

Methadone Use in Relation to Hepatitis C Virus Testing in British Columbia

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ABSTRACT

Objective: We examined methadone use among a large cohort of individuals undergoing serologic testing for hepatitis C virus (HCV) infection.

Methods: In British Columbia, community pharmacy methadone dispensations are recorded in the PharmaNet database and HCV antibody (anti-HCV) test results are recorded by the Provincial Public Reference Laboratory. Provincial HCV laboratory testing records from 1992 to 2004 were linked to methadone dispensation records from 1995-2006. We describe methadone maintenance treatment (MMT) among individuals undergoing anti-HCV testing between 1992 and 2004.

Results: Between 1992 and 2004, 404,941 individuals were tested for anti-HCV in BC; 32,918 (8%) were positive. Overall, methadone was dispensed to 10,314 (2.5%) of individuals tested for anti-HCV; 1% of negative testers and 21% of positive testers. Of 10,314 individuals receiving methadone, 6,732 (65%) had a positive anti-HCV test during the study period. Laboratory anti-HCV serostatus was known at MMT initiation in 70%; of these, 2,596 (36%) were anti-HCV negative and 4,638 (64%) were anti-HCV positive at first methadone dispensation. Seroconversion from anti-HCV negative to positive following MMT initiation was confirmed in 288 persons.

Conclusion: Methadone used in conjunction with other harm reduction initiatives can reduce the transmission of blood-borne infections among individuals who inject opiates, however many who enter the BC Methadone Program are already anti-HCV positive and others seroconvert after MMT initiation. Our data suggest there are missed prevention opportunities for MMT and other harm reduction services. Linkage of laboratory and health service data can provide a population lens to identify and evaluate potential prevention strategies.

Key words: Hepatitis C; injection drug use, methadone, addiction; harm reduction

La traduction du résumé se trouve à la fin de l'article.

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Hepatitis C virus (HCV) infection is highly prevalent among persons who inject drugs (IDU) as well as patients receiving methadone maintenance treatment (MMT). Seroprevalence rates for antibody to HCV (anti-HCV) range from 27-96% among IDU populations and 67-96% in patients in MMT programs.¹ In British Columbia (BC), HCV seroprevalence among subjects of a longitudinal cohort study, in an inner city neighbourhood characterized by poverty, mental illness and drug use, was estimated at 10% in 1992 and 90% by 2004, based on laboratory data linkage.^{2,3} Drug injection duration is clearly important, with up to half of new injectors acquiring HCV infection within the first 4 years and greater than 90% after a decade or more of injecting.^{1,4,5}

MMT has been shown to be effective in the treatment of opiate substance dependence such as addiction to heroin and morphine. Studies have found that among opiate-dependent patients, sustained MMT reduces morbidity and mortality, diminishes involvement in crime^{6,7} and helps drug users to gain control of their lives.⁸

MMT programs have been shown to reduce the transmission of HIV more effectively than HCV.^{9,10} High HCV prevalence among IDU, coupled with the efficient parenteral transmission of HCV, play a role in ongoing HCV seroconversions, even in MMT recipients who only occasionally inject.¹¹ Among individuals who injected opiates in Amsterdam during the period 1995-2005, HCV infection was shown to decrease with full participation in harm reduction programs combining syringe distribution programs and MMT.¹²

From previous studies, the HCV status of those initiating MMT is unclear. Therefore we examined methadone use in a large cohort of individuals undergoing serologic testing for HCV infection. Specifically, we describe HCV testers with laboratory-confirmed serostatus at the time of entry into the BC Methadone Program.

METHODS

In BC, methadone is dispensed by community pharmacies in accordance with the methadone maintenance program policies of the BC PharmaCare program, most often by directly observed therapy. Dispensations are tracked in the PharmaNet data system using methadone drug identification numbers (DINs).¹³ The DINs for methadone prescribed for maintenance related to opioid addiction and for the management of chronic pain differ. PharmaNet excludes medications provided in emergency departments or to hospitalized patients.

HCV testing in BC is centralized at the Provincial Public Reference Laboratory at the BC Centre for Disease Control (BCCDC). The laboratory has performed approximately 95% of anti-HCV tests since testing became available in 1992, enabling the longitudinal

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Table 1. Age, Sex, and Methadone Use Among Anti-HCV Testers, 1992-2004

| | | All Testers N=404,941 | Single Negative 283,722 (70.1%) | Multiple Negative 88,301 (21.8%) | First-time Positive 30,045 (7.4%) | Seroconverter 2873 (0.7%) |
|-----------|--------|----------------------------------|--|---|--|--------------------------------------|
| Age | Median | 38* | 39* | 35* 38† | 42* | 29* 32† |
| | IQR | 23* | 25* | 20* 20† | 13* | 14* 14† |
| Sex | Male | 185,744 (45.9%) | 126,718 (44.7%) | 38,084 (43.1%) | 19,359 (64.4%) | 1583 (55.1%) |
| | Female | 219,194 (54.1%) | 157,003 (55.3%) | 50,216 (56.9%) | 10,685 (35.6%) | 1290 (44.9%) |
| Methadone | Yes | 10,314 (2.5%) | 1273 (0.5%) | 2309 (2.6%) | 5606 (18.7%) | 1126 (39.2%) |
| | No | 394,627 (97.5%) | 282,449 (99.5%) | 85,992 (97.4%) | 24,439 (81.3%) | 1747 (60.8%) |

* Age at time of first (or only) anti-HCV test on record.

† For those subjects with multiple tests on record, multiple negative testers and seroconverters, we also provided the age at last test on record.

study of HCV testers. Individuals who underwent anti-HCV testing between April 1, 1992 and July 16, 2004 – when laboratory data were extracted to be linked to administrative data as part of a larger linkage study – were linked to PharmaNet records of MMT dispensations. MMT dispensations from September 1, 1995, when PharmaNet was initiated, to December 31, 2006, were available at the time of the linkage. The linkage used a multi-step, anonymized process outlined by the BCCDC, BC Ministry of Health, and College of Pharmacists of BC.^{14,15}

The full anti-HCV testing history was considered in assigning each subject's serologic testing status. Four categories were defined: 1) single negative testers (one non-reactive anti-HCV test), 2) multiple negative testers (serial non-reactive anti-HCV tests), 3) first-time positive testers (baseline reactive anti-HCV test), and 4) seroconverters (non-reactive anti-HCV test followed by a reactive test). HCV-RNA testing by polymerase chain reaction was available for just a subset of subjects, therefore anti-HCV testing results only were used to assign HCV serostatus. Subjects whose only anti-HCV test result was equivocal were excluded and equivocal test results within a series of tests were considered anti-HCV negative. Only the first positive anti-HCV test was considered. For those subjects with only one test on record – single negative and first-time positive testers – we calculated the age at time of testing. For those subjects with multiple negative tests, age at first and last negative test was calculated; for those who seroconverted, age at first negative and HCV diagnosis was calculated.

We described the age and sex distribution of all anti-HCV testers and the subgroup who had been dispensed methadone across the four categories of serologic testing status. The proportion of males to females in each category was compared between all HCV testers and the study group of MMT clients by z-testing (95% confidence level, 2 tailed). Median age was compared between all testers and the study group using the Mann-Whitney test.

Testers' HCV serostatus at the time of MMT initiation was defined as follows: 1) A negative anti-HCV test following the first methadone dispensation date confirmed that the individual was HCV seronegative at MMT initiation; 2) A positive anti-HCV test preceding the first dispensation confirmed seropositivity at MMT initiation (a positive test result within 30 days of MMT initiation also confirmed seropositivity, taking into account the seroconversion window period); 3) A negative test preceding MMT initiation or a positive test >30 days after MMT initiation were considered as unknown status at MMT initiation.

RESULTS

There were 404,941 individuals in the provincial laboratory dataset who had anti-HCV testing and were linked with PharmaNet records. Table 1 gives age and sex distribution and methadone dis-

pensation by serologic testing group. The majority 283,722 (70%) were single negative testers; 22% were multiple negative testers; 7% were first-time positive testers; and <1% seroconverted from negative to positive. Overall, more females had anti-HCV testing, but males made up a higher proportion of the first-time positive and seroconverter groups. Methadone use was low (2.5%) among all HCV testers, 1% in negative testers and 21% in anti-HCV positive testers.

In total, 10,314 individuals underwent anti-HCV testing and received MMT; individuals who received MMT but who did not have an anti-HCV test are not included. Table 2 provides the age, sex and timing of MMT initiation in relation to anti-HCV testing. MMT subjects were significantly younger than all testers (median age 33 versus 38 years, respectively). In addition, there were proportionally more male MMT subjects across every serostatus group. The relative proportion of men and women was statistically different between all testers and the study group ($z=33.881$). Among seroconverters, the median age at first negative test was 26 years and 29 years at the first positive test, indicating an interval of approximately 3 years between first negative and positive tests. Overall, MMT initiation was within +/- 1 year of the first anti-HCV test for about half of the MMT recipients.

Of 10,314 MMT subjects, anti-HCV serostatus was confirmed at MMT initiation on 7,234 (70.1%); of these 2,596 (35.9%) were negative and 4,638 (64.1%) were positive (Table 3). The median age among those confirmed negative at MMT initiation was 30 years (IQR 25-37) compared with 35 years (IQR 28-41) among those who were confirmed positive. Of the 3,080 subjects among whom anti-HCV serostatus at MMT initiation was unknown, 1,806 (58.6%) were found to be HCV positive >30 days after MMT initiation with a median age of 40 years (IQR 32-46) at the time of diagnosis.

Among seroconverters, 288 (25.6%) were anti-HCV negative at MMT initiation. Finally, of the 6,732 subjects who tested HCV positive during the study period, 4,638 (68.9%) were positive at MMT program entry.

DISCUSSION

We found 64% of individuals whose HCV status was known at MMT initiation were HCV positive. This suggests that the timing of MMT is, for many, too late to prevent HCV infection. However, at least 25% of subjects were anti-HCV negative at MMT initiation, indicating there is an opportunity to prevent HCV infection for some.

Full participation in harm reduction programs, including syringe distribution and MMT, is necessary to reduce HCV infection risk.^{10,12} In our study, 288 individuals underwent HCV seroconversion after initiating MMT; this warrants further exploration of MMT dosage and adherence, as well as access to other harm reduction initiatives.

Table 2. Age, Sex, and Timing of Methadone Use Among Anti-HCV Testers Prescribed MMT, 1992-2004

| | | All MMT Subjects n=10,314 | Single Negative Testers 1273 (12.3%) | Multiple Negative Testers 2309 (22.4%) | First-time Positive Testers 5606 (54.4%) | Seroconverter Testers 1126 (10.9%) |
|---|--------|--|---|---|---|---|
| Age | Median | 33* | 30* | 26* 29† | 37* | 26* 29† |
| | IQR | 15* | 14* | 12* 13† | 12* | 11* 11† |
| Sex | Male | 6469 (62.7%) | 880 (69.1%) | 1448 (62.7%) | 3570 (63.7%) | 571 (50.7%) |
| | Female | 3845 (37.3%) | 393 (30.9%) | 861 (37.3%) | 2036 (36.3%) | 555 (49.2%) |
| 1 st MMT ±1 year of 1 st HCV test | Yes | 5322 (51.6%) | 892 (70.1%) | 1211 (52.4%) | 2891 (51.6%) | 328 (29.1%) |
| | No | 4992 (48.4%) | 381 (29.9%) | 1098 (47.6%) | 2715 (48.4%) | 798 (70.9%) |

* Age at time of first (or only) anti-HCV test on record.

† For those subjects with multiple tests on record, multiple negative testers and seroconverters, we also provided the age at last test on record.

Table 3. HCV Serostatus at MMT Initiation

| | All MMT Subjects n=10,314 | Single Negative 1273 | Multiple Negative 2309 | First-time Positive 5606 | Seroconverter 1126 |
|--------------------------------------|--|-------------------------------------|---------------------------------------|---|-------------------------------|
| Anti-HCV Negative at MMT Initiation* | 2596 (25.2%) | 571 (44.9%) | 1737 (75.2%) | – | 288 (25.6%) |
| Anti-HCV Positive at MMT Initiation† | 4638 (45.0%) | – | – | 4040 (72.1%) | 598 (53.1%) |
| Unknown status at MMT Initiation‡ | 3080 (29.9%) | 702 (55.1%) | 572 (24.8%) | 1566 (27.9%) | 240 (21.3%) |

* A negative anti-HCV test following the first MMT dispensation confirmed seronegativity at MMT Initiation.

† A positive anti-HCV test preceding the first dispensation confirmed seropositivity at MMT initiation and a positive test within 30 days after MMT initiation also confirmed seropositivity at MMT initiation based on HCV seroconversion window period.

‡ A negative test preceding MMT initiation or a positive test >30 days after MMT initiation were non-confirmatory.

MMT only addresses opiate addiction and is not appropriate for many anti-HCV testers. Some single negative testers are at low risk of HCV infection and are tested for screening purposes (e.g., insurance or tissue donation). In addition, some single negative and first-time positive testers are tested due to past risk factors, such as prior IDU or receipt of blood products. However, multiple testers are more likely to have ongoing risk factors.

While multiple MMT attempts are common, we used the date of first MMT dispensation to mark the individual's initial contact with the program. Adequate daily dosing of methadone is crucial to initial retention and return to treatment.^{16,17} Using BC PharmaNet data on MMT dispensations from 1996-2007, Nosyk et al. found that persons with multiple methadone treatment attempts were maintained for successively longer periods; and higher methadone doses were associated with longer treatment episodes.¹⁸

The differing timeframes of the two datasets may affect the descriptive findings. MMT has been available in Canada for almost 50 years.^{16,19} However, the BC program began to expand in 1995. Nosyk identified 2,827 persons as having received at least one dose of MMT in BC in 1996; this number rose to 8,841 individuals in 2004 (personal communication, January 4, 2010). Although information about patients on MMT prior to 1995 is limited, there were likely fewer than 2000. Therefore, the PharmaNet inception data of 1995 provide reasonable capture of MMT history for our study cohort. HCV testing data for the study cohort end in 2004, thus, there may be some misclassification of negative testers as continued follow-up may have revealed another negative test or new infection.

Engaging IDU in harm reduction is complex; barriers include limited access to MMT and/or sterile syringes. At-risk and street youth, and new IDU, have a lower HCV prevalence and therefore harm reduction initiatives have the potential to prevent HCV infection. However, it may be challenging to engage youth in addiction, harm reduction, or other social services²⁰ and lack of awareness of HCV risk makes them especially susceptible to acquiring HCV infection soon after injection initiation.²¹

HCV testing and diagnosis represents a point of access to IDU and may coincide with a period in which individuals both are receptive to substance use behaviour change and increase engagement with addiction services and syringe distribution programs. We found methadone was initiated within a year of the first HCV test in about half of cases. In 2002, Kwiatkowski et al. reported an awareness of HCV positive status was associated with safer injection practices among older, but not younger IDU.²² McCusker et al. similarly found that the knowledge of HCV infection led to a positive behavioural change.²³

Accessibility of MMT and other services for HCV positive individuals is important to prevent subsequent HIV infection.²⁴ In another BC data linkage study, over half of cases co-infected with HCV-HIV were found to have been diagnosed with HCV first with a median 3.5 years before HIV diagnosis.²⁵

Sex and age differences occur in testing behaviours and underlying risk. In our study, more females than males were tested for anti-HCV overall, with males making up a higher proportion of the seropositive groups. An evaluation of testing patterns in Alberta also found females were more likely to undergo anti-HCV testing and identified that repeat testers were younger.²⁶ Although females make up 57% of multiple negative testers in our study, less than 40% of multiple negative testers who receive MMT are female. Further exploration of testing and drug use patterns are needed to determine why females are less likely to initiate MMT.

A major strength of this study is its inclusion of subjects from the entire province tested for HCV and receiving MMT. In BC, evaluations of harm reduction initiatives often focus on Vancouver where services may be more available and/or on large cohort studies of individuals in specific regions, limiting generalizability to less urban areas and the province as a whole.^{27,28}

Prospective linkages of centralized laboratory and health services data have the potential to provide a population lens for describing the health trajectories of at-risk populations and evaluating the effectiveness of harm reduction and other prevention services to stem ongoing transmission of HCV.

Our unique cohort of provincial anti-HCV testers linked with pharmaceutical data enabled us to evaluate HCV serostatus in relation to MMT initiation for a large, high-risk population. Our findings suggest there are missed prevention opportunities and support the need for integrated care models for at-risk groups, to ensure that appropriate HCV testing, education, MMT and other harm reduction and addiction services are widely available.

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RÉSUMÉ

Objectif : Étudier l'utilisation de la méthadone dans une vaste cohorte de sujets ayant passé un test sérologique de dépistage du virus de l'hépatite C (VHC).

Méthode : En Colombie-Britannique (C.-B.), les distributions de méthadone par les pharmacies communautaires sont enregistrées dans la base de données PharmaNet, et les résultats des tests de sérodétection des anticorps anti-VHC sont enregistrés par le laboratoire de référence provincial. Nous avons relié les données des épreuves de laboratoire provinciales pour le VHC de 1992 à 2004 aux données de distribution de méthadone de 1995 à 2006. Nous décrivons le traitement de maintien à la méthadone (TMM) chez les sujets ayant subi un test sérologique anti-VHC entre 1992 et 2004.

Résultats : Entre 1992 et 2004, 404 941 personnes ont passé un test anti-VHC en C.-B.; 32 918 de ces tests (8 %) étaient séropositifs. Dans l'ensemble, la méthadone a été distribuée à 10 314 (2,5 %) des personnes testées pour le VHC : 1 % des sujets séronégatifs et 21 % des sujets séropositifs. Sur les 10 314 personnes ayant reçu de la méthadone, 6 732 (65 %) avaient eu un test anti-VHC positif durant la période de l'étude. L'état sérologique pour le VHC déterminé en laboratoire était connu au début du TMM dans 70 % des cas; sur ces personnes, 2 596 (36 %) étaient séronégatives pour le VHC et 4 638 (64 %) étaient séropositives pour le VHC à la première distribution de méthadone. La séroconversion d'un statut séronégatif pour le VHC à un statut séropositif après le début du TMM a été confirmée chez 288 personnes.

Conclusion : La méthadone, utilisée conjointement avec d'autres méthodes de réduction des méfaits, peut réduire la transmission des infections véhiculées par le sang chez les utilisateurs d'opiacés par injection, mais un bon nombre des sujets qui s'inscrivent au programme de méthadone de la C.-B. sont déjà séropositifs pour le VHC, et d'autres le deviennent après le début du TMM. Ces données montrent qu'il pourrait y avoir des occasions de prévention manquées par le TMM et d'autres services de réduction des méfaits. Le jumelage des données des laboratoires et des services de santé peut fournir une optique en population pour définir et évaluer les stratégies de prévention possibles.

Mots clés : hépatite C; toxicomanie intraveineuse, méthadone, dépendance; réduction des dangers