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Unintended impacts of regulatory changes to British Columbia Methadone Maintenance Program on addiction and HIV-related outcomes: an interrupted time series analysis

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Abstract

Background—In February 2014, several regulatory reforms were introduced to the methadone maintenance treatment (MMT) program in British Columbia, Canada, including a switch to a ten-times more concentrated methadone formulation and restrictions in pharmacy delivery services. We evaluated possible unintended effects of these changes on illicit drug use patterns and HIV treatment outcomes among HIV-positive opioid users.

Methods—Data was drawn from ACCESS, a prospective community-recruited cohort of HIV-positive people who use illicit drugs in Vancouver, Canada. Interrupted time series analyses were used to evaluate impacts of the policy change on monthly rates of MMT enrollment, illicit heroin injection, antiretroviral therapy (ART) adherence, and HIV viral suppression among HIV-positive opioid users between November 2012 and May 2015.

Results—A total of 331 HIV-positive opioid users were included. The MMT policy change led to a significant immediate 11.5% increase in heroin injection, and 15.9% drop in optimal ART adherence. A gradual increase in the prevalence of MMT enrolment after the policy change was also documented (0.9% per month). No changes in viral suppression rates were observed.

Conclusions—We observed immediate increases in illicit heroin injection and decreases in ART adherence in the wake of regulatory changes to the local MMT program. These findings underscore the need to consider potential unintended effects of altering health programmes for vulnerable populations, the need to develop appropriate mitigation strategies, as well as to involve all relevant stakeholders in the planning and implementations of new policies.

Keywords

methadone maintenance treatment; HIV; antiretroviral therapy; opioid use disorders; health policies; opioid agonist treatment

Background

Settings throughout North America are experiencing epidemics of opioid-associated morbidity and mortality driven by increases in the prescribing rate of opioid analgesics, increased availability of heroin and other illicit opioids, and the emergence of novel forms of illicit opioids (Carter & Graham, 2013; Compton, Jones, & Baldwin, 2016; King, Fraser, Boikos, Richardson, & Harper, 2014). Indeed, accidental opioid-related overdose deaths have become one of the leading causes of injury deaths in North America, exceeding deaths from motor-vehicle accidents in many American states and Canadian provinces (Compton, et al., 2016; Gourevitch, et al., 1999; King, et al., 2014). In addition to overdose deaths and other medical complications related to chronic opioid use, opioid use disorder (OUD) has been linked to increased risk of transmitting and acquiring blood-borne viruses, including HIV and viral hepatitis, through the sharing of injection equipment (Degenhardt & Hall, 2012).

Treatment of OUD is a key element in the response to the North American opioid crisis (Volkow, Frieden, Hyde, & Cha, 2014). Opioid agonist therapies (OAT), either with methadone or buprenorphine/naloxone, have proved to be effective in reducing illicit opioid use and retaining patients in treatment (Mattick, Breen, Kimber, & Davoli, 2014). OAT has also been shown to reduce illicit drug-related mortality, involvement in criminal activity, as well as to improve HIV and hepatitis C (HCV) prevention and treatment outcomes (Ahamad, et al., 2015; Altice, et al., 2011; Gowing, Farrell, Bornemann, Sullivan, & Ali, 2011; Low, et al., 2016; MacArthur, et al., 2012; Nosyk, et al., 2015; Perlman, et al., 2015). In Canada, methadone maintenance therapy (MMT) has historically been the standard of care of OUD. The delivery of MMT is mostly regulated at the provincial or territorial levels, which results in large variations of service delivery models and funding schemes across the country (Luce & Strike, April 2011).

In February 2014, several regulatory changes were introduced to the MMT program in the province of British Columbia (BC) (College of Physicians and Surgeons of British Columbia, January 2014), the second largest MMT program in Canada, and significantly expanding over the past decade. The existing methadone formulation, a compounded anhydrous formulation (1 mg/ml) mixed with orange-flavor juice, was replaced with a pre-mixed cherry flavored and 10-times more concentrated methadone solution (10 mg/mL, Methadose®) (College of Pharmacists of British Columbia, 2013b). Following the change, persons on methadone were transitioned to prescriptions of an equivalent dose of the new formulation (e.g., from 100 ml to 10 ml). The rationale given for this decision was to improve patient safety and quality control (e.g., more consistent dosing, no need for refrigeration) and to reduce the risk of misuse and diversion (College of Physicians and Surgeons of British Columbia, January 2014). In addition, a new policy was introduced

restricting methadone home deliveries to only “extraordinary circumstances” (e.g., clients with severe mobility restrictions) and with a written authorization by the prescribing physician (College of Pharmacists of British Columbia, 2013c).

As documented by qualitative studies and quantitative surveys, subsequent to the regulatory changes, concerns were voiced among persons on methadone that the new methadone formulation did not adequately control withdrawal symptoms, and that discontinuation of home delivery services resulted in interruptions in MMT and co-dispensed medications (e.g., antiretroviral therapy, psychiatric medications) (Greer, et al., 2016; McNeil, et al., 2015). However, to our knowledge, the broader effects of the new MMT policies, including on HIV prevention and treatment outcomes, have not been characterized. In the context of increasing health policy reforms to address the North American opioid epidemic, identifying and understanding the intended and unintended health and social consequences of these regulatory changes is highly relevant. Thus, the aim of this study was to longitudinally assess the impacts of the changes in methadone formulation and dispensation on engagement on MMT, drug injecting behaviors and HIV treatment patterns among a community-based sample of HIV-positive opioid users in Vancouver, BC, Canada.

Methods

Study setting

In British Columbia (BC), the provincial MMT program is administered by the Ministry of Health; the College of Physicians and Surgeons of BC (CPSBC), which is responsible of administering physicians’ authorization to prescribe MMT and setting treatment guidelines (College of Physicians and Surgeons of British Columbia, 2016); and the College of Pharmacists of BC (CPBC), which establishes requirements and standards for methadone delivery and monitoring practices (College of Pharmacists of British Columbia, 2013a). In order to be able to prescribe methadone, physicians require an exemption under the Controlled Drugs and Substance Act from the federal Ministry of Health, which is obtained through the CPSBC. Pharmacists also must undergo training and certification in order to dispense methadone, as per the CPBC requirements. Community pharmacies play a key role in MMT programs due to restrictions on MMT prescribing that requires frequent dispensation (e.g., daily) and directly witnessed ingestion. Typically, care and prescription drugs received in the context of OAT are fully publicly funded for low-income BC residents; while other individuals who are not eligible for this benefit are responsible for paying for a percentage of the medication cost either through private insurance plans or out of pocket (Luce & Strike, April 2011).

Data sources

Data for this study were drawn from the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS), an ongoing prospective cohort of HIV-positive adults who use illicit drugs in Vancouver, Canada that began recruitment in 2005. Eligibility criteria include HIV-seropositivity, age ≥ 18 years, residency within the Greater Vancouver Regional District, and having used illicit drugs other than or in addition to cannabis in the previous month. Individuals are recruited through snowball sampling and extensive street outreach with a

focus in the Downtown Eastside neighborhood, an area with an open drug market and high levels of illicit drug use, poverty and HIV infection. Recruitment and study procedures have been described in detail previously (Strathdee, et al., 1998; Wood, et al., 2008).

In brief, after providing written informed consent, at baseline and semi-annually thereafter, participants complete an interviewer-administered questionnaire that collects information on socio-demographic characteristics, drug use patterns, health care access and utilization, including HIV and addiction care, as well as other relevant exposures. At each of these visits, participants provide blood samples for HCV serological testing and HIV disease monitoring, and are examined by a study nurse, who provides basic medical care and referrals to additional health services when needed. As has been described elsewhere (Wood, et al., 2008), information gathered at each semi-annual visit is augmented by confidential data linkages with the British Columbia Centre for Excellence in HIV/AIDS (BC-CfE) Drug Treatment Program, which provides HIV care, including free ART to all people living with HIV in the province of British Columbia. These linkages allow for a complete longitudinal clinical and laboratory profile for each participant, including all CD4 counts and HIV plasma viral load (VL) tests conducted either through the aegis of the study or in the course of clinical care, and details of each dispensation of ART. Participants receive CAD \$30 stipend at each study visit. The ACCESS study has received ethical approval by the University of British Columbia/Providence Health Care Research Ethics Board.

Study population and study period

For this analysis, we included participants who reported any history of opioid use, with at least one follow-up visit in both the pre- (November 1, 2012 – January 31, 2014) and post-policy periods (March 1, 2014 – May 31, 2015). Thus, we included data from 15 months prior to the change in the MMT program and up to 15 months after.

Outcomes of interest

We assessed four dichotomous outcomes (yes/no), each of which was summarized as monthly proportions based on interview date. First, we evaluated current engagement in MMT (self-reported). Next, we examined the extent to which changes in BC MMT program might have affected individuals who were enrolled in OAT at the time of the policy change. Selection of these outcomes was informed by hypotheses generated in a previous qualitative study (McNeil, et al., 2015). For these outcomes, the study population was further restricted to opioid users with at least one visit in the pre-policy period where they report being on MMT. Outcomes evaluated included self-reported illicit heroin injection (in the six months prior to the interview), and optimal ART adherence (≥ 95%) and VL suppression, as a measure of the extent to which the MMT policy change might have affected access to related health services and outcomes. ART adherence was measured using pharmacy refill data, and calculated as the percentage of days for which ART was dispensed over the number of days for which ART was prescribed in the six month period before the interview, dichotomized at 95%. This validated pharmacy refill measure has been shown to predict virologic response and survival (Grossberg, Zhang, & Gross, 2004). Viral suppression was defined as having a VL < 50 copies/mL (yes versus no) in the previous six months. In the case of multiple VL measurements within a six-month follow-up period, the median of all the observations was

utilized. This number was then used to dichotomize participants at $< \text{ or } \geq 50$ c/mL as virally suppressed or not for that observation point.

Statistical analysis

To estimate the impacts of the change in the MMT program on each of the four outcomes we conducted separate interrupted time series analyses (Jandoc, Burden, Mamdani, Levesque, & Cadarette, 2015; Wagner, Soumerai, Zhang, & Ross-Degnan, 2002). This method allows to control from pre-existing trends by comparing observed outcomes after the policy change with those expected had the policy not occurred. The study period was divided into pre- (15 months) and post-policy (15 months) segments. The month of the policy change (February 2014) was considered a transition period and excluded from the analysis. The final data set contained 30 months of data, with an average of 44 (range 34–58) observations at each time point.

As a first step, we visually inspected the data (e.g., scatter plot of the time series, autocorrelation and partial autocorrelation functions plots) to determine the underlying trend, outliers and potential seasonal patterns (Jandoc, et al., 2015). No seasonal patterns were identified, which is in alignment with the lack of *a priori* reasons to suggest seasonal changes in any of the studied outcomes. Although, some outliers were observed, these were considered to be caused by random variation, and thus treated as regular data points (Wagner, et al., 2002). Segmented regression analyses were then used to evaluate the immediate (i.e., change in level) and longer-term impacts (i.e., change in slope) of the MMT provincial program changes in each of the outcomes, controlling for pre-existing secular trends. The models included terms for the baseline level for each outcome at the beginning of the observation period, trend in the pre-policy period, level change in the outcome immediately after the policy change, and trend in the post-policy period. We tested for autocorrelation over time using the Durbin-Watson test and included autocorrelation orders in the models where appropriate (Durbin & Watson, 1950). Using the models, we further estimated the prevalence of each outcome 12 months after the policy change, and calculated the absolute difference (with 95% Confidence Intervals [CI]) with the estimated prevalence if the regulatory changes had not occurred (Zhang, Wagner, Soumerai, & Ross-Degnan, 2009). All statistical analyses were performed using the SAS software version 9.4 (SAS, Cary, NC), and all p-values are two-sided.

Results

A total of 331 opioid users were included in the present analysis. Socio-demographic characteristics of the study population are presented in Table 1. Median age at the time of the policy change was 47 years (Interquartile range [IQR] 41–52), and 196 (59%) were male.

Enrolment in MMT

Figure 1 presents the monthly proportion of opioid users who reported being enrolled in MMT. As shown in this figure, at the beginning of the study period (November 2012), our model estimated an 86.1% (95% Confidence Interval [95% CI]: 82.3%, 89.9%) prevalence

of enrolment in MMT, and indicated a statistically significant decreasing trend before the policy change (-0.9% per month, 95% CI: -1.3% , -0.4%). Thus, in the month prior to the policy change (January 2014), 74.1% (95% CI: 70.4%, 77.8%) HIV-positive opioid users were enrolled in MMT. Although no immediate changes in the prevalence of MMT enrolment were observed (level change = 3.2% , 95% CI: -2.6% , 9.1%) after the regulatory changes were introduced in the provincial MMT program, the enrolment rate gradually increased (0.9% per month, 95% CI: 0.2% , 1.5%). By March 2015, 12 months after the policy change, the estimated MMT enrolment rate was 77.4% (95% CI: 74.8%, 80.1%), 13.6% (95% CI: 4.3%, 22.9%) higher than the rate if the regulatory changes had not occurred.

Illicit heroin injection

Figure 2 shows the proportion of opioid users who reported injecting heroin in the prior six months during the study period. As indicated in this figure, before the policy change there was a non-significant decreasing trend (-0.3% per month, 95% CI: -0.7% , 0.2%) in the prevalence of recent heroin injection changing from 46.7% (95% CI: 43.0%, 50.3%) in November 2012 to 42.8% (95% CI: 39.3%, 46.4%) in January 2014. The regulatory changes in the MMT program were associated with an immediate increase of 11.5% (95% CI: 5.6%, 17.4%) in the proportion of opioid users reporting recent heroin injection, with no changes in the monthly trend after the policy change (-0.03% per month, 95% CI: -0.63% , 0.56%). This resulted in an estimated heroin injection prevalence of 50.7% (95% CI: 48.2%, 53.1%), twelve months after the regulatory changes in the MMT program, 11.1% (95% CI: 2.1%, 20.1%) higher than the expected rate if these changes had not occurred.

ART adherence and viral load suppression

Monthly prevalence rates of optimal ART adherence and VL suppression are presented in Figure 3 and 4, respectively. At the beginning of the study period, the model estimated that 62.2% (95% CI: 55.0%, 69.5%) of HIV-positive opioid users in this study achieved optimal ART adherence, showing a non-significant increasing trend in the pre-policy period (0.4% per month, 95% CI: -0.4% , 1.3%). We observed a statistically significant drop of 15.9% (95% CI: 5.0%, 26.7%) in ART adherence after the implementation of the regulatory changes in the MMT program, with no monthly changes thereafter (0.5% per month, 95% CI: -0.7% , 1.8%). Thus, twelve months after the policy change, the estimated prevalence of optimal ART adherence was 64.3% (95% CI: 59.1%, 69.5%), 9.4% (95% CI: -8.6% , 27.4%) lower than expected. In contrast, as shown in Figure 4, we did not observe a significant change in either the level (-2.7% , 95% CI: -14.4% , 9.0%) or trend (0.4% per month, 95% CI: -0.9% , 1.8%) of VL suppression after the regulatory changes.

Discussion

This study revealed several potential unintended, albeit mixed consequences of the regulatory changes recently introduced to the BC MMT program. Many of the findings presented herein are consistent with previous results from qualitative research (McNeil, et al., 2015). Specifically, although the policy change was associated with a gradual increase in the proportion of HIV-positive opioid users enrolled in MMT, rates of illicit heroin injection

increased sharply immediately after the implementation of the policy and remained elevated throughout the study period. Importantly, changes in the MMT program appeared to also have affected engagement in HIV care as demonstrated by a significant drop in ART adherence immediately after the policy change. However, this change was not accompanied by a corresponding decrease in viral suppression rates.

Our findings indicated that during the pre-policy period in 2013 there was a significant 12% decrease of MMT enrolment rates, which is in contrast with relative stable number of MMT patients during the same period in Vancouver (Office of the Provincial Health Officer, July 2015). A possible explanation to these findings might be the higher prevalence of social-structural inequalities that participants from our study face (e.g., homelessness, violence) compared to the greater population of opioid users in Vancouver that, in turn, may hamper their access to addiction treatment (Prangnell, et al., 2016; Urban Health Research Initiative, 2013). Somewhat unexpectedly, this downward trend was gradually reversed after the policy change in February 2014. To our knowledge no other intervention that could potentially affect MMT enrolment was introduced at the same time. This might be a result of the intensive public health campaign that was conducted during the transition period to raise awareness of the methadone formulation change resulted in more opioid users hearing about OAT and consequently enrolling in MMT (British Columbia Harm Reduction Program., January 1, 2014). In addition, this might reflect increased access to low-threshold MMT clinics in Vancouver's Downtown Eastside where over half of the study participants live (Ammassari, Trotta, Shalev, Marconi, & Antinori, 2012).

We did not find evidence that the observed increases in engagement in MMT translated into better drug-use treatment outcomes. On the contrary, our results demonstrated a significant 11.5% increase in rates of heroin injection immediately after the policy change. These findings are in line with previous research documenting high rates of what has been defined as "change intolerance" to the introduction of new methadone formulations (Silver & Shaffer, 1996; Steels, Hamilton, & McLean, 1992). Although limited clinical evidence support a psychological (e.g., perceived lower efficacy due to lower volumes) rather than a biological or pharmacological basis underlying withdrawal symptoms (Gourevitch, et al., 1999), it may also be partially explained by dispensation challenges with the new formulation, including difficulties in titrating doses (McNeil, et al., 2015). Regardless, its adverse social and health effects cannot be overlooked. Indeed, in other settings, change intolerance has been associated with treatment disruptions, decreased social stability, relapse to illicit drug use, and involvement in illegal income-generation activities (Greer, et al., 2016; McNeil, et al., 2015; Silver & Shaffer, 1996; Steels, et al., 1992).

Collectively, these findings highlight the need for interventions that support MMT clients upon introduction of new medication formulations or other changes that affect medication dispensation. First and foremost, the affected community should be consulted and involved in the planning, development and implementation phases of proposed new approaches. Persons on methadone's input on key aspects of implementation strategies and their capacity to provide insights into potential unexpected outcomes (positive and negative) is of paramount importance. Other important considerations include the potential benefits of longer transition periods where both formulations would be available, closer clinical

monitoring and dose modifications in response to withdrawal and overdose symptoms, as well as psychological support, particularly for more vulnerable individuals (Greer, et al., 2016; McNeil, et al., 2015; Silver & Shaffer, 1996).

Finally, given that engagement in OAT has been consistently associated with superior HIV treatment outcomes among HIV-positive opioid users (Altice, et al., 2011; Low, et al., 2016; Nosyk, et al., 2015), we speculated that regulatory changes in the BC MMT program might have also affected HIV-related outcomes. The present analysis, though, yielded mixed results. While a significant drop of 16% in the proportion of participants with optimal ART adherence was observed immediately after the MMT policy change (from 68% to 52%), fortunately this did not translate into reduced levels of viral suppression. These somewhat divergent results may reflect the characteristics of contemporary ART regimens. For instance, due to the higher potency and genetic barrier of newer ARV drugs, contemporary ART regimens may still be able to suppress HIV replication even during intermittent and brief periods of ART adherence below 95% (Viswanathan, et al., 2015). Regardless, given the critical role of optimal ART adherence for sustained viral suppression, and long-term outcomes among HIV-positive individuals (including prevention of HIV transmission) (Ammassari, et al., 2012), this negative effect of the MMT policy change should not be disregarded. Equally concerning is the fact that the reduction in the level of ART adherence rates temporally coincided with an increase in the level of heroin injecting, which could have potentially led to breakthrough HIV viremia (not captured in our laboratory records), and increased risk of HIV transmission in the community.

The major strength of this study is the use of a strong longitudinal, quasi-experimental design to evaluate the impacts of regulatory changes in BC MMT program on both addiction and HIV-related treatment outcomes among HIV-positive opioid users in Vancouver, BC. Importantly, this study design allows to control from pre-existing levels and trends of each of the outcomes evaluated. However, in the absence of an external control group (e.g., out-of-province HIV-positive opioid users not exposed to the policy change), we cannot exclude the possibility that the observed changes were the result of other events that occurred simultaneously with the BC MMT policy change. However, we are unaware of such co-interventions. In addition, the sharp changes in levels of heroin injection and ART adherence that occurred immediately after the policy change provide further evidence for a potential causal link between the MMT policy and these two outcomes. Another strength of the present analysis is the utilization of a closed cohort (i.e., inclusion of participants with observations in both the pre- and post-policy periods), which reduces the possibility of selection-attrition biases.

Our study has also some limitations. First, our study sample was not randomly selected, and thus, might not be representative of the larger population of HIV-positive opioid users in Vancouver. Likewise, results from this study may not be completely generalizable to HIV-negative opioid users or to settings with different health policies and clinical practices (e.g., low threshold MMT services, universal and comprehensive coverage for HIV care). Second, we relied on self-reported data for some of the outcomes evaluated, which may be subject to social-desirability bias. However, previous research has shown PWUD's reports of drug use and addiction treatment to be reliable (De Irala, Bigelow, McCusker, Hindin, & Zheng,

1996; Langendam, van Haastrecht, & van Ameijden, 1999). Third, the use of aggregated individual-level data does not allow making inferences about individual-level outcomes. Fourth, the relatively small number of observations per data point and related variability within the data, as reflected by the presence of some outliers, may have resulted in reduced power to detect small changes in the outcomes. Finally, given that we only measured heroin injection the impact of the policy change on other forms of opioid misuse could not be assessed.

In summary, our study provides empirical evidence detailing possible unintended consequences of the regulatory changes introduced to the BC MMT program in February 2014, changes that were made with the goals of improving the quality of OAT. Importantly, adverse effects were documented not only in drug use behavior (increase in illicit heroin injection), but also in HIV-related treatment outcomes (decrease in ART adherence). In light of escalating actions to address the opioid epidemic in North America, findings from this study may help inform the development and implementation of policies targeted to individuals with opioid use disorders (and related comorbidities). Particularly, results from the present analysis underscore the need to consider potential unintended effects of altering health policies targeting vulnerable populations, the need to develop appropriate mitigation strategies, as well as to involve all relevant stakeholders, including the affected community in the planning and implementation of these new policies.

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Figure 1. Methadone maintenance treatment enrolment rates among HIV-positive opioid users in Vancouver, Canada, before and after the regulatory changes to British Columbia's Methadone Program in February 2014

Observed monthly rates are presented with dots, estimated monthly rates with full line, and predicted monthly rates had the Methadone policy change not occurred with dash lines. Estimated and predicted rates represent estimates from our Interrupted Time Series analyses. The grey box represents the month when the new Methadone policy was implemented.

Figure 2. Illicit heroin injection rates among HIV-positive opioid users in Vancouver, Canada, before and after the regulatory changes to British Columbia's Methadone Program in February 2014

Observed monthly rates are presented with dots, estimated monthly rates with full line, and predicted monthly rates had the Methadone policy change not occurred with dash lines. Estimated and predicted rates represent estimates from our Interrupted Time Series analyses. The grey box represents the month when the new Methadone policy was implemented.

Figure 3. Optimal ART adherence rates among HIV-positive opioid users in Vancouver, Canada, before and after the regulatory changes to British Columbia's Methadone Program in February 2014

Observed monthly rates are presented with dots, estimated monthly rates with full line, and predicted monthly rates had the Methadone policy change not occurred with dash lines. Estimated and predicted rates represent estimates from our Interrupted Time Series analyses. The grey box represents the month when the new Methadone policy was implemented.

Figure 4. HIV viral load suppression rates among HIV-positive opioid users in Vancouver, Canada, before and after the regulatory changes to British Columbia's Methadone Program in February 2014

Observed monthly rates are presented with dots, estimated monthly rates with full line, and predicted monthly rates had the Methadone policy change not occurred with dash lines. Estimated and predicted rates represent estimates from our Interrupted Time Series analyses. The grey box represents the month when the new Methadone policy was implemented.

Table 1

Socio-demographic characteristics of 331 HIV-positive opioid users in Vancouver, Canada (November 2012 – May 2015)

	Period; n (%) of participants			
	First observation in study period	Last observation before the policy change	First observation after the policy change	Last observation in study period
Age (med, IQR)	46 (40–52)	47 (41–52)	48 (42–53)	48 (42–54)
Male gender	196 (59.2)	196 (59.2)	196 (59.2)	196 (59.2)
White ethnicity	176 (53.2)	176 (53.2)	176 (53.2)	176 (53.2)
Formal employment *	51 (15.4)	55 (16.6)	65 (19.6)	67 (20.2)
Homeless *	36 (10.9)	39 (11.8)	37 (11.2)	38 (11.5)
Residence in the DTES *	210 (63.4)	193 (58.3)	177 (53.5)	174 (52.6)

* Refers to the 6-month period prior the interview

DTES, Downtown Eastside