV seroconversion ($\geq 60\%$ vs $<60\%$; HRs=3.40, 1.07 to 10.85). Being unmarried (HRs=1.59, 1.15 to 2.20), injecting drugs in the past 30 days (HRs=2.17, 1.42 to 3.32), having sexual intercourse in the past 3 months (HRs=1.74, 1.22 to 2.47) and taking an average MMT dose of over 60 mL (HRs=1.40, 1.01 to 1.94) predicted higher risk of HCV seroconversion. Participants who were female (HRs=3.56, 2.25 to 5.64)

Figure 2 (A) HIV, hepatitis C virus (HCV) and syphilis seroconversion rate among drug users over the course of methadone maintenance treatment (MMT). (B) Risk factors associated with HIV, HCV and syphilis seroconversions during the course of MMT, based on multivariate Cox regression.



and infected with HCV at baseline (HRs=2.40, 1.38 to 8.36) demonstrated a significantly higher seroconversion rate of syphilis (see online supplementary table S2; and figure 2B).

DISCUSSION

Our results demonstrated moderate-to-sharp declines in HIV and HCV seroconversion rates among MMT clients over the 7-year follow-up period, while the seroconversion rate of syphilis remained stable. During the course of treatment, seroconversion rates of all three targeted infections (HIV, 0.20/100 pys; syphilis, 0.77/100 pys; and

HCV, 20.54/100 pys) among participants were substantially lower than the corresponding rates among the community of drug users in China (HIV, 0.48–8.01/100 pys; syphilis, 2.41–5.84/100 pys; and HCV, 21.24–39.35/100 pys^{18–22}). The seroconversion rates of HIV, HCV and syphilis among MMT participants in our study were similar to those in other studies in China.^{16 23 24}

Despite high efficacy in reducing new HCV incidence, MMT is less effective in reducing HIV and syphilis incidence. This is consistent with previous findings.²⁵ A plausible explanation may be the disparities in transmission routes and the impacts of MMT on high-risk behaviour. HIV can be transmitted by blood exchange

and also through sexual contact. In contrast, HCV is readily blood-borne but transmits much less efficiently via sexual intercourse,²⁶ whereas syphilis predominately transmits through sexual contact. As a harm reduction intervention, MMT is much more effective in reducing injecting behaviours than in reducing unsafe sexual practice.²⁷ Previous studies have indicated that the percentage of injecting drug use among Chinese MMT clients dropped dramatically from 81.9% to 8.1% within the first 2 years of treatment, whereas the frequency of sexual contacts and proportion of condom use remained largely unvaried.⁷ Biologically, HCV can remain infectious *ex vivo* much longer than HIV,²⁸ and therefore reducing injection practices expectedly results in greater observable decline in seroconversion of HCV than HIV among MMT clients. Given the low seroconversion rate of HIV among MMT participants, our findings suggested that HCV seroconversion rate could be a more sensible biological indicator for assessing the effectiveness of MMT in reducing blood-borne infectious diseases.

Our findings suggest that frequent positive urine test, injecting drug use and high MMT dosage predict higher risks of HIV and HCV seroconversion. Urine testing is a routine monitoring technique for opioid use among MMT clients. A higher proportion of positive urine test results infers more frequent drug use.²⁹ Injecting drug use often leads to sharing of injection equipment among drug users and is a well-documented risk factor for HIV and HCV transmission.^{12 15} Further, clients with a higher daily methadone dosage may represent drug users with prolonged drug use and more acute addiction.^{30 31} This may imply a subgroup of drug users with high-risk behavioural patterns and treatment difficulties who are hence more prone to the infections.³² Notably, recent evidence has suggested that HCV can also be transmitted through sexual contact,³³ particularly when co-infected with sexually transmitted diseases such as syphilis. Participants who were already married had relatively stable family relationships. In contrast, participants who were unmarried and who had sexual intercourse in the past 30 days had more likelihood of engaging in risky sexual behaviour, thus increasing the risk for HCV infection.

Females are more susceptible to syphilis infection than males, anatomically.^{34 35} In China, a high proportion of female drug users are reportedly involved in commercial sex.¹⁴ Among them, multiple sexual partnerships and unprotected sexual activities are common.³⁶ These risky sexual behaviours increase their risk of syphilis infection. Besides, HCV infection is known to synergise syphilis transmission among drug users,³⁷ which contributes a greater likelihood of syphilis acquisition.

The present study has several limitations. First, frequency of HIV, HCV and syphilis testing was every 6 months. Similar to other studies, the estimated timing of seroconversion relied on the consecutive measurements of negative and positive testing results, rather than a biological test for recent infection. Second, individuals

with certain characteristics, especially those with high-risk behaviour, are more likely to drop-out from MMT; exclusion of this subgroup leads to underestimation of the actual seroconversion rates. Third, the percentage of drug use may be under-reported as study participants may tend to provide socially desirable responses to surveys. Fourth, due to the scarce number of HIV seroconverted cases, only one significant independent variable has been found to predict HIV seroconversion.

The finding that MMT effectively reduces seroconversion of HIV and HCV, highlights the importance of improving programme coverage and client retention of MMT in China. Integration of effective HIV intervention strategies, such as needle and syringe exchange, and condom distribution programmes, should be promoted to reduce high-risk behaviours at the early stage of treatment. Although MMT clinics provide free condoms to clients, the proportion of condom use among MMT clients is reportedly low in China.³⁸ Low perception of risks for blood-borne and sexually transmitted infections is a major barrier for health service utilisation.³⁹ Condom programmes should be integrated as one of the auxiliary services in MMT clinics. Health education and counselling services regarding disease prevention and treatment targeting clients, particularly those at high risk, should also be routinely provided in MMT clinics in China. China has actively responded to the HIV epidemic and substantial achievements have been made in the last decade. Antiretroviral treatment is provided freely to eligible HIV-positive individuals, but treatment for HCV and syphilis may incur substantial financial burdens for drug users. Given the currently high cost of direct-acting antiviral agents for HCV infection, its treatment is unlikely to be provided free to the needy in the near future. Although MMT clinics offer treatment referral for positive HCV and syphilis diagnoses, few clients can afford the medical cost for treatment, resulting in delay and missed opportunities for timely treatment.⁴⁰ In the absence of a national treatment programme, the MMT programme could thus be a feasible alternative for preventing HCV transmission among drug users. Further, linking antiretroviral treatment to MMT may reduce mortality among drug users living with HIV.⁴¹ With the new development of a HCV cure,⁴² expansion of HCV treatment for MMT clients may be considered a priority.

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Contributors LL, LZ and XZ conceived the study. LL contributed to study coordination. LZ participated in data collection and analysis, and drafted the manuscript. LZ and LL finalised the manuscript. All the authors read and approved the final manuscript.

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Patient consent Obtained.

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