INJECTION CAREER TRAJECTORIES AMONG ILLICIT DRUG USERS IN VANCOUVER, CANADA

by

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ABSTRACT

Background: Though vast resources have been allocated toward the prevention of illicit drug use, the prevalence of injection drug use remains high globally. This thesis therefore sought to identify factors that influence the natural history of injection drug use by: systematically reviewing the epidemiologic literature on the prevention of injecting initiation; identifying the role of drug-related and personality-based risk factors in increasing the risk of injecting initiation; and evaluating the role of harm reduction interventions in potentially modifying the likelihood of injecting cessation among injection drug users (IDU).

Methods: Street-involved youth and IDU participating in ongoing prospective observational cohorts in Vancouver, Canada, completed semi-annual interviewer-administered questionnaires. Longitudinal epidemiologic methods were applied to assess the association between selected drug-related, personality-based (e.g., sensation seeking level), and structural factors on the outcomes of interest, while controlling for a variety of potential sociodemographic and behavioural confounders.

Results: The systematic review found that a limited set of interventions to prevent injecting has been scientifically evaluated and implemented. A longitudinal analysis of injecting initiation found that non-injection crystal methamphetamine use was significantly associated with injecting initiation among street-involved youth. The adaptation of a sensation seeking scale for use in a related longitudinal analysis found that higher sensation seeking was associated with injecting and risk factors for injection initiation. Finally, in a longitudinal analysis conducted over a span of 15 years, rates of injecting cessation among a cohort of IDU increased significantly despite a substantial expansion in needle and syringe program (NSP) implementation.

Conclusions: This thesis identified gaps in current responses to preventing injection drug use. A set of drug-related and personality-based factors associated with increased risk of injecting initiation among street-involved youth was also identified, including non-injection crystal methamphetamine use and higher sensation seeking. Further, an increase in the rate of injecting cessation among IDU occurred during a period of substantial expansion of NSP sites in Vancouver. These results suggest that resources should be allocated towards the development of interventions to prevent injection initiation, and that harm reduction interventions should be considered complementary to broader efforts to reduce both injection drug use and related harms.

PREFACE

This statement certifies that the work presented in this thesis was conceived, conducted, written and disseminated by Dan Werb (DW). All research described in this dissertation was conducted under the University of British Columbia/Providence Health Care Research Ethics Board approval (certificate H12-02419). The co-authors of the manuscripts, including Dr. Evan Wood (EW), Dr. Jane Buxton (JB), Dr. Jeannie Shoveller (JS), Dr. Chris Richardson (CR), Dr. Thomas Kerr (TK), Dr. Julio Montaner (JM), and Mr. Greg Rowell (GR) made contributions only as is commensurate with supervisory committee, collegial or co-investigator duties. The principal investigators of the ARYS study (EW) and the VIDUS study (TK), from which the data-driven analyses were derived, had access to all of the data and as corresponding authors take full responsibility for the integrity of the results and the accuracy of the statistical analyses. With substantive input from co-supervisors EW and JB, DW designed the studies and wrote the research protocol. With guidance and input from EW, JB, JS, CR, TK, and JM, DW performed the research and conducted all statistical analyses described in Chapters 4, 5 and 6. DW designed and led the systematic review presented in Chapter 3 and, in collaboration with GR, conducted the search strategy and selected eligible studies for final inclusion. EW, JB, JS, CR, and GR reviewed the material presented in Chapter 3 and approved the final version of the manuscript for submission. EW, JB, JS, CR, TK, and JM contributed scientific input to the material in Chapter 4 and approved the final version of the manuscript for submission. EW, JB, JS, CR, TK, and JM provided scientific input and approved the final version of the manuscript presented in Chapter 5. EW, JB, JS, CR, TK, and JM provided scientific input and approved the final version of the manuscript presented in Chapter 6. All manuscripts contained in this thesis were prepared, written and edited by DW. Final drafts of the manuscripts were prepared following the inclusion of material based on comments from all co-authors listed above, the journal editors and external peer reviewers. The analysis presented in Chapter 6 is currently in press:

1.   Werb D, Kerr T, Buxton J, Shoveller J, Richardson C, Montaner J, Wood
        E. Patterns of injection drug use cessation during an expansion of
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        Dependence*, 2013.

The analyses presented in Chapters 3, 4 and 5 are under review:

1.   Werb D, Buxton J, Shoveller J, Richardson C, Rowell G, Wood E.
        Strategies for preventing the initiation of injection drug use: A
        systematic review. Under review.
2.   Werb D, Kerr T, Buxton J, Shoveller J, Richardson C, Montaner J, Wood
        E. Crystal methamphetamine and injecting initiation among street-
        involved youth in a Canadian setting. Under review.
3.   Werb D, Richardson C, Kerr T, Buxton J, Shoveller J, Montaner J, Wood
        E. Development of a brief substance use sensation seeking scale:
        Validation and prediction of injection drug use. Under review.

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DEDICATION

For my parents

CHAPTER 1: BACKGROUND, RATIONALE AND OBJECTIVES

1.1   The epidemiology of injection drug use and blood-borne diseases

Beginning in the early 19th century, techniques to synthesize water-soluble crystalline salts were applied to the production of many pharmacotherapies, thus facilitating injection of these substances directly into the bloodstream.[1] This technological advance spurred the popularization and standardization of intravenous drug administration, vastly improving the efficiency of pharmacotherapy delivery.[1] The practice of administering psychotropic substances through injection outside of a clinical therapeutic context was, subsequently, taken up by illicit drug users in a variety of settings, particularly among those using stimulants and opioids.[2, 3] Internationally, this behaviour now represents a critical source of health and social harm.[4]

Despite the introduction of international criminal sanctions aimed at suppressing illicit drug markets,[5] interdiction strategies,[6] and a variety of preventive interventions,[7, 8] injection drug use[*] is at historically high levels in settings across the globe.[9] A global estimate published in 2008 suggested that there are approximately 16 million people who inject drugs (IDU) worldwide,[10] the majority of whom are located in China, the United States, and the Russian Federation. The United Nations Office on Drugs and Crime estimates that the number of countries reporting injection drug use has increased over the past

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[*] For the remainder of this thesis, "injection drug use" refers to the illicit intravenous administration of psychotropic substances outside of a clinical therapeutic context

decade,[9] with roughly 75% of the world's 200 countries now reporting this behavior among their populations.[10]

The spread of injection drug use represents a major challenge to public health systems given the many serious health harms associated with this activity, particularly the dramatically heightened risk of human immunodeficiency virus (HIV) and hepatitis C (HCV) transmission,[11, 12] fatal drug overdose,[13] drug dependence,[14, 15] and infections at injection puncture sites.[16-18] Indeed, injection drug use has been implicated in approximately one-third of all HIV infections outside of Sub-Saharan Africa, which has resulted in an estimated 3 million IDU infected worldwide, with some settings particularly impacted by injection-driven HIV epidemics.[19] In China, the United States and the Russian Federation, HIV prevalence among IDU exceeds 10%.[10] Further, HIV prevalence also remains high among IDU in Latin America (29% of IDU infected), Eastern Europe (27%), and Southeast Asia (17%).[9] Additionally, IDU are burdened with unacceptably high levels of HCV infection, with estimates suggesting that over 50% of IDU are infected with HCV across 49 countries and territories, with IDU populations in some settings experiencing HCV prevalence of up to 95%.[20] In response to these ongoing epidemics, a large body of scientific literature has identified a number of risk factors for blood-borne disease transmission among IDU populations, and as a result, a set of evidence-based international guidelines have been developed in an effort to reduce the global burden of disease experienced by IDU.[21]

1.2   Modifying injection career trajectories

In recognition of the negative health impacts associated with injection drug use, experts have long called for the prioritization of the prevention of injecting and the expansion of strategies to reduce injecting, such as addiction treatment.[4, 22] Despite these calls, governments often continue to allocate resources towards ineffective abstinence-oriented anti-drug education and social marketing campaigns,[7, 8] with substantially less effort devoted to develop, implement or bring to scale proven interventions to modify the incidence of injection transition events (e.g., decreasing initiation and increasing cessation of injection drug use) or the risks associated with ongoing injection. This situation persists despite the fact that experts have called for the prioritization of interventions to prevent the initiation of injection drug use and related harms.[4, 22] For example, clinical, evidence-based interventions such as methadone maintenance therapy have been shown to promote injection cessation and contribute to reductions in the length of injection trajectories,[23, 24] while also reducing HIV risk behaviours such as used syringe sharing[24-26] and improving uptake of HIV antiretroviral therapy.[27-29] Despite these positive outcomes, however, the provision of methadone maintenance therapy remains low globally. In the United States, for instance, it is estimated that less than 1 in 8 opioid-dependent IDU have access to some form of opioid substitution treatment, while in China, it is estimated that only 1 in 33 IDU have access.[30] In the Russian Federation, the use of methadone is illegal, with dire consequences, as outlined above. Similarly, while needle and syringe programmes (NSPs) have been shown to contribute to reductions in used syringe sharing and thereby reduce the

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risks associated with ongoing injection, coverage of these services worldwide is critically low, with an average of 22 sterile syringes distributed annually per IDU in the United States, 32 sterile syringes distributed annually per IDU in China, and 4 sterile syringes distributed annually per IDU in the Russian Federation.[30]

The development and implementation of interventions to modify injection careers, including those that reduce the harms associated with ongoing injection, represent urgent public health priorities. In addition to barriers related to the implementation of currently available effective interventions, many scientific challenges remain. For example, while clinical treatment exists for opioid users (e.g., opioid agonist therapy), no equivalent treatment options have been developed for stimulant users, including individuals experiencing amphetamine and cocaine dependence.[4] This has implications for a range of injection-related harms, particularly among stimulant users.[31, 32] A further complication arises from the fact that IDU experience a set of complex, evolving risks across their injection drug-using careers, ranging from varied levels of HIV risk behaviours associated with differing injection career trajectories,[14, 15, 33] to the potential that ongoing injecting among established IDU may facilitate injecting initiation among non-injecting drug users.[31, 34, 35]

1.3   Research aims

Despite the existing research in this area, major gaps remain in the scientific evidence base regarding injection transition events, defined as the initiation and cessation of injection use. First, a relatively small body of quantitative literature has

investigated factors that heighten the risk of injection initiation,[22, 31, 36-42] with most of these largely restricted to examinations of the impact of sociodemographic (e.g., gender and ethnicity) and specific drug-related risk factors (e.g., frequency of heroin and cocaine use).[31, 35, 36, 43-47] However, the potential impact of the use of other drugs, such as crystal methamphetamine, as well as psychosocial factors, such as sensation seeking, on the risk of injection initiation among street-based drug-using populations remains obscure. This situation persists despite the U.S. National Institute of Drug Abuse having identified research into psychosocial risk factors for drug-related harms as a priority research area.[48, 49] Second, studies have suggested that established IDU may play roles in modifying the likelihood of injection transition events among their peers – both with respect to initiation[31, 35] and cessation[50] of injection – though more research into the nature of this phenomenon is required. Third, ongoing injection careers are marked by risk behaviours associated with HIV and HCV transmission.[15, 51] Reducing such risk behaviours remains a public health priority, and the implementation of harm reduction services such as NSPs has repeatedly shown to be effective in this regard.[52-55] Fourth, evaluating the risk for injection cessation events within the context of an expansion of NSPs is therefore necessary to address unproven concerns that NSPs may lead IDU to prolong their injection drug use or result in other drug-related harms such as overdose fatality.[56, 57] As such, further research into the impact of NSP implementation on the likelihood of injection drug use cessation is required.

Collectively, the aforementioned four fields of inquiry represent an important program of research that has the potential to inform public health efforts

to reduce blood-borne disease transmission and other negative health outcomes associated with the injection career trajectories experienced by IDU populations. It is hoped that this dissertation may therefore be valuable for policymakers seeking to implement comprehensive approaches to injection-related harm by considering predictors of injection transition events and the risks associated with ongoing injection. This is done within a conceptual framework that takes into account the changing risks experienced by drug users at different stages of their injection drug use careers. The aim of this dissertation is therefore to investigate sociodemographic, drug-related, psychosocial, peer-based and policy factors associated with injection transition events within a risk environment framework, and to assess how interventions to reduce the risks of ongoing injection may impact the likelihood of these transition events among street-based drug-using populations.

1.4   Study setting

Vancouver, Canada is the site of one of North America's largest open-air illicit drug markets. Located in the downtown eastside neighbourhood of Vancouver, this area is marked by high levels of poverty, ready access to illicit drugs, high levels of drug dependence, and a disproportionately high prevalence of drug-related harms including HIV and HCV transmission, and fatal overdose.[58] Beginning in the early 1990s, the absence of effective and accessible health interventions such as NSPs for people who use drugs in Vancouver, coupled with a shift from the injection of heroin to the injection of cocaine, contributed to a rapidly escalating HIV epidemic among the city's IDU population.[59] This crisis reached its peak in the mid-1990s, when a

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public health emergency was declared in Vancouver after data demonstrated an HIV incidence rate of approximately 19 per 100 person-years among the city's IDU.[60] In response, Vancouver implemented a large, centralized needle exchange program in an effort to reduce injection-driven HIV incidence. However, despite the presence of this intervention, HIV incidence remained high.[60] Researchers concluded that this ongoing crisis pointed to the need for further expanding access to sterile injecting equipment and the implementation of a comprehensive set of public health and harm reduction measures to control the HIV epidemic among the city's IDU population.[60] However, critics opposed to harm reduction approaches argued that the ongoing high rates of HIV incidence were evidence that harm reduction itself was ineffective policy.[61]

Since that time, Vancouver has experimented with a variety of harm reduction-oriented interventions including decentralizing and expanding its NSP,[62] implementing a medically supervised injection facility,[63] and expanding methadone maintenance therapy and opioid substitution programs.[64, 65] This has been coupled with the provision of highly active antiretroviral therapy (HAART) free of charge to all eligible HIV-seropositive individuals in British Columbia, as well as more recent provincial efforts to aggressively seek out, test, treat and retain marginalized populations of HIV-positive individuals such as IDU in HAART.[66] These efforts have been supported by evidence from observational cohort studies of IDU and street-involved youth located in and around Vancouver.[32, 60] Research from these studies has demonstrated that Vancouver's evolving public health-oriented approach has

led to decreasing HIV incidence and reduced incidence of risk behaviours for blood-borne disease transmission (e.g., syringe sharing) among Vancouver's IDU.[62]

Additionally, levels of amphetamine-type stimulant use, including methamphetamine use, have risen globally, with amphetamine-type stimulants now the second most widely-used class of drug worldwide.[9] In Vancouver, this has manifested in particularly high levels of crystal methamphetamine use among the city's street-involved youth.[58] To date, research has demonstrated that crystal methamphetamine use is associated with a variety of harms,[67-70] and preliminary research from Vancouver has suggested that crystal methamphetamine may be associated with an increased risk of initiation of injection among the city's street-involved youth,[71, 72] though more research is needed to clarify this phenomenon.

1.5   Conceptual framework

This research project is primarily grounded in the risk environment framework, with important modifications incorporating two complementary approaches; namely, aspects of personality theory (e.g., sensation seeking) and life course theory. It is hoped that this conceptual approach will facilitate a more comprehensive portrait of the factors that influence injection transition events and related harms across individuals' injection careers. Figure 1 presents a visual depiction of the conceptual framework employed in this dissertation.

1.5.1 Risk environment framework

The risk environment framework, originally developed by Rhodes,[73] allows for the investigation of the social and structural environment experienced by people

who use drugs and an identification of how this environment may modify the range of choices that individuals are able to make regarding drug-related behaviours and other related outcomes. Within this conceptual framework, investigations of drug-related risk and service utilization consider a range of social, structural, policy, economic, and geographic factors and their intersection with individual-level factors at the micro,[74, 75] meso[71, 76] and macro[77, 78] levels to delineate how these mediate the capacity of IDU to refrain from engaging in risky behavior (e.g., used syringe sharing[79] or drug overdose[80]) or from accessing a range of health services including NSPs.[81] This approach is particularly useful in delineating how the application of policies and responses to the risks experienced by street-level drug-using populations are constrained by environmental factors.[82] This approach has previously been employed to demonstrate how the implementation of policies of street-based drug law enforcement, as well as structural factors such as unsanitary public settings, intersect with individual-level safety concerns among IDU to increase the risk of unsafe injection practices such as rushed injecting.[76] Similarly, Rhodes et al. have demonstrated how a lack of sterile syringe distribution as a result of government policies can heighten the risk of unsafe injection practices, while situational factors such as a fear of street-level police enforcement can further impede IDU from injecting safely.[74] The model of the risk environment applied to this dissertation is presented in Figure 1.

Of note, while investigations utilizing the risk environment framework have considered individual-level variables such as the types of drugs used,[83] social network features,[84, 85] and sociodemographic factors,[79] no such study has yet to

consider the psychosocial factor of sensation seeking among street-involved youth, which has previously been shown to heighten the risk of drug use. Chapter 5 of this dissertation therefore includes an investigation of sensation seeking as one individual-level factor that may intersect with environmental factors to heighten the risk of injection drug use among street-involved youth (see Figure 1).

1.5.2 Personality Theory: Sensation Seeking

To complement the risk environment framework, this dissertation draws on personality theory, and on the concept of sensation seeking in particular, which posits that individuals possess an underlying personality trait that influences their innate desire for experiences that are varied, complex and intense, the pursuit of which often involves a measure of risk-taking.[86] Researchers have broadly characterized individuals as either low or high sensation seekers, with high sensation seekers more likely to engage in a variety of risky behaviours;[87, 88]additionally, young people generally report higher sensation seeking scores compared with the older general population.[89, 90] While scientific literature spanning five decades has examined the role of sensation seeking in determining the risk of an individual's involvement in a range of potentially dangerous activities,[86, 90-94] to our knowledge no studies have yet assessed the impact of sensation seeking among street-based drug-using populations such as street-involved youth within a risk environment framework. Individual differences in the personality trait of sensation seeking are considered within the risk environment framework in an investigation of the impact of this psychosocial factor on the risk of injection drug

use and risk factors for injection initiation experienced by street-involved youth, as outlined in Chapter 4.

1.5.3 Life course theory

The investigation of the natural history of injection drug use can be conceptualized as a natural extension of the "life course" approach to sociological research, developed in the 1960s by Mannheim and others as a way to assess the impact of a structural context, social change, or personal events on individual trajectories.[95, 96] Formally, the life course is defined as "a sequence of socially defined events and roles that the individual enacts over time,"[96] and is particularly suited to investigating causal linkages between distal events. This approach has been employed by social epidemiologists, as it offers a way of conceptualizing how underlying sociodemographic or structural factors experienced at various transition stages can impact health outcomes or alter personal trajectories across an individual's life course.[97]

As outlined in Figure 1, the risk environment framework has been extended in two important ways for this dissertation. First, it incorporates personality traits in the form of individual differences in sensation seeking within the range of factors that restrict decision-making around drug-related behaviours. Second, it explicitly seeks to consider injection transition events and injection trajectories over time as socially-defined events, consistent with life course theory. This includes a focus on peer-based factors impacting risk across injection careers. With respect to specific chapters of this dissertation, the risk environment framework will guide variable

selection and methodological approaches of all the analyses presented in Chapters 4-6, with the psychosocial trait of sensation seeking investigated in Chapter 5. Furthermore, life course theory will be employed primarily in Chapters 4, 6 and 7 to conceptualize how the risk environment may vary over time, with a particular focus on exploring how injection transition events are socially-defined through peer influence between individuals at varying stages of their injection careers. It is hoped that this conceptual framework will inform a more comprehensive overall understanding of how factors associated with one stage of the natural history of injection drug use may impact other stages.

1.6   Study objectives and hypotheses

This project thus has four main objectives:

1. **To systematically review the scientific literature on interventions to prevent the initiation of injection drug use, and to critically assess the effectiveness of these interventions among vulnerable populations such as street-involved youth.** To address this objective, Chapter 3 presents the results of a systematic review of peer-reviewed studies that evaluated interventions to prevent injection initiation.

2. **To examine the impact of crystal methamphetamine use on the risk of injection drug use initiation among street-involved youth, and to present micro-setting characteristics of injection initiation events.** Despite high levels of crystal methamphetamine use in a range of settings including Vancouver,[9] little is still known regarding the impact of the use of

this drug on the risk of injection initiation. Furthermore, data delineating the specific characteristics of injection initiation events may help to contextualize efforts to determine the risk factors that contribute to injection initiation. The analyses presented in Chapter 4 will therefore test the hypothesis that use of crystal methamphetamine is independently associated with the risk of initiation of injection drug use among street-involved youth in Vancouver.

3. **To adapt and validate a psychometric tool to assess the impact of sensation seeking on the risk of injection drug use among vulnerable drug-using individuals.** While high sensation seeking has been previously identified as a predictive factor for drug use among the general population,[98] little is known regarding its role as a determinant of risky behaviours among drug-using populations, and in particular among street-involved youth. Additionally, although a wide range of sociodemographic, behavioural, social and structural risk factors for injection-related harms have been identified in the epidemiologic literature, the impact of sensation seeking on the risk of injection drug use among vulnerable, drug-using individuals remains unclear. The analysis presented in Chapter 5 will therefore test the hypothesis that participant score on a modified substance use-specific brief sensation seeking scale is associated with injection drug use, crystal methamphetamine use, and other risky drug-related behaviours among a cohort of street-involved youth in Vancouver.

4. **To investigate the incidence of injection drug use cessation within a high-risk setting, and to determine the impact of an expansion of syringe distribution services on this setting over time.** A large body of literature has demonstrated that NSPs are effective in reducing the risk of used syringe sharing, which remains a primary mode of blood-borne disease transmission among IDU in many settings.[99, 100] However, concerns remain among policymakers and the general public regarding the potential of such interventions to cause IDU to delay the cessation of injection.[56] This concern has contributed to low levels of implementation of these interventions internationally.[30] The analysis presented in Chapter 6 seeks to address this concern by investigating the incidence of injection cessation among a cohort of IDU in a high-risk setting in Vancouver characterized by an expansion of NSP sites.

1.7 Study design and methods

The analyses presented in Chapters 4-6 of this dissertation employ data from ongoing, linked studies of street-involved youth and IDU in Vancouver, Canada. While the analytic approaches differ for each chapter and will be described therein, the data sources and methodological commonalities are delineated here to avoid duplication.

Vancouver Injection Drug Users Study

The Vancouver Injection Drug Users Study (VIDUS) is an ongoing, prospective community-recruited cohort study of IDU that has been in operation

since 1996. Beginning in May of that year, recruitment began for IDU who reported injecting drugs in the previous month and resided in the Greater Vancouver region,[60] and this recruitment has been undertaken on an ongoing basis since that time. All participants are recruited through street outreach and self-referral, and provide written informed consent prior to entering the study. At baseline and regular semi-annual follow up visits, study participants complete interviewer-administered questionnaires, provide blood samples for diagnostic testing, and undergo physical examination from a trained research nurse to inspect for stigmata of drug injecting. Participants are provided with a $20 CND honorarium for each visit and, when appropriate, are referred to additional health care services. Ethical approval for VIDUS, as well as for the analysis undertaken in Chapter 6 of this dissertation project that employs VIDUS data, have been granted by the University of British Columbia/Providence Health Care Ethics Review Board.

At-Risk Youth Study

The At-Risk Youth Study (ARYS), established in 2005, is an open and ongoing prospective cohort of street-involved youth aged 14 to 26 based in Vancouver, Canada.[32] All ARYS participants are recruited through street outreach and self-referral, and participants are eligible if they reported using illicit drugs other than marijuana in the 30 days prior to recruitment. Once enrolled, participants complete an interviewer-administered questionnaire at baseline, as well as physical and mental health assessments, including blood sampling for diagnostic testing, and assessment for physical stigmata of drug injecting. Subsequently, participants complete physical examination and interviewer-administered questionnaires semi-

annually, which solicit basic sociodemographic and drug use data, along with data on other relevant behaviours including drug injecting. Participants are provided with a $20 CND honorarium at each visit and, when appropriate, are referred to additional health care services. The study, along with the analyses undertaken in Chapters 4 and 5 of this dissertation that employ ARYS data, have been approved by the University of British Columbia/Providence Health Care Ethics Review Board, and all study participants provided written consent prior to enrolment.

1.8 Summary

This dissertation includes seven chapters. The introductory chapter provides an overview of the evidence pertaining to injection-related harm, with a particular focus on describing the current research gaps related to the initiation and cessation of injection drug use as well as the conceptual framework employed throughout. It also identifies limitations in the existing scientific literature on the natural history of injection drug use, and frames how this dissertation will contribute to the scientific literature in this area. Chapter 2 provides a narrative overview of the natural history of injection drug use in order to contextualize empirical analyses undertaken in Chapters 4-6. Chapter 3 presents the results of a systematic review describing scientifically evaluated interventions to prevent the initiation of injection drug use. Chapters 4 to 6 present the quantitative empirical analyses of this dissertation. First, the impact of crystal methamphetamine use on the risk of injection initiation among street-involved youth, as well as micro-setting characteristics of injection initiation events are investigated in Chapter 4. The adaptation and validation of a substance

use-specific sensation seeking scale, and an investigation of how sensation seeking may impact the risk of injection drug use and risk factors for injection initiation among street-involved youth is presented in Chapter 5. Finally, an investigation of the risk environment influencing injection drug use cessation among IDU during a period of substantial expansion of NSPs is presented in Chapter 6. Chapter 7 summarizes and synthesizes the key findings of this dissertation. The implications of the findings are discussed, particularly within the context of informing new and ongoing efforts to comprehensively address the incidence of injection transition events and injection-related harms. The limitations of the methodological and conceptual approaches employed in this work are also described. Finally, Chapter 7 provides a set of key recommendations for future research.

Figure 1. Conceptual model to investigate injection transition events among illicit drug users in Vancouver

Macro-Structural Environment
- Drug policies
- Housing policies
- Economic policies

Meso-Social/Physical Environment
- Spatial distribution of services
- Spatial distribution of treatment
- Spatial distribution of networks
- Housing availability
- Illicit drug availability
- Intensity of policing

Individual-Level Factors
- Gender
- Age
- Ethnicity
- Drugs used
- Drug dependence
- Sensation seeking
- Trauma

Intermediate Pathways
- Access to preventive interventions
- Access to harm reduction services (NSPs)
- Drug dealing
- Sex trade
- Public drug

Intermediate Outcomes
- Sensation seeking
- Crystal methamphetamine
- Exposure to

Primary outcomes
- Injection initiation
- Injection cessation

Micro-Social/Physical Environment
- Initiation event setting
- Interactions with police
- Income acquisition strategies
- Social/sexual relationships
- Clean drug equipment

Individual-level and psychosocial factors interact with macro-structural, meso- and micro-social/physical environments to determine socially-defined events and roles that facilitate injection transition events via intermediate pathways and outcomes *(Adapted from Rhodes, 2002, 2009;Mannheim, 1928; Elder. 1998)*

CHAPTER 2: THE NATURAL HISTORY OF INJECTION DRUG USE

2.1   Introduction

Beyond blood-borne disease transmission and drug overdose,[101] a range of other health and social harms are associated with injection drug use, including cellulitis,[16] abscesses,[17] incarceration,[102] and engagement in acquisitive and drug market-related crime.[103, 104] However, these harms are not static over individuals' injection drug-using careers, and IDU at different stages of their drug use exhibit varying levels of risk. For instance, studies have shown that young and recently-initiated IDU have a higher risk of overdose and blood-borne disease transmission compared with older or more established IDU.[105, 106] As such, while a variety of interventions to reduce the harms of injection drug use have been developed, challenges remain in ensuring that these interventions both address the needs of, and are effective at delivering services to, IDU at various stages of their injecting careers.

The investigation of the natural history of injection drug use requires research focused on multiple stages of injection careers: the identification of risk factors for injecting initiation; the characterization of specific injection career trajectories and injection cessation patterns; and the evaluation of injection-related morbidity and mortality. Despite a substantial literature examining these issues individually, there do not appear to be any published reviews summarizing this research in the context of the overall natural history of injection drug use. The present narrative review seeks to address this gap by broadly describing the scientific literature in this area.

2.2 Methods

2.2.1 Search strategy

We searched the following 10 electronic databases: PubMed, PsycINFO, EMBASE, Cochrane CENTRAL, CINAHL, Web of Science, TOXNET, AIDSLINE, AMED and ERIC. We also searched the internet (Google, Google Scholar), relevant academic conference abstract lists, and scanned the references of potentially eligible studies. Each database was searched for English language articles from its inception to January 4, 2013. We reviewed all studies and included the most representative examples to illustrate the state of research on this topic. Keywords included "natural history of injection drug use", "injection initiation", "mortality", "injection career trajectory", "injection drug use", "injecting trends" and "injecting pattners".

2.3 Results

2.3.1 Initiation of injection drug use

Street-involved youth are at highest risk of initiating injection drug use,[31, 40, 46] and research into injecting initiation has thus focused almost exclusively on this population. In a study of data from a prospective cohort of street-involved youth in Montreal, researchers investigated predictors of injection initiation among cohort participants that reported never having injected at baseline (n = 415).[26] After five years (1995-2000), 74 of the street youth had initiated injection for an incidence rate of 8.2 per 100 person years. Further, the researchers identified key structural and peer-based factors that significantly increased the risk of initiation. In particular, having been homeless in the last 6 months was associated with the largest increase in risk of initiating injection among all study participants. Among female

participants, however, having an IDU friend was associated with an even greater –
fourfold – risk of initiating injection. Other factors that significantly increased
initiation risk included being under 18 years old, use of heroin in the previous
month, and having experienced extra-familial sexual abuse.[26]

Similarly, a qualitative study undertaken by Harocopos et al. found that,
among a cohort of newly-initiated New York City-based IDU (n = 54), decisions to
begin injecting were influenced by exposure to injecting.[38] Within this context, the
authors describe how, among newly-initiated IDU, exposure to injecting was
associated with a decrease in the fear of injecting and a corresponding increase in
the acceptability and, in certain cases, feeling of inevitability regarding injection
initiation.[38] Further, despite the oft-reported unwillingness of established IDU to
initiate injection-naïve individuals, the authors describe the tenacity of many newly-
initiated IDU in seeking help in initiating injection from IDU in their social
networks.[38]

In an effort to determine the impact of spatial, network, and
sociodemographic factors on the age of injecting initiation, Baltimore-based IDU
were enrolled in the REACH II study between July 1997 and May 1999 (n = 144).
Researchers then investigated the impact of neighbourhood characteristics (e.g.,
employment level, poverty level, education level, and ethnic composition),
participation in a high-risk drug-using network, and IDU ethnicity on initiation. In
logistic regression analysis, injecting before the age of 21 years old was, among
African-American participants, significantly associated with residing in a
neighbourhood with a large minority population and low levels of education.

Further, after adjustment for neighbourhood effects, those who initiated prior to the age of 21 were, after initiation, subsequently more likely to participate in a high-risk network within two years. This association between neighbourhood of residence and risk of injecting has been identified in other settings.[71, 107]

Recent research has identified specific drug-related behaviours that also appear to place individuals at higher risk of injecting. For example, Trenz and colleagues, noting that early onset polysubstance use has been identified as a predictor of subsequent substance use problems, sought to investigate the role of polysubstance use on subsequent risk of injection initiation among IDU and non-IDU using cross-sectional and retrospective data from the Baltimore-based NEURO-HIV cohort study.[108] After adjustment for a variety of potential confounders, the authors found that reporting early onset polysubstance use (e.g., 15 years old or younger) was significantly associated with reporting injection drug use. In a separate study, researchers in Vancouver conducted an investigation of drug-related factors potentially associated with early adolescent initiation of injection drug use (e.g., 16 years or younger) among participants in the Vancouver Injection Drug Users Study (described in full in section 1.7).[109] In multivariate analysis, the proportion of IDU that initiated injecting in early adolescence was greater among those that reported binge drug use, involvement in the sex trade, and a history of incarceration.[109] Additionally, a separate study from Des Jarlais and colleagues examined the impact of the implementation of needle exchange programs on the risk of injecting.[110] The authors found that, among the roughly 2,000 patients entering a methadone clinic annually in New York City for treatment, the period during and after the large-scale

implementation of needle exchange programs was associated with a decreased number of patients reporting opioid injecting at admission, and an increase in the number of those reporting intranasal opioid use ($p < 0.001$). The authors therefore concluded that the implementation of needle exchange programs in the study setting was unlikely to have resulted in an increase in injecting.

The vast majority of studies on injection initiation are undertaken among youth residing in urban studies. However, one recent study investigated risk factors for injection initiation among a cohort of rural drug users residing in and around Appalachia, a region of the United States that spans the southern edge of New York state to northern Alabama, Mississippi, and Georgia.[47] Among this cohort (IDU n = 394; non-IDU n = 109), illicit use of the prescription opioid OxyContin, as well as other prescription opioids, was associated with a significantly increased hazard of injection drug use.[47]

While research regarding personality-based risk factors for injection initiation is limited, a small evidence base has investigated this association. For instance, Semple and colleagues employed measures of sensation seeking, impulsivity, depression, self-perceived stigma, and self-perceived social support as potential predictors of injection drug use among a cohort of crystal methamphetamine-using men who have sex with men.[92] The authors found that, while sensation seeking score or depression were not significantly different between those who did and did not report injecting, injection drug users reported significantly higher levels of impulsivity and stigma, and significantly lower levels of social support. It should be noted, however, that the sensation seeking scale items

employed were restricted to a subscale measuring risk-taking, one of the four domains underlying sensation seeking. Similarly, a Baltimore-based study of young recently-initiated IDU using REACH data found that the majority of participants (43%) reported initiating injection as a result of curiosity or thrill-seeking,[111] though this was measured using a single questionnaire item. Interestingly, a greater proportion of female participants (48%) than male participants (38%) reported curiosity/thrill-seeking as the primary motivation to initiate.

2.3.2   *Longitudinal patterns of injecting drug use*

Because of the many harms of ongoing, untreated injection drug use, identifying the major longitudinal patterns of injecting is of central importance to public health efforts to reduce the incidence of this behaviour. To that end, research from the AIDS Linked to the Intravenous Experience (ALIVE) study, a community-based cohort of IDU in Baltimore (n = 1,176), has identified five major injection trajectories: early cessation (e.g., sharp decline in injecting within five years), delayed cessation (e.g., less steep decline within 10 years), late cessation (e.g., less steep decline within 15 years), frequent relapse (e.g., relatively consistent injecting within 15 years and decline thereafter), and persistent injection (e.g., high and sustained level of injection drug use).[51] Using data collected over the study period (1988 to 2008), ALIVE researchers assessed the frequencies of these five trajectories, and found that, among Baltimore IDU, persistent injection was most commonly reported (32%), followed by early cessation (19%), late cessation (18%), delayed cessation (16%), and frequent relapse (16%) (n for each trajectory not

reported). In an adjusted model, those participants exhibiting early cessation were significantly more likely to exclusively inject heroin, report non-injection heroin use, and have injected for fewer years at baseline compared with those exhibiting late or delayed cessation patterns. They were also significantly less likely to report having had sex with an IDU partner or having been incarcerated.[51] Additionally, those who ceased injecting early were more likely to report a history of addiction treatment compared with individuals in the persistently injecting or relapse groups. Interestingly, neither age nor HIV-serostatus differed significantly between injection trajectories.

The Drug Abuse Treatment Outcome Study (DATOS) is a longitudinal multi-site cohort of illicit drug users located in eight US cities.[15] In a five year study restricted to IDU enrolled in the cohort (n = 1,393), researchers investigated injection risk trajectories using growth mixture modeling to identify latent classes by slope or trajectory.[15] Using this approach, the study authors identified four distinct injection risk trajectories, including low and stable injecting risk (n = 1,100, 79%), moderate and stable risk (n = 176, 13%), high and decreasing risk (n = 69, 5%), and high and increasing risk (n = 48, 3%). Compared to all other participants, those individuals reporting high and increasing risk of injection exhibited higher levels of incarceration, mental illness, residential and outpatient drug treatment experience, and receipt of HIV/AIDS-related services of any kind.[15] The authors did not detect significant differences in level of mean income between participants by trajectory type. Participants reporting high and moderately high risk of injection did, however, report higher levels of heroin use, while those with low and stable risk of

injection reported higher levels of cocaine use. The study authors reported that these differences remained consistent after five years, though injection risk and related behaviours declined among all trajectory groups over this period. Relatedly, a study of syringe sharing conducted by Brook and colleagues found that male IDU in New York City that reported higher sensation seeking (based on responses to a single questionnaire item) were more likely to report sharing used syringes, which may signal an increased risk of HIV transmission among this subgroup.[94] Among female IDU, however, sensation seeking was not significantly associated with syringe sharing.[93] In a separate study conducted by Fenaughty and colleagues, measures of sensation seeking were also significantly associated with high-risk sexual activity (e.g., having multiple partners, inconsistent condom use and involvement in the sex trade) among a cohort of IDU in Anchorage, Alaska.[91]

A study by Bruneau et al. investigated sustained cessation of injection drug use among a cohort of IDU in Montreal, Canada ($n = 1,004$) over a four year period, with sustained cessation defined as at least seven consecutive months of no injection drug use.[33] In total, 186 (19%) IDU participants reported a sustained cessation event during the study period. In logistic regression, initiating injection drug use after 35 years of age and crack cocaine use were both significantly associated with cessation, while HIV-seropositivity, a greater reliance on illegal income versus legal income, and a higher cumulative time spent incarcerated were all significantly inversely associated with cessation. The authors also identified a trend wherein greater intensity of injection was associated with a lower likelihood of injection cessation, though this did not reach statistical significance. The authors

therefore suggest that it is likely that IDU who inject intensely are at higher risk of continuing to inject in the near future.[33] Consistent with prior research,[112] non-injection crack use was also associated with injection cessation in this study,[33] which highlights the role that the use of specific drugs may play in personal decisions concerning mode of drug administration. Further, a 4-strata categorical measure of addiction treatment uptake, ranging from zero time to over 24 weeks enrolled in treatment, was not significantly associated with injection cessation. The authors suggest that this finding, "illustrates the spontaneity of the occurrence of injection cessation among IDUs in this study and its independence from previous or current drug treatment," while also suggesting that this lack of association may be the result of a high proportion of cocaine users in the cohort, a group for whom effective clinical treatment modalities remain largely elusive.[113]

Additionally, in a subanalysis restricted to those reporting sustained injection cessation, in which participants were stratified by sources of syringe acquisition, those IDU that injected at least once daily and acquired syringes from NSPs or pharmacies were more likely to report sustained cessation events.[33] The authors suggest that this may be because NSPs and pharmacies provide counseling, HIV testing and formal referral to addiction treatment in their study setting, which likely increases the capacity of frequent IDU to initiate addiction treatment and thus cease injecting. This finding should, however, be considered within the context of the lack of significance between addiction treatment enrolment and cessation events observed in the larger adjusted regression model.

Finally, a study by Latkin and colleagues specifically investigated the impact of peer influence on the injection career trajectories of IDU enrolled in the Stop AIDS For Everyone (SAFE) cohort (*n* = 338), which was nested within the Baltimore ALIVE cohort.[114] The SAFE study investigated HIV risk behaviours among IDU who were randomly enrolled in either a six-session cognitive-behavioural HIV/AIDS preventive intervention or standard HIV testing and counseling on risk reduction. Further, all participants underwent a 'network interview' and were asked to bring two members of their drug-using network to the study site. These protocols were put in place to determine the characteristics of participants' drug-using and support networks. This information was then integrated into a single variable that defined an individual's network characteristics based on the relative proportion of contacts they have in their drug use network, sexual network, and support network. After 5 months of follow-up, participants that reported ceasing injection were found to have a significantly smaller drug-using network relative to the size of their sexual or support networks.[114] Finally, the authors found no association between enrolment in detoxification programs and likelihood of ceasing injection drug use, though they did observe a marginally significant association (*p* = 0.06) between enrolment in methadone maintenance therapy and injection drug use cessation.

2.3.3   *Injection-related mortality*

A number of studies have investigated excess mortality among cohorts of IDU, with some research documenting death rates among samples of IDU more than 10 times that expected among age-matched non-drug-using populations.[115-118]

Degenhardt and colleagues recently conducted a series of systematic reviews and meta-regressions on mortality data from cohorts of individuals using opioids, cocaine, amphetamines, and benzodiazepines, many of whom were IDU.[119-122] Across all studies assessing mortality among heroin users (*n* = 58), 36 (62%) reported on injection-related mortality outcomes. In total, the authors calculated a standardized mortality ratio (SMR) of 14.66 (95% CI: 12.82-16.50) for opioid users, with the SMR of female opioid users higher than that of male opioid users. Causes of death varied, with fatal overdose being the most common cause of mortality (0.65 deaths per 100 person-years), followed by trauma (0.25 deaths per 100 person-years) and suicide (0.12 deaths per 100 person-years).[120]

While results of a systematic review of cocaine-related mortality were limited (*n* = 7), injection cocaine-related causes of death were reported for the ALIVE cohort of IDU in Baltimore and the Vancouver Injection Drug Users Study (VIDUS).[119] Among ALIVE participants that reported injecting cocaine, the majority of deaths (35.4%, 95% CI: 24.4-46.4) were due to AIDS-related illnesses, while among VIDUS participants, these were responsible for the second-largest proportion of all deaths (20.0%, 95% CI: 12.2-27.8). Overdose mortality was responsible for the second-largest proportion of deaths among ALIVE participants that only reported using cocaine (11.4%, 95% CI: 6.1-16.7), and was the primary cause of death among all VIDUS participants (35.5%, 23.8, 46.9).

The results of the other two systematic reviews undertaken by Degenhardt and colleagues suggest that there exists a dearth of scientific research on mortality among people who use amphetamines and benziodiazepines.[121, 122]

Researchers have also examined the risk of mortality among IDU at different stages of their injecting career. For example, Vlahov and colleagues found that a sample of IDU in Baltimore that had initiated injection drug use within the previous two years (*n* = 256) experienced significantly increased levels of mortality compared with demographically-similar, established IDU.[123] Davoli and colleagues also assessed mortality longitudinally among IDU in Rome (*n* = 4,200) between 1980 and 1992, and found that the age-adjusted all-cause mortality rate increased from 7.8/1,000 person-years in 1980 to 27.7/1,000 person-years in 1992.[124] This persistent increase in the mortality rate among IDU was attributed primarily to AIDS-related illnesses. The cumulative risk of death among cohort participants was 29.3% by the age of 40.[124]

2.4   Discussion

Decades of research on the predictors of injection-related behaviours have enabled the identification of long-term patterns of injection drug use, and, by extension, have allowed researchers to delineate the natural history of injection drug use in a variety of settings. Research conducted to date in this area has highlighted the role of structural, social, personality-based and sociodemographic factors in modifying the risk of injection initiation, including the impact of ethnicity, neighbourhood of residence, and IDU peer influence on risk of initiation; common injecting trajectories (some of which are associated with increased blood-borne disease transmission risk); and major causes of injection-related mortality such as AIDS-related illnesses and fatal overdose.

These results have implications for the development of interventions that seek to limit drug use and drug-related harms including mortality across an individual's injecting career. For example, those IDU that exhibit a high and increasing risk of injecting have been shown to be at higher risk of engaging in risky behaviours such as syringe sharing.[33] However, as noted above in the study by Bruneau and colleagues, IDU that injected frequently and attended a NSP were significantly more likely to cease injecting compared to non-attenders. Interestingly, similar results were not observed among IDU that attended a NSP but injected less frequently. This may suggest that, in certain settings, more frequent exposure to NSPs may result in a greater uptake of secondary public health services such as addiction treatment, as may have been the case in the study undertaken by Des Jarlais and colleagues in New York City.[110] Though counterintuitive in some respects, these results suggest that interventions such as NSPs may have the potential to provide a range of services to hard to reach subpopulations, and should be considered within the continuum of interventions to reduce ongoing injection.[4, 21, 125]

As is evident from the literature described above, the vast majority of studies on the natural history of injection drug use are undertaken with data from cohorts of individuals that are already actively injecting at baseline. As such, there are few longitudinal studies on the natural history of injection drug use involving populations at risk of initiating injection, such as street-involved youth. Conversely, studies of injecting initiation have generally structured this event as a discrete

outcome, rather than exploring initiation within the context of an emerging drug-using career.

Research has identified exposure to injecting as a key predictor of initiation of injection drug use among populations at risk, such as street-involved youth.[34] Similarly, as described above, the composition and magnitude of an individual's injecting network may play a key role in enabling injecting initiation or prolonging an individual's injecting career,[114] as has been found with other sources of ill health such as tobacco smoking and obesity.[126, 127] In both these cases, research demonstrates that tobacco smoking and obesity may both arise as a result of the selection of individuals in an individual's social network, which may then reinforce an individual's behavior.[128, 129] Structural interventions such as supervised injection facilities, which have the potential to both reduce community exposure to injecting and facilitate the entry of IDU into the addiction treatment continuum, may therefore be effective in disrupting high-frequency injecting trajectories.[63, 125]

Finally, high rates of mortality among IDU point to the urgent need to develop effective interventions in this area. Indeed, with respect to AIDS-related illnesses, the adoption of expanded access to antiretroviral therapy among IDU populations as part of a 'seek, test, treat, and retain' strategy has the potential to dramatically reduce AIDS-related mortality among IDU population, while also reducing the incidence of HIV transmission.[66, 130] Additionally, the ongoing high incidence of overdose experienced by IDU highlights the need for the dissemination of primary response interventions such as take home naloxone, both in isolation and as part of a comprehensive package of interventions to reduce drug-related

morbidity and mortality.[131-133] In this regard, research has demonstrated the potential of supervised injecting facilities in reducing neighbourhood-level overdose mortality among IDU.[134]

In sum, this review described a variety of studies relevant to the delineation of the natural history of injection drug use. While individual patterns of use vary, researchers have identified a variety of factors that impact the risk of injecting initiation, along with primary injecting patterns,[14, 15] and major causes of injection-related mortality. In light of accumulating evidence, policymakers should prioritize interventions that comprehensively seek to prevent injecting,[114] address immediate drug-related harms (e.g., NSPs and other harm reduction interventions),[21] and work to modify long-term high-risk injecting trends (e.g., methadone maintenance therapy).[24]

CHAPTER 3: A SYSTEMATIC REVIEW OF INTERVENTIONS TO PREVENT INJECTION DRUG USE

3.1 Introduction

Street-involved youth and newly-initiated IDU are at particularly high risk for a variety of drug-related harms. For example, young IDU populations have been shown to engage in high levels of needle and syringe sharing,[105, 135, 136] and as a result are at elevated risk of HIV and HCV transmission. Research has also demonstrated that street-involved youth who begin injecting are more likely to experience overdose, violence, lack of education about drug use, mental illness,[31, 37, 137, 138] and to engage in polysubstance use,[108] highlighting the challenges in developing public health and harm reduction interventions tailored to this population.[4, 22, 139] As outlined in Chapter 2, while studies have demonstrated a range of risk factors for injection initiation, interventions to prevent injection drug use have not been subjected to systematic review and impact assessment.

We therefore sought to systematically search the existing peer-reviewed scientific literature in order to identify and assess interventions to prevent the initiation of injection drug use.

3.2 Methods

We employed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for the development of systematic reviews.[140]

3.2.1 Eligibility criteria

In order to be eligible for inclusion, studies had to be peer-reviewed and had to assess a specific intervention to prevent the initiation of injection drug use among non-injectors. Studies that did not assess original data (i.e., reviews) were not eligible for inclusion. Randomized controlled trials (RCTs) and observational studies were both eligible for inclusion. However, studies that identified risk factors for the initiation of injection drug use but did not identify or evaluate an intervention to prevent injecting were not eligible for inclusion. Further, studies that assessed interventions to reduce the frequency of ongoing injecting or those that seek to transition current injectors into non-injection or abstention from drug use were not eligible for inclusion.

3.2.2 Information sources

We searched the following 10 electronic databases: PubMed, PsycINFO, EMBASE, Cochrane CENTRAL, CINAHL, Web of Science, TOXNET, AIDSLINE, AMED and ERIC. We also searched the internet (Google, Google Scholar), relevant academic conference abstract lists, and scanned the references of potentially eligible studies.

We searched all English-language studies and abstracts and set no date limits. Search terms included "initiation," "injection drug use," "prevention," "intervention," and "injecting." The terms were searched as keywords and mapped to database specific subject headings/controlled vocabulary terms when available, including MeSH terms for PubMed searches. Each database was searched from its inception to its most recent update as of December 1st, 2012 for English language articles.

3.2.3   Study selection

Two investigators (DW, GR) conducted the search independently and in duplicate using a predefined protocol. The investigators scanned all abstracts and obtained full texts of articles that potentially met the eligibility criteria. Validity was assessed in duplicate based on eligibility criteria. After all potentially eligible studies were collected, consensus was achieved by comparing the two review datasets. Any differences were reviewed by two investigators (DW, GR) and a final decision to include or exclude was then made.

3.2.4   Data collection process

Between December 1st, 2011 and June 1st, 2012, data were extracted using a standardized form that solicited information on study design, setting, sample size and characteristics, study length, type of intervention, and measures of effectiveness. The data were then entered into an electronic database.

3.2.5   Quality assessment

The methodological quality assessment checklist developed by Downs & Black was employed to evaluate the relative quality of reporting for all studies included in the review. This approach evaluates studies with respect to five different areas: reporting of hypotheses, outcomes, measurement, results, and conclusions; external validity; controlling for potential bias; controlling for potential confounders; and statistical power. Studies are given a score between 1 and 18, with 18 representing a perfect score.[141]

3.2.6   Risk of publication bias

The scientific literature on anti-drug interventions such as education-based prevention campaigns has been shown to be affected by publication bias through a lack of publication of studies with negative or null findings.[142] Given the similarity in outcomes between these interventions and those designed to prevent injecting initiation, a similar bias may affect the publication of studies relevant to this systematic review.

3.3 Results

3.3.1 Study selection and characteristics

As shown in Figure 1, the initial search yielded 384 studies, of which 78 met the eligible criteria. Sixty-one studies were excluded because they did not directly evaluate an intervention to prevent injecting initiation, while nine additional studies were excluded because they consisted of reviews and did not present original data. Eight studies (combined n = 2,414), published between 1992 and 2011, met the eligibility criteria and were included in the review.

3.3.2 Methodological quality assessment

Out of a possible score of 18, the Downs & Black scores for individual study quality ranged from 10 to 17, with a median score of 13.5 (IQR = 11.0 – 16.5).[141] Lower scores were most often related to a lack of reporting study characteristics, with only 5 studies (62.5%) providing full details on sample characteristics, outcome measures, analytic approaches, and findings. Additionally, only 4 studies (50.0%) provided information on, or adequately adjusted for, potential confounders.

Only one study (12.5%) provided detailed information such as intervention implementation and materials/processes used.

3.3.3 *Results of individual studies*

Eligible studies are presented in Table 1. As shown, sample sizes ranged from 86 to 900 participants (Median = 125, Interquartile Range [IQR]: 91 – 682). Five studies (62.5%) were conducted in North America, and one each (12.5%) in Europe, Australia, and Central Asia. Four major types of preventive interventions were evaluated in the studies: social marketing,[143] peer-based behavior modification,[144-146] addiction treatment,[147] and deterrent/enforcement-based interventions.[148-150] Seven studies (87.5%) employed quantitative methods; one study (12.5%) employed qualitative methods.[143] Of the seven quantitative studies, three (42.9%) employed a longitudinal observational design,[146, 147, 150] two studies (28.6%) used a RCT design,[144, 145] and two (28.6%) employed a lagged cross-sectional design.[148, 149] Among longitudinal studies, the median study period was 18 months (IQR = 4.5 – 78.3). The majority of studies (75.0%) involved human participants and assessed rates of injecting initiation via self-report. Two studies (25.0%) employed US metropolitan centers as the unit of measurement and extrapolated annual metropolitan-specific rates of injection drug use based on surveillance and administrative data.[148, 149]

Social marketing

One study evaluated the impact of a social marketing intervention to prevent injecting initiation.[143] This study involved the targeted dissemination of addiction-

themed posters to Montreal street youth over the period of two and a half months. Each poster communicated a unique injection-related harm (e.g., increased drug dependence, blood-borne disease transmission, sex trade involvement) and public postering was undertaken in and around 61 participating establishments known to cater to street-involved youth in Montreal.[143] Data from in-depth qualitative interviewing suggested that campaign penetration was high, and the vast majority of study participants (84-93%) agreed with the statement that the posters were effective in preventing young people from initiating injection.[143]

Peer-based behavior modification

Three studies assessed the impact of peer-based behavior modification on risk of injecting initiation,[144-146] and tested the hypothesis that peer injectors contribute substantially to the initiation of injection-naïve drug users. Two of these studies evaluated an intervention dubbed "Break the Cycle" in the United Kingdom, Uzbekistan and Kyrgyzstan.[145, 146] Break the Cycle involves engaging with peer injectors to reduce injection-naïve drug users' exposure to, and to provide education regarding the harms of, injecting.[145] The first study evaluating "Break the Cycle" in the United Kingdom (n = 86) found that IDU had a significantly lower likelihood of reporting having injected in front of non-IDU in the 3 months after the intervention (p = 0.047). Further, requests to initiate non-IDU dropped by more than half, from 36 to 15, in the 3 months after exposure to the intervention (p = 0.038). Additionally, there was a significant association between exposure to the intervention and a decreased likelihood of IDU reporting willingness to initiate non-IDU (p < 0.001). The second "Break the Cycle" study conducted in Uzbekistan and Kyrgyzstan (n =

856) reported similar findings: after exposure to the intervention, the proportion of IDU that reported helping non-IDU initiate injection decreased significantly from 23.2% of the cohort to 9.8% ($p < 0.001$), and the authors estimated that the overall number of new injecting initiates decreased from 67 in the year prior to the intervention to 30 in the year after implementation.[146]

The third study assessed the impact of a social learning program on risk of injecting initiation among a cohort of intranasal heroin users (i.e., heroin 'sniffers') in New York City ($n = 104$).[144] The intervention consisted of four AIDS education and injecting prevention sessions, which participants were randomly selected to attend four times over a period of two weeks, and which included group discussion, informational materials, and skill-building to avoid injecting. The control condition involved basic AIDS education and HIV antibody test counseling. At a 9-month follow-up, approximately twice as many control arm participants had initiated injection compared to experimental arm participants (33% *vs.* 16%), and those participants in the experimental arm were found to be significantly less likely to report injecting drugs despite adjustment for potential confounders (Adjusted Odds Ratio [AOR] = 0.51, 95% Confidence Interval [CI]: 0.27 – 0.99, $p < 0.05$).[144]

Treatment

One study examined the impact of addiction treatment access on injecting initiation among a cohort of intranasal heroin users.[147] The authors employed a two-stage design; initially, a case-control approach was used in which intranasal heroin users, newly-initiated injection heroin users, and established injection heroin users were grouped separately, and compared on their reported access to heroin

addiction treatment. The second stage of the analysis investigated whether access to addiction treatment during the period of intranasal heroin use affected transition patterns into injecting. In a Cox regression analysis, the authors found that an increased number of times in treatment was significantly associated with a decreased likelihood of injecting (Adjusted Hazard Ratio [AHR]: 0.72, $p < 0.001$), suggesting that access to treatment may increase the length of time that individuals avoid injecting.[147]

Deterrence

Three studies examined the impact of drug law enforcement on the initiation of injection drug use.[148-150] Two of these studies investigated the long-term deterrent impact of legal repressiveness on the prevalence of injecting initiation in metropolitan centers in the United States. In the first,[148] legal repressiveness was measured by the number of drug-related arrests per metropolitan center, the number of police employees per capita, and expenditures on corrections per capita for the years 1994 to 1997. The overall annual prevalence of IDU in the year 1998 was the dependent variable. Despite adjustment, the authors found no significant association between any of the measures of legal repressiveness and the subsequent prevalence of IDU. However, the authors did observe a significant association between the measures of legal repressiveness and increased HIV prevalence among IDU (all three $p < 0.05$). In a follow-up study,[149] the authors examined the prevalence of injection drug use among 93 US metropolitan centers from 1992 to 2002 that employed similar surveillance data on injection drug use and measured legal repressiveness through the rate of 'hard drug' arrests (e.g. arrests for the

unlawful possession of opium or cocaine or their derivatives, such as morphine, heroin, or codeine) per metropolitan center. Consistent with their initial study, they found that the rate of hard drug arrests per metropolitan center was not significantly associated with changes in the prevalence of IDU over the study period.[149]

The third study investigated the impact of decreased availability of heroin in Australia,[151, 152] which was attributed by some to targeted enforcement-based supply reduction.[153] The authors employed Australian government surveillance data on the annual prevalence of heroin injectors, the prevalence of treatment-enrolled heroin injectors, heroin-related arrests, and fatal overdoses across the country. These data were used to estimate the total reduction in the incidence of injecting initiation among heroin users. The authors estimated that between 2,745 and 10,560 individuals did not initiate heroin injection as a result of the heroin shortage. However, the authors observed an increase in the number of new injectors of amphetamine, and stated that it was unclear how much of the reduction in new heroin injectors was offset by an increased incidence of amphetamine injection.[150]

3.4   Discussion

This systematic review included all English-language peer reviewed studies that evaluated interventions to prevent injecting initiation. The number of eligible studies was limited. Those studies included in the final review evaluated four major types of interventions: social marketing, peer-based behavior modification, addiction treatment, and deterrent/enforcement-based interventions. The eligible

studies employed a variety of methodological approaches and included data from a diverse set of regions. Four studies (50.0%) reported a significant positive impact of peer-based behavior modification and treatment-based interventions on the prevention of injecting initiation.[144-147]

The small number of studies eligible for this review suggest that the development and evaluation of interventions to prevent injecting remains underserved as an area of research, despite the well-known harms of injection drug use and expert calls to prevent this phenomenon.[4, 22] This is of concern, given the estimated 16 million individuals worldwide who engage in injection drug use.[10] Further, while this review outlines preventive interventions that appear to be effective, none of these have been resourced to scale. Indeed, aside from enforcement-based interventions, only 'Break the Cycle,' which has been adapted to three settings,[146] appears to currently be implemented.

Despite the limited number of studies, these results have implications for efforts to reduce injecting. Several studies included in this review highlighted the influence of social networks on initiation risk, as previously noted in Chapter 2. Indeed, exposure to injectors and injecting environments appears to increase risk for initiation.[154-156] Expanding access to addiction treatment and behavior modification interventions among established injectors may thereby reduce exposure to injecting among injection-naïve drug users. However, interventions that provide access to addiction treatment among established injectors[147] may have a greater overall impact on community-level injection-related harms, given that this approach may have the secondary effect of reducing the total number of injectors. If

brought to scale, such interventions would be supplementary to current efforts to reduce both drug use and drug-related harm. However, the present lack of a strong evidence base to support the scale-up of addiction treatment represents a substantial barrier to pursuing this hypothesis. Given the many serious harms associated with injecting, however, the development of new modalities to investigate and modify the risk of injection initiation posed by exposure to injecting should be prioritized. These should take into account the fact that a variety of intersecting economic concerns and vulnerabilities can influence drug injectors' decisions to initiate others into injecting,[157] which may limit the impact of interventions that rely on individual behaviour modification, such as Break the Cycle. As such, access to evidence-based treatment modalities such as methadone maintenance therapy, and other clinical treatment options should be investigated as potential approaches to preventing the incidence of injecting initiation. By contrast, the results of this review suggest that approaches relying on legal repressiveness are likely to be ineffective deterrents.[148, 149]

This review has a number of limitations. First, there was a limited peer-reviewed literature that evaluated interventions to prevent injecting initiation, and the systematic review was thus restricted to eight studies. Those studies that were included in the review utilized a diverse set of methodologies to evaluate a variety of interventions in a wide range of settings. Second, experts have demonstrated the potential for publication bias in studies evaluating education-based interventions to prevent drug use,[142] as well as in studies evaluating the overall effectiveness of drug law enforcement in reducing drug-related harms.[158, 159] It is possible that a similar

bias exists in the scientific literature on the prevention of injecting initiation, which would have skewed our results away from null findings. Third, some studies included in the review assessed the indirect effects of interventions on levels of injecting initiation, which limits the conclusions that can be drawn regarding the causal linkages between these interventions and patterns of injecting initiation.

To conclude, this review found that those interventions that seek to limit the exposure of injection-naïve drug users to injecting environments, either through peer-based behavior modification or enrolment of drug users in addiction treatment, may be effective in reducing the incidence of injecting initiation. By contrast, interventions that rely on drug law enforcement to produce a deterrent effect appear to be ineffective. However, the peer-reviewed literature on this topic is quite limited, with the development of interventions to prevent injection representing a critically underserved area of research.

384 potential studies identified in electronic databases

306 excluded based on exclusion criteria

61 papers excluded (no direct evaluation of injecting prevention interventions)

9 papers excluded (no original data)

8 paper included in systematic review
    5 studies from North America
    1 study from Europe
    1 study from Australia
    1 study from Central Asia
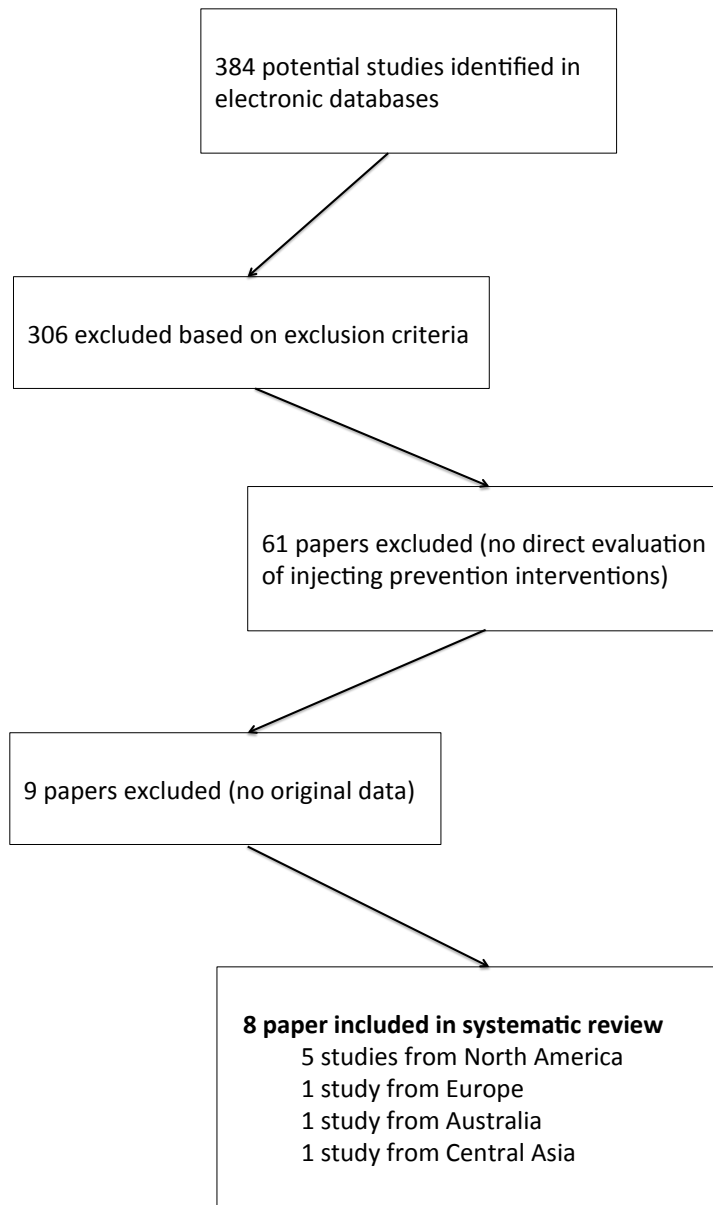
Figure 2. Flow chart of screening and selection process

Table 1. Studies evaluating interventions to prevent the initiation of injection drug use

Author & Year	Location	N	Study period	Study Design	Participant Characteristics			Intervention	Proportion Exposed	Main Findings	Quality Score
					Mean age (range)	% Female	Ethnicity				
Hunt et al., 1998	Kent, UK	86	3 months	RCT	29.8	22%	NR	Peer-based behaviour modification	100%	Participants injected with fewer non-injectors after exposure (97 *vs.* 49). Initiation requests fell (36 to 15) and the number of initiates decreased (6 to 2).	11
Roy et al., 2007	Montreal, Canada	146		Cross-sectional observational study, qualitative interviews	19 (15-23)	25%	NR	Anti-injection media campaign	92%?	Participants reported believing campaign was effective. A certain number of young people testified to the dissuasive effect the campaign had had on them directly.	13
Des Jarlais et al., 1992	New York, US	104	8.9 months	RCT	27.3 (16-48)	30%	51% white	Peer-based behaviour modification	48% (40)	Being in the experimental group for this study was associated with a lower probability of injecting (AOR = 0.51; 95% CI: 0.27 - 0.99)	15
Friedman et al., 2006	US MSAs	89 US MSAs	1 year (1993)	Lagged cross-sectional analysis	--	--	--	Drug law enforcement	100%	No association between injection drug use and police deterrence.	17
Friedman et al., 2011	US MSAs	96 US MSAs	1992-2002	Longitudinal observational study	--	--	--	Drug law enforcement	100%	No association between injection drug use and police deterrence.	17
Kelley et al., 2004	South Florida, US	900	July 1997 - August 1999	Longitudinal observational study	Sniffers: 34.7 // New injectors: 32.1 // Established injectors: 43.0	Sniffers: 30.1 // New injectors: 30.7 // Established injectors: 32.0	Sniffers: 24.2% white // New injectors: 27.6% white // Established injectors: 30.6% white	Addiction treatment	Mean treatment days: heroin sniffers: 237.6 // injection initiators: 191.6	The number of times that heroin sniffers (*n* = 604) were in treatment was inversely associated with a time to injecting (AHR = 0.73, *p* < 0.001).	14
Day et al., 2006	Australia	158	1996-2004	Longitudinal observational study				Heroin drought	100%	2,745-10,560 young people may have averted heroin injecting in 2001. Potentially offset by amphetamine injecting.	11
					NR	NR	NR				
Gray, 2008	Uzbekistan and Kyrgyzstan	856	April 2006-April 2008	Longitudinal observational study	NR	NR	NR	Peer-based behaviour modification	100%	Injectors initiated by established IDU decreased from 67 to 30 (2006-2008)	10

Note: RCT = randomized controlled trial; MSA = metropolitan statistical area; IDU = injection drug user; AOR = adjusted odds ratio; AHR = adjusted hazard ratio NR = not reported

CHAPTER 4: CRYSTAL METHAMPHETAMINE AND INJECTING INITIATION AMONG STREET-INVOLVED YOUTH IN A CANADIAN SETTING

4.1 Background

As described in Chapter 3, there are few evidence-based strategies specifically proven to prevent injecting initiation among street-involved youth. This is in large part because little is known regarding the risk factors for injecting initiation among this population, though Chapter 2 noted that crack and powder cocaine use, along with early-onset polysubstance use, may play a role in heightening risk.[31, 108, 160] However, much less is known regarding how the use of specific synthetic drugs, such as methamphetamine, may impact an individual's risk of initiating injection.[32] This is of concern given that the United Nations Office on Drugs and Crime recently reported that amphetamine-type stimulants are now the second most commonly used illicit drug globally.[161] Research also suggests that the use of drugs including amphetamines may be associated with subsequent reductions in spatial working memory, increased disinhibition, and a range of impaired cognitive function.[162-165] Given growing concerns regarding increasing methamphetamine use globally and in the present study setting,[32, 67] as well as the harms of injecting drug use as delineated in Chapter 1, we sought to investigate the impact of crystal methamphetamine use on risk of injecting initiation among a cohort of street-involved youth in Vancouver.

4.2 Methods

These analyses employed data from the At-Risk Youth Study (ARYS), described in full in section 1.7.[32] For the present study, data from ARYS participants who were

injection naïve, enrolled in the cohort between October 1, 2005 and November 30, 2010, and completed at least one follow up interview were used. The outcome of interest was defined as the first episode of any injection drug use. The primary independent variable of interest was defined as any non-injection crystal methamphetamine use (i.e., smoking and/or intranasal use) in the previous six months. Potential confounders included: age, gender (e.g., male *vs.* female or male to female transgender), Aboriginal ancestry (yes *vs.* other), recent non-injection heroin use, recent powder cocaine use (i.e., smoking and/or intranasal use), recent crack cocaine smoking, recent cannabis use, and recent alcohol use. Aboriginal ancestry was considered given the extensive literature from the study locale indicating a higher risk profile among Aboriginal people who use illicit drugs.[166-168] All drug-related variables refer to behaviours in the previous 6 months and all were lagged by one follow-up questionnaire to protect against reverse causality (e.g., the potential that participants began using specific types of drugs as a consequence of initiating injection drug use).

First, Kaplan-Meier methods were used to calculate the cumulative hazard of injecting initiation. We then employed an *a priori* two-step approach as recommended by Greenland.[169] First, univariate Cox regression analyses were conducted to determine whether the independent variable of interest and potential confounders predicted initiation of injection drug use at the $p < 0.05$ level. Next, a multivariate confounding model was constructed that included all potential confounders, which were removed sequentially using a backward selection approach to produce restricted models. The relative coefficient change for crystal methamphetamine use was then calculated among these restricted models and those variables that, once removed, changed the model

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coefficient by more than 5% relative to the full model were included in a final model. Finally, a retrospective subanalysis investigating circumstances of first injection was undertaken among all ARYS participants that reported ever injecting drugs at baseline or during study follow-up in an effort to identify specific micro-setting phenomena accompanying injecting initiation events. All statistical analyses were performed using SPSS software version 17.0 (SPSS, Chicago, IL).

4.3 Results

A total of 991 participants completed the ARYS baseline questionnaire between October 2005 and December 2010, among whom 395 (39.9%) reported using crystal methamphetamine at baseline and 390 (39.4%) reported injecting drugs at baseline. Those with a history of injection drug use at baseline were more likely to use crystal methamphetamine than those without a history of injecting (47% *vs.* 34%, *p* < 0.001). Among the 601 individuals who were injection-naïve at baseline, 395 (65.7%) had a follow up visit to assess for injecting initiation and were therefore eligible for inclusion in the present study. The overall recruited ARYS sample did not differ significantly in age, gender, ethnicity or baseline crystal methamphetamine use compared to those injection-naïve participants that were included in the analysis.

Among eligible participants (*n* = 395), 126 (31.9%) were female and 85 (21.5%) reported Aboriginal ancestry. Median participant age at baseline was 22 (Interquartile range [IQR]: 20 – 23), and the median follow-up time was 21 months (IQR: 13 – 26). Overall, 141 (35.7%) participants reported non-injection crystal methamphetamine use at baseline.

Sixty-four (16.2%) participants reported initiating injection drug use during the study period for an incidence density of 21.7 (95% Confidence Interval 1.7 – 41.7) per 100 person years. The median age of first non-injection drug use among those who subsequently initiated injection drug use was 14 (IQR: 12 – 16), while among persistently injection-naïve participants it was 12 (IQR: 10 – 13). Table 2 presents characteristics of study participants stratified by non-injection crystal methamphetamine use at baseline.

Figure 3 shows the results of a Kaplan-Meier analysis of time to injecting initiation stratified by crystal methamphetamine use among the study sample. As shown here, after 36 months the cumulative hazard of injecting initiation was 33.0% among participants that reported crystal methamphetamine use compared with 13.3% among those participants that did not report crystal methamphetamine use (p = 0.010).

The results of the univariate Cox regression analyses and the final multivariate confounding model are presented in Table 3. As shown here, in multivariate analysis, recent crystal methamphetamine use (Adjusted Hazard Ratio [AHR] = 1.78, 95% Confidence Interval [CI]: 1.24 – 2.56, p = 0.002) and recent heroin use (AHR = 1.89, 95% CI: 1.22 – 2.93, p = 0.004) were associated with an increased risk of injecting initiation. By contrast, recent cannabis use (AHR = 0.63, 95% CI: 0.40 – 0.99, p = 0.046) was negatively associated with risk of injecting initiation, though this association approached non-significance.

Among ARYS participants that reported ever injecting drugs at baseline or during follow-up (n = 369), almost half (46.9%) reported receiving their first injected drug as a gift. The drugs of first injection were most commonly heroin (25.7%) and crystal methamphetamine (24.1%), followed by cocaine (20.1%). Roughly two-thirds of

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participants (36.6%) reported that they did not believe that their use of drugs was out of control prior to first injection. Further, 49.6% of participants reported that they had never considered injecting prior to the initiation event.

While participants reported diverse injecting initiation micro-settings, 39.8% reported initiating injection in an outdoor public space. In terms of geographic setting, the largest proportion of participants reported initiating injection in Vancouver's downtown eastside neighbourhood (19.0%), the site of a large open-air illicit drug market, while 17.9% reported initiating injection in the downtown south, an adjacent neighbourhood previously identified as a potential geographic area of transition into increased drug use among street-involved youth.[71, 72, 170] Further, participants reported that a variety of individuals were present at initiation events, including friends (44.4%), family members (8.4%), and strangers (4.1%). However, 7.5% of initiates reported initiating injection alone. Almost three quarters (72.6%) of participants reported being injected by someone else during their injection initiation event. During their first injection experiences, 18 initiates (4.9%) reported sharing needles. Finally, 80.8% of participants reported subsequently becoming regular injectors within 5 years.

4.4   Discussion

Among a sample of street-involved youth in a Canadian setting, recent non-injection crystal methamphetamine use was independently associated with an increased risk of subsequent initiation of injection drug use. First-time injectors were also more likely to inject crystal methamphetamine compared to other drugs. A substantial proportion of the subsample of initiates reported having been injected by someone else

during initiation events, and nearly all reported that they had not considered injection drug use prior to first injection. Half of the subsample reported receiving the injected drug as a gift.

Canadian surveillance data suggest that reported levels of crystal methamphetamine use among street-involved youth in Canada rose significantly from 2.5% in 1999 to 9.5% in 2005.[171] This is consistent with global patterns of elevated crystal methamphetamine use,[161] as methamphetamine remains widely available, with levels of use particularly high among youth in Southeast Asia and North America.[161] This likely reflects the relative ease with which amphetamine-type stimulants can be produced.

The data presented here have immediate policy implications. For instance, while previous research has identified a variety of serious health harms associated with crystal methamphetamine use,[67] the current study identifies use of this drug as a potential risk factor for injecting initiation. This has implications for current approaches to curtail the supply of amphetamine-type stimulants and precursor chemicals, which appear to be largely ineffective in the North American context, given the persistent widespread availability of this drug.[9, 58, 171] In this context, the findings of this study indicate that resources dedicated to supply reduction may be better spent on proven approaches to reduce methamphetamine-related harms.

Specifically, given the previously-identified harms of methamphetamine use and the findings presented in this Chapter,[67] policymakers should work to implement and scale up evidence-based treatment for methamphetamine-dependent individuals. However, it is important to note that a recent review of clinical treatment for

methamphetamine dependence noted the dearth of effective treatment options for this drug, and stated that one barrier to the development of treatment has been inadequate research on the characteristics and consequences of use of this drug.[172] Therefore, a policy recommendation to come out of this research is to expand research into novel treatments for methamphetamine addiction.[173-175] Given that this study identified established IDU as facilitators of injection initiation events, an avenue for future research could include how structural interventions, such as supervised consumption facilities,[176] may reduce population mixing effects that increase the exposure of non-IDU to established IDU.

Contrary to a study of injecting initiation among street youth in Montreal,[31] which found an increased risk of initiation among street youth that used crack and powder cocaine, the current analysis found no significant association between recent powder cocaine or crack use and injecting initiation. In this regard, the current findings also diverge from those of a study of IDU in Baltimore that observed a protective effect of powder cocaine use on risk of injecting initiation.[160] Clearly, further research is required to develop and test evidence-based interventions to prevent injecting in ways that accommodate the complexities of polysubstance use and other micro-environmental features that modify risk in the lives of young street-based drug users. With respect to our findings concerning the fact that participants perceived that drug dependence was not a motivation for their decisions to initiate injection, these are consistent with data from studies such as the Collaborative Injection Drug Users Study (CIDUS) and the Montreal Street Youth Cohort, both of which have noted that drug dependence is not commonly cited as a factor by individuals in their decisions to initiate injection.[177] These

studies also concluded that individuals identified as at high risk of initiating injection drug use require more network- and peer-delivered information regarding the negative consequences of injection drug use.[31, 35] To that end, some studies have suggested that older IDU should be enlisted in efforts to educate young people who use drugs regarding the harms of transitioning into injection drug use.[178]

In this context, the current study's findings regarding the micro-setting characteristics of injecting initiation events elucidate the context-specific roles that other injectors likely play in determining risk of injecting initiation among street-involved youth. Specifically, roughly half of the sample of ARYS injectors reported receiving the injected drug as a gift and almost three quarters of participants reported being injected by someone else during their initiation event. These findings suggest that, consistent with the research presented in Chapters 2 and 3, drug-using peers and established injectors likely play a critical role in initiating street-based young people into injection drug use through a variety of roles. By extension, they may also represent untapped potential for preventing injecting initiation, as they represent a source of peer education on the negative health and social impacts of injecting initiation among injection-naïve drug users,[145] though the evidence base, as noted in Chapter 3, is limited in this regard. However, one potential avenue to mitigate the impact of established injectors in increasing risk of injecting initiation may be increasing community access to addiction treatment, as described in the study by Kelley and colleagues in Chapter 3,[147] or implementing supervised consumption facilities, which may work to minimize the exposure to injecting and the influence of established injectors that appear to facilitate injection transition events.

This study has limitations consistent with observational studies of drug-using populations. First, although the ARYS cohort reflects many characteristics representative of street-involved youth living in Vancouver,[179] the lack of registries of street-involved youth meant that the sample was not randomly recruited. Second, illicit drug use remains highly stigmatized and this may have affected participant responses,[180] although this bias may not have affected the response patterns of initiators and non-initiators differently. Third, we cannot rule out the potential for confounding as a result of exposures or participant traits that were not measured as part of the present study. For instance, illicit stimulant use has been associated with psychiatric disorders including Attention Deficit Hyperactivity Disorder (ADHD).[181, 182] Unfortunately, standardized assessment of psychiatric disorders was not undertaken as part of the ARYS study. Similarly, there is increasing recognition of genetic factors which may predispose individuals to addictive disorders and high-risk drug use,[183] including sensation seeking,[98, 184] and these data were also not available in the present study because of concerns regarding statistical power, though the role of this personality trait is investigated in Chapter 5. Nevertheless, the present study identified a strong association between crystal methamphetamine use and subsequent injection drug use, a finding with immediate policy implications. Finally, data were not available on the circumstances of injecting for all incident cases of injection initiation. Future research should seek to better elucidate the specific mechanism by which crystal methamphetamine use may increase the risk of initiation, by considering whether use of this drug may interact with, or mediate the relationship between injection initiation and other potential risk factors such as childhood trauma or latent personality-based factors such as sensation seeking.

In sum, this study found that non-injection crystal methamphetamine use was independently associated with an increased risk of injecting initiation among ARYS participants, despite adjustment for sociodemographic and drug-related confounders. Further, in a subanalysis of circumstances of first injection, the second largest proportion of participants reported initiating injection with crystal methamphetamine use, and established injectors appeared to play a critical role in initiation events. These findings highlight the need to address the dual impact of crystal methamphetamine use and the presence of established injectors in increasing the risk of injecting initiation among injection-naïve street-involved youth.[4, 22] Considered within the context of the review presented in Chapter 3, the development and evaluation of appropriate interventions to prevent injection among crystal methamphetamine users is critically needed.

Table 2. **Baseline characteristics of injection-naïve street-involved youth according to non-injection crystal methamphetamine use in Vancouver, Canada (*n* = 395).**

Characteristic	Crystal Methamphetamine Use		
	Total (%) (*n* = 395)	No (%) (*n* =254)	Yes (%) (*n* = 141)
Sociodemographic factors			
Median age (IQR)*	21.6 (19.6 - 23.3)	21.7 (19.5 - 23.6)	21.4 (19.7 – 22.8)
Male gender	269 (68.1)	177 (65.8)	92 (34.2)
Aboriginal ancestry	85 (21.5)	64 (25.2)	21 (14.9)
Drug-related behaviors			
Recent heroin use	63 (15.9)	31 (49.2)	32 (50.8)
Recent cocaine use	194 (49.1)	127 (65.5)	67 (34.5)
Recent crack use	221 (55.9)	137 (62.0)	84 (38.0)
Recent cannabis use	355 (96.2)	252 (64.8)	137 (35.2)
Recent alcohol use	69 (17.5)	50 (72.5)	19 (27.5)

Note: All drug use variables refer to non-injection use in the preceding six months
* IQR = Interquartile Range

Table 3. Unadjusted and adjusted hazard ratios for factors related to initiation of injection drug use among street-involved youth in Vancouver, Canada, 2005-2010 (*n* = 395).

Characteristic	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	*p* value*
Recent crystal methamphetamine use	1.51 (1.19 - 1.99)	1.78 (1.24 - 2.56)	0.002
Participant age (per year younger)	0.91 (0.86 - 0.97)	--	--
Male gender	0.61 (0.42 - 0.88)	--	--
Aboriginal *vs.* other	1.02 (0.69 – 1.52)	1.67 (0.87 – 3.23)	0.122
Recent cocaine use	0.94 (0.73 - 1.21)	0.81 (0.54 - 1.22)	0.305
Recent crack use	1.20 (0.93 - 1.56)	0.93 (0.63 - 1.37)	0.704
Recent heroin use	1.39 (1.06 - 1.82)	1.89 (1.22 - 2.93)	0.005
Recent cannabis use	0.94 (0.67 - 1.26)	0.63 (0.40 - 0.99)	0.046
Recent alcohol use	1.02 (0.77 - 1.37)	0.93 (0.58 - 1.50)	0.759

Note: All drug use variables refer to non-injection use in the preceding six months and are lagged by one follow-up
Note: HR = hazard ratio; CI = confidence interval
* *p* value for adjusted hazard ratio
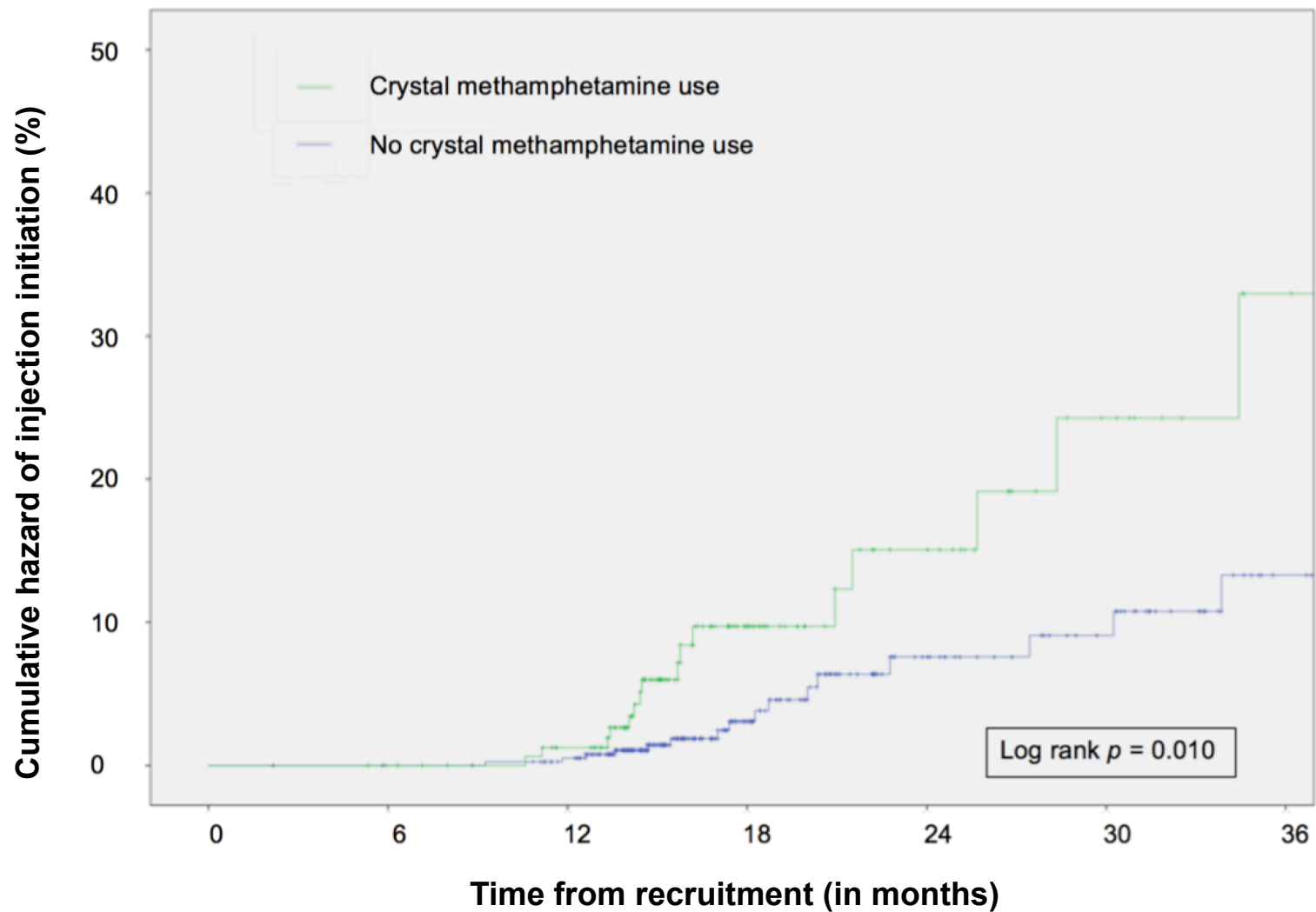
Figure 3. Cumulative hazard of injection initiation among street-involved youth stratified by crystal methamphetamine use in Vancouver, Canada, October 2005 - December 2010 (*n* = 395)

CHAPTER 5: THE DEVELOPMENT OF A BRIEF SUBSTANCE USE SENSATION SEEKING SCALE: VALIDATION AND PREDICTION OF INJECTION DRUG USE

5.1   Introduction

Sensation seeking, a personality trait first identified in the 1950s and frequently measured using the Sensation Seeking Scale (SSS) developed by Zuckerman, can be briefly defined as a desire for novel and potentially risky experiences.[185] A large body of scientific literature has demonstrated that sensation seeking increases dramatically between the ages of 12 to 14, remains relatively stable throughout young adulthood (e.g., until approximately 25 years old), and then declines slightly as individuals age.[90] While consisting of four subdomains, sensation seeking has been modeled as a single unidimensional trait, and past research has shown sensation seeking to be a reliable measure of an individual's willingness to engage in risky behaviours.[86, 98, 186-188] In particular, the SSS has been employed as a tool to identify individuals who may be at higher risk of substance use.[98] For instance, anti-drug public service announcements have been designed for an audience of high sensation seekers in order to reduce the initiation of drug use among this group.[189, 190] A recent randomized controlled trial also found that cognitive-behavioural interventions that worked to lower sensation seeking among youth were efficacious in reducing levels of alcohol misuse.[191] Additionally, changes in sensation seeking have been associated with the escalation of adolescent use of alcohol, marijuana and tobacco, with those youth who experienced a less rapid variance in sensation seeking level over time also less likely to rapidly increase their use of marijuana or tobacco compared with youth who experienced rapid changes in sensation seeking level.[184] This may be related to the fact that higher sensation

seeking among adolescents has shown to be associated with childhood sexual abuse, which in turn has been shown to be a risk factor for injection initiation.[192] As such, an investigation of sensation seeking among street-based drug-using populations may contribute to a greater understanding of the linkages between distal factors and psychosocial variables that may heighten the risk of drug-related behaviours such as injecting.

Kalichman and colleagues suggest that sensation seeking may act as a mediating factor in sexual transmission of HIV, but that the SSS may be an inappropriate tool for individuals in subpopulations at high risk because many scale items refer to behaviours that are irrelevant or not suitable for certain subpopulations (e.g., the SSS item regarding a willingness for "Discussing your sex life with friends" would likely not be a valid measure of sensation seeking among a cohort of individuals who report engaging in sexual risk-taking; similarly, "Trying the drug LSD" would not accurately measure a desire for risk-taking among a cohort of experienced illicit drug users).[193, 194] To address this limitation, Kalichman and colleagues adapted a brief version of the SSS to specifically measure sexual risk-taking among a cohort of gay men with a history of high risk sexual activity. The authors found that their adapted SSS consistently predicted sexual risk-taking among the sample, as indicated by higher frequency of unprotected sexual intercourse and a greater number of sexual partners.[195]

This thesis outlines a variety of risk factors for initiation (see section 2.3.1 and Chapter 4),[32, 36, 46, 177, 192, 196, 197] and in the present Chapter seeks to employ the risk environment framework to consider not only social, structural, economic, peer-based and policy factors, but also to specifically consider the underlying personality

trait of sensation seeking. In this way, it is hoped that researchers will be able to provide a more comprehensive portrait of the suite of factors that may impact decisions surrounding injecting. Though prior studies have been undertaken among IDU samples incorporating the SSS,[91, 93] these have not ensured the cultural appropriateness of the scale for this street-based drug-using population and have not sought to modify this scale to correct this potential source of error. Experts have also previously suggested that future research in the area of sensation seeking and drug-related risk-taking requires a clinically-validated scale.[198] Indeed, to our knowledge, no research has been conducted on the role of sensation seeking in increasing the risk of injection drug use among street-involved youth.

Given the findings presented in Chapter 3 identifying crystal methamphetamine use as a risk factor for initiation among ARYS participants, it is important to determine whether sensation seeking may be associated with use of this particular drug among street-involved youth in Vancouver. Additionally, as delineated in Chapter 2, both polysubstance use and binge drug use have previously been identified as potential predictors of injection drug use.[108, 109] Determining the association between these behaviours and sensation seeking may further improve our understanding of the role of sensation seeking in youth drug use behaviour and ultimately contribute to the development of interventions that prevent injection in this population. We therefore sought to modify and validate a brief SSS for use among street-involved youth and to then examine its potential utility in assessing the risk of injection drug use, use of crystal methamphetamine, polysubstance use, and binge drug use among a sample of street-involved youth.

5.2   Methods

This study included individuals enrolled in the At-Risk Youth Study (ARYS), as described in section 1.7.[32] For the present study, ARYS participants completed an interviewer-administered questionnaire soliciting sociodemographic, behavioural, and drug use data, including data on drug injecting, and also completed the modified SSS during one follow up interview.

5.2.1   Scale Development and Evaluation

The modified SSS was developed by adapting items from the SSS Form-V[185] using a four-stage process. First, 11 items in the SSS Form-V that were amenable to adaptation for a high-risk drug-using population were identified. Second, item modification was undertaken in consultation with experts in psychology, drug use, and youth behavior to ensure that the modified scale items reflected themes relevant to a street-involved youth population.

The modified scale was then administered to ARYS participants and exploratory factor analysis (EFA) was conducted on these data in order to assess the dimensionality of the modified scale. Confirmatory factor analysis (CFA) was then undertaken to assess the internal validity and reliability of the modified scale.

With respect to the EFA, this was undertaken to ensure that the modified SSS was essentially unidimensional, consistent with the original SSS.[199] To do so, we engaged in a series of tests to determine the optimal number of factors to retain in the measurement model, as previously recommended.[200] To accommodate potential skewing, the ordinal nature of the item responses, and to allow for correlated factors, robust EFA was performed. This is because the estimated correlation matrix derived through classical EFA techniques is susceptible to bias in cases when the

distribution of data departs from normality.[201] To account for non-normal distributions, robust EFA employs Weighted Least Squares Estimation with Mean and Variance Adjustment (WLSMV) with a GEOMIN rotation supporting oblique factors, which is less susceptible to influence from outliers and skewed data.[201] This was done using Mplus Version 6 (Mplus, Los Angeles, CA).[202]

Evaluating the results of the EFA involved a series of *a priori* determined steps, including generating a scree plot of eigenvalues and comparing the size of the largest eigenvalue relative to that of the next largest eigenvalue. A parallel analysis approach suitable for ordinal data was employed as previously recommended by experts in the field.[200, 203] Specifically, this technique uses a Monte Carlo simulation modeling approach,[204] in which the eigenvalues derived from an original dataset are compared with eigenvalues extracted from a series of random datasets matched to the original on the number of cases and scale items.[203] The mean eigenvalues of the random data generated at a desired percentile, generally recommended as the 95th percentile, then serve as the comparative baseline to assess the dimensionality of the scale.[203] Those eigenvalues generated from the scale data are subsequently retained if they are greater than the corresponding eigenvalues generated by the random dataset, and the number of eigenvalues retained by this process is interpreted as the number of factors measured by the scale items. When only one eigenvalue is retained, this indicates that the pool of items being assessed is essentially unidimensional.[203] This calculation was performed using a macro package developed by O'Connor for use in SPSS 20.0 (IBM, New York, NY).[203]

The CFA approach involves the use of statistical methods to assess the fit of the model derived from the EFA, and also provides a measure of construct validity

for the scale. As with the EFA, WLSMV was employed to accommodate potential skewing and the ordinal nature of the data.[202] Construct reliability was then calculated according to the approach recommended by Gerbing and Anderson,[205] which assesses reliability based on the variance across items explained by one underlying latent construct (e.g., sensation seeking). This approach is used for measuring scale reliability in cases wherein scale items load onto the same construct but have loadings unequal in magnitude.[205, 206] In addition to assessing construct reliability, the Comparative Fit Index (CFI),[207] and the Root Mean Square Error of Approximation (RMSEA) were used to evaluate the fit of the CFA model.[208, 209] The CFA was performed using Mplus Version 6 (Mplus, Los Angeles, CA).[202]

5.2.2   Hypothesis Testing

First, correlations between sensation seeking score and a range of sociodemographic, drug-related, and psychosocial factors were generated in order to determine whether higher sensation seeking scores were associated with specific sociodemographic factors or behaviours. These included: ethnicity (Aboriginal Ancestry *vs.* other), gender, age, non-injection crystal methamphetamine use, non-injection heroin use, non-injection powder cocaine use, non-injection crack cocaine use, injection use of any drugs, binge drug use, polysubstance use, overdose, alcohol use, childhood sexual abuse, CES-D Depression Scale score, Self-Efficacy to Avoid Injecting Scale score, and Limiting HIV Risk Behaviours Scale score. All behavioural variables refer to the previous six months. Pearson's test of significance was conducted for all correlations.

Second, the hypothesis that the modified SSS scores predict injection drug use and drug-related behaviours identified as risk factors for injection initiation

among street-involved youth was tested using a series of generalized estimating equation (GEE) models. This approach allows for the determination of factors independently associated with injection drug use among participants throughout the study period.[210] It also provides modified standard errors adjusted by multiple observations per person using a first-order autoregressive correlation structure.[210]

Specifically, four multivariate GEE models were constructed, all of which included participant score on the modified SSS as the primary independent variable of interest. The dependent outcomes for the four models were defined as: recent (e.g., in the six months previous to follow-up interview) injection drug use, recent crystal methamphetamine use, recent polysubstance use, and recent binge drug use. Injection drug use was defined as illicit injection of any drug. Binge drug use was defined as using more drugs than normal in the previous six months.[211] Length of drug-using career was included in all four models as a within-subject variable. Sociodemographic and drug-related variables potentially associated with the four outcome variables and included in the analyses were: age, gender, Aboriginal ancestry (yes *vs.* other), recent non-injection heroin use, recent non-injection powder cocaine use, recent non-injection crack cocaine use, and recent non-injection crystal methamphetamine use. All drug-related variables except for length of drug-using career refer to behaviours undertaken in the previous six months, and all were lagged by one follow-up questionnaire to protect against reverse causality whereby factors associated with the outcome variable may instead result from this behaviour. The multivariate model was fit using an *a priori* defined model building protocol of adjusting for all variables that were statistically significant at the *p* <

0.05 level in bivariate analyses along with basic sociodemographic variables (e.g., age, gender, and ethnicity).

All statistical analyses for hypothesis testing were performed using SAS software version 9.2 (SAS Institute Inc., Cary, North Carolina, USA). All *p*-values are two-sided.

5.3   Results

Overall, between October 2005 and May 2012, 226 ARYS participants completed the SSS and were eligible for the present study. This sample included 73 (32.3%) female participants, and 66 (29.2%) participants reporting Aboriginal ancestry. Median age at baseline was 22 years (Interquartile Range [IQR]: 20 – 23). Median follow up was 33 months (IQR: 27 – 46).

One hundred and sixty-three (72.1%) participants reported injection drug use during the study period. Compared to the overall ARYS sample (*n* = 991), the subsample of ARYS participants that completed the modified SSS did not differ significantly on age, Aboriginal ancestry, frequency of injecting at baseline, or length of drug-using career.

Frequency distribution of scale responses

Table 4 presents the modified SSS items and potential responses measured on a 5-point Likert scale. Among ARYS participants, median SSS score was 21 (IQR = 15 – 27, Standard Deviation [SD] = 8). While the test statistics for the distribution of scale items 2 and 10 suggest that these were particularly right-skewed, the skewness for the test statistic assessing the distribution of responses for the total score was 0.75 (Standard Error [SE] = 0.16), denoting moderate skewing and an approximately symmetrical distribution.[212] Additionally, the computation of

kurtosis suggested that the distribution of scale items 3 and 10 were highly leptokurtic (i.e., data points lie close to the mean), though the test statistic for the distribution of responses for the total score was 0.73, suggesting that the frequency distribution approached mesokurtosis (i.e., the distribution approached normality).[213]

Exploratory Factor Analysis

Figure 4 shows a scree plot delineating the eigenvalues from the EFA solution. As can be seen, the plot contains a sharp drop in eigenvalues between the first and second factors, with the eigenvalue for the first factor almost five times larger than the eigenvalue for the second largest factor. Furthermore, in parallel analysis,[203] the first eigenvalue generated at the 95th percentile of the random dataset was 1.37. By contrast, the eigenvalue associated with the first factor in the EFA for the modified SSS dataset was 5.43, while the eigenvalue associated with the second factor was 1.19. The second eigenvalue associated with the 95th percentile of the random dataset was 1.27, and thus exceeded that associated with the second factor in the dataset of responses to the modified SSS. The results of the scree plot and parallel analysis therefore support a one-factor or unidimensional solution for the modified SSS items.[203]

Confirmatory Factor Analysis

A construct reliability estimate of 0.804 was derived for the unidimensional model.[214, 215] The CFI suggested an acceptable level of agreement between the model and the data (CFI = 0.914),[216] and while the point estimate for the RMSEA was high, the range estimate approached the cutoff point indicating acceptable fit (RMSEA = 0.111, 95% CI: 0.093 – 0.129).[207, 208]

Hypothesis Testing

Table 5 presents correlations between sensation seeking score and a range of sociodemographic, drug-related factors and psychosocial variables. As shown, age, male gender, non-injection powder cocaine use, non-injection crack cocaine use, non-injection crystal methamphetamine use, alcohol use, polysubstance use, binge drug use, childhood sexual abuse, CES-D Depression Scale score, and Limiting HIV Risk Behaviours Scale score were all significantly associated with participant sensation seeking score ($p < 0.05$).

Table 6 presents results from the four multivariate GEE models investigating the association between participant SSS score and injection drug use, crystal methamphetamine use, polysubstance use, and binge drug use. As shown, total SSS score was significantly associated with injection drug use (Adjusted Odds Ratio [AOR] = 1.04, 95% CI: 1.02 – 1.05 [per one unit score increase]), non-injection crystal methamphetamine use (Adjusted Odds Ratio [AOR] = 1.03, 95% CI: 1.00 – 1.07 [per one unit score increase]), polysubstance use (Adjusted Odds Ratio [AOR] = 1.06, 95% CI: 1.03 – 1.09 [per one unit score increase]), and binge drug use (Adjusted Odds Ratio [AOR] = 1.03, 95% CI: 1.01 – 1.05 [per one unit score increase]) (all $p < 0.05$), despite adjustment for potential confounders. These correspond to an AOR of 1.37 for injection drug use, an AOR of 1.27 for crystal methamphetamine use, an AOR of 1.59 for polysubstance use, and an AOR of 1. 27 for binge drug use, for each one standard deviation increase (i.e., 8 point increase) in total score.

5.4   Discussion

The present study sought to develop a brief SSS suitable for use among a street-based drug-using population. The results of the EFA and CFA provided preliminary support for the reliability and validity of the modified SSS. Furthermore, despite adjustment in multivariate confounding GEE models, participant score on the modified SSS was independently associated with injection drug use, non-injection crystal methamphetamine (a risk factor for injection initiation identified in Chapter 3), polysubstance use and binge drug use, both also previously identified as predictors of initiation of injection drug use.[108, 109] Additionally, while the AORs for sensation seeking and all four drug-related outcomes were relatively small for a one-unit increase in total score, the differences between scores one standard deviation apart were substantial. As such, there may be a role for the use of the modified SSS to assess the impact of the intersection of sensation seeking and traditional risk factors for injection drug use within investigations focusing on specific drugs or the socio-structural context of drug use.[69, 73, 177] In particular, the inclusion of the modified SSS in epidemiologic analyses of the risk environment experienced by street-based drug-using populations could extend the range of potential risk factors for initiation or other drug-related risks to include sensation seeking, given that this psychosocial trait appears to limit the capacity of individuals to avoid such high-risk drug behaviours.

The association between sensation seeking and a range of drug-related behaviours also offers a potential avenue for both future research and intervention development. These findings suggest that those who score higher on the modified SSS are also more likely to be non-injection crystal methamphetamine users,

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involved in the drug trade, and engaged in risky drug-related behaviours. Furthermore, in bivariate analysis, higher sensation seeking score was also associated with reporting lower scores for self-efficacy in avoiding HIV risk behaviours. Taken together, these findings appear to place higher sensation seekers at heightened risk of a variety of drug-related harms, and, in particular, of injection initiation. Indeed, the street-involved youth population in our study setting is marked by high levels of crystal methamphetamine and polysubstance use,[68] ready access to drugs,[58, 69, 217] a high level of exposure to injecting,[34] ongoing structural and social barriers to housing,[218] overdose,[196] and high levels of involvement in the illicit drug trade.[219] These intersecting factors increase the risk of negative health outcomes, most notably injection initiation.[31, 35, 36, 38, 109, 160, 220] Future research should determine whether preventing these behaviours, and in turn injection initiation, may be achieved by reducing the level of sensation seeking among high-risk street-based drug users. Additionally, previous research has found that among a sample of polysubstance users in Chicago, high sensation seeking was associated with risky sexual practices among HIV-seropositive participants,[221] while multiple studies of gay men have found that sensation seeking partially accounts for the association between drug use and high-risk sexual behaviours.[222, 223]

More research is therefore needed to determine what specific role sensation seeking may have on risks related to injection initiation, and whether behavioural interventions, or the use of particular drugs, may impact the expression of this personality trait. In particular, future research should seek to disentangle the association between non-injection crystal methamphetamine, as well as the other drug-related risk behaviours identified in this chapter, which are both associated

with sensation seeking and with an increased risk of injection initiation. Of critical importance in this regard is determining the direction of causality between drug use and sensation seeking, given that research has demonstrated that use of amphetamines and other stimulants by youth may increase levels of sensation seeking.[224] This, then, presents multiple potential causal pathways for injection drug use related to sensation seeking and crystal methamphetamine use: first, the relationship between sensation seeking and injection initiation may be mediated by ccrystal methamphetamine use among street-involved youth.[164] Second, crystal methamphetamine use might cause neurological changes that may then impact the degree of sensation seeking and risk-taking that street-involved youth engage in, which in turn may precipitate the initiation of injection drug use.

Prior research has also demonstrated that sensation seeking may be a mediating factor between childhood sexual abuse and increased HIV risk among adolescents.[225, 226] Importantly, the ARYS sample of street-involved youth is, consistent with street-involved youth samples in other settings,[31] characterized by high levels of childhood sexual abuse.[227] Interestingly, reporting childhood sexual abuse and sensation seeking score were negatively correlated in bivariate analysis. This association should be explored in efforts to further refine the modified SSS. Indeed, while childhood sexual abuse has been shown to be positively associated with sensation seeking,[225] future research should focus on ensuring the divergent validity of the modified SSS from closely related psychosocial constructs such as impulsivity,[90, 184] given that both have been found to be associated with childhood sexual abuse.[228, 229]

These findings have implications for the development of interventions to prevent injection initiation, which have been largely overlooked by policymakers, as described in Chapter 3.[22] If future research further confirms that the modified SSS can reliably identify street-involved youth at high risk for injecting initiation, it may aid in the development of novel, evidence-based preventive interventions for this high-risk population. For example, recent research has demonstrated the potential effectiveness of interventions specifically focused on reducing an individual's level of sensation seeking through cognitive behavioral therapy,[191, 230] and studies have also examined the impact of sensation seeking on retention in addiction treatment.[187, 231, 232] Additionally, from a life course perspective, preventive interventions may benefit from identifying high sensation seeking youth at an early stage of development. This may entail standardized testing of sensation seeking and complementary psychosocial factors such as impulsivity, self-esteem, depression, and resilience among youth in pre- and early adolescence.[233] This approach may then facilitate the development of preventive interventions tailored to those at highest risk of problematic drug use, such as injection initiation or related risk factors like crystal methamphetamine use, polysubstance use, and binge drug use. Such interventions should be informed by a public health approach and, crucially, should not replicate previously employed social marketing and educational interventions that have proven ineffective.[7, 89] Developing the necessary tailored or stepped interventions presents substantial challenges as interventions need to be established across a number of geographic and temporal settings along the drug-using trajectories of street-involved youth. In this regard, interventions established in settings characterized by either large number of street-involved youth or public

injecting settings, or both,[71, 72] should be considered a priority. Such interventions should be designed to provide harm reduction materials, and referrals to addiction treatment, vocational training and other services relevant for this population.

This study has limitations. First, it should be noted that the modified SSS presented in this study represents a first step in this scale's development. Additionally, the EFA and CFA reported in this study were performed on the same dataset in order to maximize the amount of information obtained on the performance of the modified SSS. Additional studies are therefore needed to further evaluate the scale's reliability and validity in independent samples. In particular, the less than optimal CFA results and skewed response patterns for several items indicate that additional revisions to the SSS involving item wording, response options and the addition of new items should be considered by researchers working to further refine this tool. Second, the relatively small sample size may have impacted the results of the analyses. However, recent research on the evaluation of scale dimensionality suggests that the results of the parallel analysis conducted for this study are likely unaffected by the size of the ARYS sample or the skewness of the data.[236] Third, the nature of the data set and a low incidence of individuals transitioning into injecting during the study period precluded the option of conducting a longitudinal survival analysis, such as that as undertaken in Chapter 4, to test the association between participant SSS score and the incidence of initiation into injection drug use. As such, we caution against inferring a causal relationship between higher participant SSS score and the initiation of drug injection. Fourth, as noted in Chapter 4, ARYS is not a randomly-selected sample and its generalizability to the broader population of street-involved youth in Vancouver cannot be assumed,

though the existence of comparative datasets suggest similarities between ARYS and other samples of street-involved youth in Vancouver.[179, 237] Fifth, as noted previously, because we relied on self-report, and given the stigmatized nature of drug use and of injection drug use in particular, these behaviours may have been underreported.[238-240] Finally, though previous research has demonstrated that sensation seeking is generally stable among individuals aged 14 to 25,[90] future research should examine the stability of scores on the modified SSS over entire drug using careers.

In sum, the results of the explanatory and confirmatory factor analyses provide preliminary support for the reliability and validity of the modified SSS as a tool to measure sensation seeking among street-involved youth. Further, analyses suggested that participant SSS score is independently associated with injection drug use, as well as with crystal methamphetamine use, binge drug use, and polysubstance use, all of which have been shown to increase the risk of injection initiation. While the intersection of sociodemographic, structural, policy and peer-based factors heavily influence the risk environment within which street-involved youth make decisions regarding injection drug use, the results of this study nevertheless suggest that sensation seeking may independently heighten risk of participation in drug-related behaviours previously identified as predictors of injection initiation. While preliminary, these results may be useful for future research seeking to prevent such behaviours through the development of targeted interventions for street-involved youth exhibiting high sensation seeking.

Table 4. Items for a modified brief sensation seeking scale

These questions are designed to help us understand how you feel about your current drug use and how it might change in the future. Please rate how much you agree or disagree with the following statements by circling a number from 1 to 5 below.

RESPONSES:

1 – Very much disagree
2 – Somewhat disagree
3 – Undecided
4 – Somewhat agree
5 – Very much agree

1. I am interested in trying out drugs that I have never tried before......... 1 .... 2 .... 3 .... 4 5

2. When I get high, I always like to take a little bit more............................. 1 .... 2 .... 3 .... 4 5

3. I would like to try doing drugs in new ways (i.e., inject, smoke, snort)... 1 .... 2 .... 3 .... 4 5

4. I am curious about trying drugs that I know can be dangerous. .... 1 .... 2 .... 3 .... 4 5

5. I like getting high with people who are unpredictable. .... 1 .... 2 .... 3 .... 4 5

6. I often like to get high without worrying about what drugs I'm doing or how much
.... 1 .... 2 .... 3 .... 4 5

7. I get bored doing the same drugs over and over. .... 1 .... 2 .... 3 .... 4 5

8. I like to hang out with people who use different drugs than I do. .... 1 .... 2 .... 3 .... 4 5

9. I am curious about many different drugs... 1 .... 2 .... 3 .... 4 5

10. I like doing drugs with groups of people I don't know well.................. 1 .... 2 .... 3 .... 4 5

11. I prefer to hook up with people who take drugs.................................. 1 .... 2 .... 3 .... 4 5

Table 5. Correlations between modified sensation seeking scale score and sociodemographic, drug-related, and behavioural variables		Correlation
Gender	Pearson Correlation	.139[**]
	p-value	.000
Ethnicity (Aboriginal *vs.* Other)	Pearson Correlation	-.008
	p-value	.770
Age	Pearson Correlation	.055[*]
	p-value	.048
Recent non-injection crystal methamphetamine use	Pearson Correlation	.110[**]
	p-value	.000
Recent non-injection powder cocaine use	Pearson Correlation	.062[*]
	p-value	.024
Recent non-injection crack cocaine use	Pearson Correlation	.040
	p-value	.149
Recent non-injection heroin use	Pearson Correlation	.045
	p-value	.106
Recent injection drug use	Pearson Correlation	.092[**]
	p-value	.001
Recent binge drug use	Pearson Correlation	.087[**]
	p-value	.002
Recent polysubstance use	Pearson Correlation	.145[**]
	p-value	.000
Recent overdose	Pearson Correlation	.006
	p-value	.828
Recent alcohol use	Pearson Correlation	.061[*]
	p-value	.028

Table 5. Correlations between modified sensation seeking scale score and sociodemographic, drug-related, and behavioural variables		Correlation
Childhood sexual abuse	Pearson Correlation	-.120[**]
	p-value	.000
CES-D Scale score	Pearson Correlation	.101[**]
	p-value	.000
Self-Efficacy to Avoid Injecting Scale score	Pearson Correlation	-.040
	p-value	.162
Limiting HIV Risk Behaviours Scale score	Pearson Correlation	-.077[**]
	p-value	.006

** Correlation is significant at the 0.01 level (2-tailed)

* Correlation is significant at the 0.05 level (2-tailed)

Table 6. Adjusted odds ratios and 95% confidence intervals for multivariate models on factors related to sensation seeking score on a modified brief scale among street-involved youth in Vancouver, Canada, 2005-2010 (*n* = 226).

Characteristic	Model 1: Injection Drug Use	Model 2: Crystal Methamphetamine Use	Model 3: Polysubstance Use	Model 4: Binge Drug Use
Sensation Seeking Score	1.04 (1.02 – 1.05)*	1.03 (1.00 – 1.07)*	1.06 (1.03 - 1.09)*	1.03 (1.01 - 1.05)*
Age (Per Year Older)	0.99 (0.94 – 1.03)	1.01 (0.87 – 1.17)	0.93 (0.87 - 0.99)*	0.98 (0.93 - 1.04)
Female Gender	1.75 (1.34 – 2.29)*	1.25 (0.73 – 2.05)	1.37 (0.91 - 2.05)	0.91 (0.66 - 1.25)
Aboriginal Ancestry *vs.* Other	0.88 (0.68 – 1.16)	0.74 (0.49 – 1.13)	0.78 (0.53 - 1.15)	0.90 (0.65 - 1.24)
Recent Crystal Methamphetamine Use	1.14 (0.88 – 1.47)	--	1.64 (1.21 - 2.23)*	--
Recent Heroin Use	1.46 (1.04 – 2.06)*	--	2.30 (1.35 - 3.91)*	--
Recent Powder cocaine Use	0.45 (0.34 – 0.60)*	--	1.86 (1.36 - 2.55)*	1.14 (0.87 - 1.51)
Recent Crack Use	1.06 (0.83 – 1.37)	--	1.75 (1.27 - 2.41)*	2.28 (1.70 - 3.06)*

Note: All drug use variables refer to non-injection use in the previous six months and are lagged by one follow-up.

Note: Models adjust for length of drug-using career as a within-subject variable

significant at $p < 0.05$
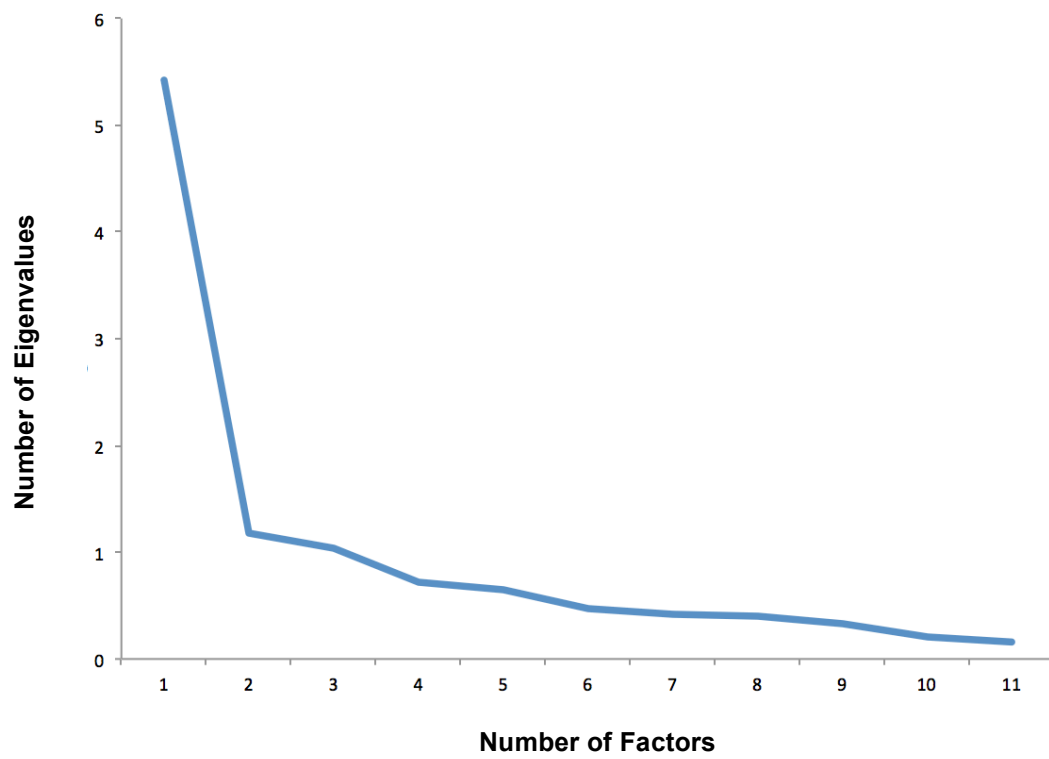
Figure 4. Scree plot for modified brief sensation seeking scale

CHAPTER 6: INJECTION CAREER TRAJECTORIES AND CESSATION DURING AN EXPANSION OF SYRINGE EXCHANGE SERVICES IN VANCOUVER

6.1   Introduction

Once individuals have initiated injection drug use and entered into an injection drug-using trajectory, the concerns of public health practitioners focus on both reducing the harms of ongoing injection drug use and ensuring that the length of these injection drug-using careers is limited. Regarding the latter, research has identified a range of structural, drug-related, and social factors that modify the risk environment for the cessation of injection drug use, as outlined in Chapter 2. These include access to methadone maintenance therapy, which has been shown to increase the likelihood of injection cessation.[50] Non-injection crack cocaine use has also been shown to increase the likelihood of injection cessation in certain settings,[33] while exposure to IDU has been shown to delay injection cessation.[114] With respect to reducing the harms of ongoing injection, decades of research have demonstrated that needle and syringe programmes (NSPs) are effective in reducing HIV and HCV incidence,[100, 241] and that they are also highly cost-effective compared to other preventive approaches among IDU populations.[242] As a result, the implementation of NSPs is a key recommendation of international guidelines for the prevention of blood-borne disease transmission among IDU.[4, 21, 243]

Yet, despite this evidence base and ongoing injection-driven epidemics in a number of settings internationally,[10, 244] NSPs have not been implemented to scale.[30] This is partially related to the fact that, while research indicates that NSPs are not associated with increased drug injecting,[99] some concerns persist regarding the possibility that NSPs may enable or encourage injection drug use, prolong the

injection drug use careers of their clients, and/or discourage clients from seeking addiction treatment.[56] This may be related to findings of early studies that found an association between NSP use and HIV risk,[60, 245] subsequently explained by the fact that NSPs attract high risk IDU.[246] However, as described in Chapter 1, global scale up of NSPs has been greatly impeded, and only an estimated 5% of drug injections worldwide are conducted using sterile equipment.[30, 247] This lack of scale up has implications for the risk environment experienced by IDU throughout the course of their injection drug use careers. In settings where they are implemented, structural interventions such as NSPs can serve as a first point of contact for IDU to engage with the health care continuum.[248] As described in Chapter 2, such contact can then increase access to a range of health and social services which may impact both the length, of and risks inherent in, ongoing injection trajectories.[33] In the absence of NSPs and other harm reduction services, however, emergency health care responders, police, and the criminal justice system represent the most frequent sources of contact for IDU.[249-251] The harms of contact between IDU populations and the criminal justice system have been well-established, and have been shown to expose IDU to risk environments which increase their likelihood of engaging in HIV risk behaviours and experiencing other negative drug-related health and social outcomes.[18, 148, 252-256]

Addressing concerns related to the impact of NSPs on the injection career trajectories of IDU could help to support approaches to reducing injection-driven blood-borne disease transmission in a number of settings marked by such harms.[257] For example, in some U.S. cities (e.g., Washington, D.C.) where HIV rates are particularly high among IDU, NSPs have been recently scaled back or closed,[258]

despite research demonstrating that increased access to NSPs improves use of sterile syringes among IDU.[259] Similarly, in Russia, with an IDU population estimated at 1.8 million,[4] policymakers continue to oppose harm reduction measures, including NSPs.[260] In Thailand, where less than 1% of IDU have access to NSPs,[30] the government's State Council recently ruled that a notification in support of harm reduction by the country's Department of Disease Control was in breach of Thailand's 1979 Narcotic Act, on the basis that syringe distribution encourages drug use.[261] Additionally, although the President's Emergency Plan for AIDS Relief (PEPFAR) recently released guidelines for funding NSPs as part of the U.S.' international response to the spread of HIV,[262] legislation has since been introduced in the U.S. House of Representatives that bars the U.S. from funding NSPs in foreign countries.[263]

Vancouver, Canada has been the site of a well-documented NSP expansion, beginning in the year 2000, when a single centralized syringe exchange program was transformed into a decentralized, multi-site syringe distribution program.[62] In the context of ongoing concerns regarding the potential for NSPs to encourage or prolong injection drug use, and within an environment that heightens the likelihood of risky injection-related practices such as syringe sharing and overdose,[264, 265] we sought to assess rates of injecting cessation among a sample of IDU in Vancouver during this period of NSP expansion.

6.2   Methods

First, to describe the pattern of NSP expansion, reports of the number of NSP sites in Vancouver during the study period were obtained from Vancouver Coastal Health, Vancouver's local health authority.[266] We then conducted trend tests to

determine whether the increase in NSP sites by calendar year was significant. Rates of injecting drug use cessation (i.e., reporting no drug injecting in the prior six months) and re-initiation (i.e., a period of injection cessation followed by a resumption of injecting) were derived from the Vancouver Injection Drug Users Study (VIDUS), described in full in section 1.7.

The primary outcome for the current study was injecting cessation, defined as reporting no injection drug use in the previous 6 months. As noted above, we derived adjusted annual estimates of the proportion of cohort participants reporting cessation, and to control for a potential cohort effect,[267] whereby the number of IDU reporting drug use cessation might be expected to increase over time,[268] the proportions of those reporting cessation were adjusted for the number of years that individuals were enrolled in the study. Annual estimates and 95% confidence intervals were then generated for the years 1996 to 2010. Data on the crude number of sterile syringes distributed annually were also acquired from the local health board, and overlaid graphically with the proportion of participants reporting injection cessation per year. Finally, a map of NSPs in Vancouver's downtown eastside neighbourhood was generated for the year 2010 in order to visually assess the spatial relations between the epicenter of injecting activity in Vancouver and the geographic coverage of sterile syringe provision.

At this stage, the graphical exploration of the data implied that the NSP site expansion coincided with increased injecting cessation. However, to better delineate the risk environment within which injection transition events occur among the study participants, we conducted generalized estimating equation (GEE) logistic regression analyses to determine what social, physical, policy, drug-related, peer-

based and economic factors were associated with the likelihood of cessation during the study period. Specifically, univariate and multivariate GEE analyses for binary outcomes were used to determine factors independently associated with injecting cessation among cohort participants. These methods provided modified standard errors adjusted by multiple observations per person using a first-order autoregressive correlation structure.[210, 269] As in the first stage of the analysis, we adjusted for year of study recruitment to control for a potential cohort effect. We used the risk environment framework to guide the selection of additional variables,[73] which included: age at study entry, gender, Aboriginal ancestry (yes *vs.* other), number of years injecting at baseline, accessing methadone maintenance therapy, accessing other addiction treatment, residency in Vancouver's downtown eastside neighbourhood (the site of a large open-air illicit drug market), homelessness, incarceration, accessing Vancouver's medically supervised injection facility (Yes *vs.* No), having a partner who was injecting, recent heroin injection, recent cocaine injection, recent speedball (i.e., heroin and cocaine in combination) injection, recent non-injection crack use, and frequent injection drug use (daily *vs.* less than daily). All behavioural variables refer to behaviours in the previous 6 months. Consistent with previous studies investigating cessation of injecting, all time-updated behavioural variables were lagged by one follow up questionnaire.[50, 270] As such, behavioural variables refer to the 6 months prior to the follow-up questionnaire immediately preceding the first report of injecting cessation.

The multivariate GEE model was fit using a two-stage protocol. First, a decision to enter the primary independent variable of interest (i.e., calendar year) and key potential confounders (i.e., year of study enrolment, enrolment in

methadone, and non-injection crack use) into the multivariate model was made *a priori*. All other independent variables were entered into the multivariate model based on a finding of statistical significance at the *p* < 0.05 level in univariate analysis.

All statistical analyses were performed using SPSS software version 19.0 (IBM, New York, NY). All *p* values are two sided.

6.3   Results

In total, 2,551 participants were recruited into the study and completed at least one follow up visit between May 1996 and December 2010, including 856 (33.6%) female and 697 (27.3%) individuals reporting Aboriginal ancestry. Participants contributed 10,180 person-years of follow up. Retention was high, with 87.6% of cohort participants reporting at least one follow-up visit, and the median number of follow up visits was 5 (Interquartile Range [IQR] = 2 – 12). Throughout the study period, 5,849 injecting cessation events were reported, while the number of NSP sites in Vancouver increased significantly from 1 in 1996 to 29 in 2010 (*p* < 0.001).

Figure 5 presents a line graph of the adjusted proportion of participants reporting injecting cessation by year and a histogram depicting the increase in the number of NSP sites during this same period. Adjusting for year of baseline recruitment into the study, the proportion of IDU reporting injecting cessation increased from 2.4% (95% Confidence Interval [CI]: 0.0% – 7.0%) in 1996 (when eligibility for the study required drug injecting) to 47.9% (95% CI: 46.8% – 48.9%, *p* < 0.001) in 2010. During the same period, the proportion of IDU reporting re-initiation of injection drug use increased from 0% in 1996 to 36.7% (95% CI: 19.1%

- 54.2%, $p < 0.001$) in 2010. Figure 6 presents a line graph of the adjusted proportion of participants reporting injection cessation by year and a histogram depicting the crude number of syringes distributed annually. Finally, Figure 7 presents a map of NSP coverage in Vancouver's downtown eastside for the year 2010. This includes the approximate range of the Mobile Access Project, which consists of a mobile van that patrols the Vancouver downtown eastside and surrounding areas and provides sterile syringes, condoms, and other supplies to individuals involved in the sex trade as well as IDU and non-IDU.[271]

In a univariate GEE analysis, increasing calendar year was positively associated with injecting cessation (Odds ratio [OR] = 1.22, 95% CI: 1.20 – 1.24, $p <$ 0.001). Full univariate results are presented in Table 6. In a multivariate GEE model, increasing calendar year (Adjusted Odds ratio [AOR] = 1.16, 95% CI: 1.15 – 1.18, $p <$ 0.001) and enrolment in methadone treatment (AOR = 1.19, 95% CI: 1.09 – 1.31, $p <$ 0.001) were positively associated with injecting cessation. Later year of enrolment into the study (AOR = 0.88, 95% CI: 0.87 – 0.90, $p < 0.001$), residence in Vancouver's downtown eastside (AOR = 0.84, 95% CI: 0.77 – 0.91, $p < 0.001$), recent involvement in the sex trade (AOR = 0.70, 95% CI: 0.61 – 0.79, $p < 0.001$), accessing a medically supervised injection facility (AOR = 0.66, 95% CI: 0.58 – 0.74, $p < 0.001$), having a partner who is an IDU (AOR = 0.74, 95% CI: 0.68 – 0.81, $p < 0.001$), recent heroin injection (AOR = 0.47, 95% CI: 0.43 – 0.52, $p < 0.001$), recent cocaine injection (AOR = 0.53, 95% CI: 0.49 – 0.59, $p < 0.001$), recent speedball injection (AOR = 0.72, 95% CI: 0.65 – 0.79, $p < 0.001$), and frequent injection drug use (AOR = 0.79, 95% CI: 0.74 – 0.84, $p < 0.001$) were negatively associated with injecting cessation. Full multivariate results are presented in Table 7.

6.4   Discussion

This analysis observed a significant increase in the proportion of IDU in Vancouver reporting injecting cessation during a 15-year period characterized by a significant increase in the number of NSP sites. This increase in the likelihood of injecting cessation over time persisted even after adjustment for other determinants of injecting cessation, including a possible cohort effect controlled for by year of recruitment.[217] [222] Further, while study participants that reported accessing methadone maintenance therapy were significantly more likely to report injecting cessation, a range of factors were associated with a reduced the likelihood of injecting cessation. These included sex trade involvement, having a sexual partner who was injecting, residing in Vancouver's downtown eastside, and reporting a higher frequency of injecting and use of heroin, cocaine, or speedballs.

This study has limitations consistent with the use of observational data. As a result, although we observed that an NSP site expansion coincided with increasing rates of injecting cessation, we are unable to explain a causal mechanism for this shift related to NSP implementation. However, based on this study's findings, we can conclude that NSP expansion is unlikely to delay injecting cessation. Additionally, cohort participants were not recruited using random sampling and the potential exists that results may not be generalizable to the overall population of illicit drug users in our study setting. However, participant recruitment was ongoing throughout the study period, and it is noteworthy that data from government surveillance systems and other studies undertaken in the same setting are consistent with our own, suggesting that the cohort is likely representative of the broader IDU population in Vancouver.[272-274] Additionally, while involvement in the

illicit drug trade and interactions with police may have impacted the odds of injection cessation among study participants, these variables were not consistently measured across cohort questionnaires throughout the study period, and were therefore not eligible for the analysis. Finally, as previously noted, it is possible that an age or cohort effect may have impacted the observed rate of injecting cessation;[55, 268] however, increasing rates of injecting cessation over time were observed despite adjustment for age and year of recruitment into the cohort.

The findings presented herein suggest that, while a period of NSP expansion was associated with an increasing proportion of IDU reporting injecting cessation, a range of intersecting factors were associated with ongoing injection, or delayed cessation. It is particularly noteworthy that residing in the downtown eastside, the epicenter of Vancouver's open-air injecting drug scene, as well as reporting having a sexual partner who was injecting, were both associated with a reduced likelihood of cessation. This suggests that ongoing exposure to injecting may prolong injection drug-using trajectories and sustain injecting risk among established IDU in a similar manner as exposure to injecting heightens risk for injection-naïve drug users.[34, 38] Indeed, among IDU in Baltimore, Latkin and colleagues found cessation to be strongly associated with reporting a lower proportion of social network contacts who use drugs.[114] Buchanan and Latkin also found that, compared with those that did not cease injecting, IDU in Baltimore reporting injection cessation had a highly reduced number of drug-using individuals in their social network,[275] while Shah and colleagues found a lower likelihood of injection cessation among IDU in Baltimore who reported having an IDU sexual partner.[50] In the present study, results suggest that accessing Vancouver's supervised injection facility was independently

associated with a lower likelihood of cessation. This may suggest that the facility attracts IDU at risk of ongoing injection, which has implications for efforts to reduce community-level exposure to injecting, given that those that inject within the facility do so alone and in a non-public setting.

With respect to neighbourhood of residence, a recent Baltimore-based study found that residing in a neighbourhood characterized by high levels of poverty (i.e., more than 30% of residents reporting living under the poverty line) was associated with a reduced odds of cessation among IDU.[276] This finding is highly relevant to the present study context, given that Vancouver's downtown eastside is among the poorest urban areas in Canada.[277] Additionally, while the spatial relationship between IDU and NSPs has been shown to restrict access to sterile injecting equipment in settings where distribution sites are distally located,[278] Figure 5 demonstrates the high level of coverage of NSPs in Vancouver's injection drug-using epicenter, with NSPs located at a maximum of approximately four blocks from any location in the downtown eastside. This is consistent with previous research that found that IDU residing in the downtown eastside reported significantly lower levels of difficulty accessing syringes compared to IDU residing in other neighbourhoods.[279] However, those residing in the downtown eastside nevertheless were significantly less likely to report injection cessation. This likely reflects a selection effect, given the known high risk profile of individuals living in this area.[58] Nevertheless, this has implications for the spatial design of competing policy responses to drug use, and suggests that policymakers should consider the potential unintended consequences of service provision and drug law enforcement clustering within high-risk areas. Specifically, research from New York City has demonstrated

that street-level enforcement of drug-related behaviours in areas of NSP implementation negatively impacted the protective effect of NSPs and reduced the likelihood of IDU injecting with sterile equipment.[280] The ongoing focus on arrest and incarceration of IDU in the downtown eastside may, similarly, contribute to lower effectiveness of NSPs in this setting, and should be reevaluated.

While the majority of resources aimed at the control and reduction of drug use are often allocated towards drug-law enforcement and criminal justice interventions (e.g., arrest and incarceration), study participants reporting recent incarceration did not have a higher likelihood of injection cessation. This finding is consistent with past research suggesting that this approach is likely ineffective in reducing problematic drug use.[148, 149, 264, 281, 282] Relatedly, participants enrolled in methadone maintenance therapy were significantly more likely to report injection cessation, suggesting that the provision of proven clinical treatment modalities for drug dependence is likely effective,[24] which further supports the steady increase in the provision of, and retention of IDU in, methadone maintenance therapy in British Columbia since the mid-1990s.[283] These results also have implications for the debate surrounding the implementation of NSPs in a variety of settings and help to address a key concern often cited by those opposed to NSPs. Specifically, the present study demonstrates an increase in injecting cessation among a sample of IDU during a period of NSP expansion in Vancouver that saw not only an increase in the number of NSP sites, but also operational changes aimed at increasing sterile syringe availability. These included longer operating hours and a shift to syringe distribution from a strict one-for-one syringe exchange system.[62] This echoes research undertaken in other settings that has found that these programs are more

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effective when they employ a syringe distribution rather than exchange model.[284-287] While the increase in NSP sites was not linear throughout the study period, with local factors such as the consolidation of health services causing fluctuations in the number of NSPs, the results nevertheless imply that NSPs are unlikely to lengthen drug-injecting careers.

This finding is consistent with a recent study from New York City that observed that large-scale implementation of NSPs was associated with a decreased proportion of methadone treatment clients reporting injection drug use.[110] This suggests that NSPs may be complementary to efforts to retain IDU in treatment and promote abstention from injection drug use. Indeed, research from other settings suggests that use of NSPs results not only in reducing risk behaviours for blood-borne disease transmission but also in increasing access to basic health services among clients,[248] and that these programs have the capacity to attract those IDU at high risk of a variety of drug-related harms.[62, 100, 243] This is highly relevant to the present study, and it is important to note that many IDU in the study who ceased injecting also experienced a period of relapse. Nevertheless, as shown in Figure 5, this study suggests that the proportion of people who use drugs who were not injecting nevertheless increased on an annual basis. Given the well-known potential for relapse among IDU seeking to cease injecting,[50, 288] NSP access is critical in reducing blood-borne disease transmission risk throughout an individual's drug-using career. Interestingly, in this study crack use was not associated with injecting cessation, suggesting that IDU who transition into non-injection crack use may nevertheless continue to inject other substances. This differs from previous research undertaken in other Canadian settings.[33, 289]

Finally, the findings presented in this chapter suggest that a variety of factors, including illicit income generation via the sex trade,[290] the drug-related behaviours of peers,[72, 107] interactions with the criminal justice system,[264, 291] and the wide availability of drugs such as heroin and cocaine[58] heighten the risk that IDU will prolong their injection careers. Nonetheless, we observed a steady increase in the proportion of participants reporting injecting cessation. This suggests that transitions into non-injection drug use can be facilitated through the provision of structural interventions in settings characterized by factors that may increase risk for ongoing injection. Policymakers should therefore implement and expand interventions such as NSPs, methadone maintenance therapy, and other interventions such as supervised injection facilities that have been shown to modify injection drug use patterns towards lower-risk and lower frequency trajectories.[24, 27, 63, 99, 283, 292-294]

In summary, the present study suggests that injection cessation occurred at a high level during a period characterized by increasing NSP availability and within a context in which IDU had a reduced capacity to cease injecting. Given a large body of research demonstrating the positive impacts of NSPs on the risk of blood-borne disease transmission and other public health concerns,[62, 100, 292, 295] as well as the low global coverage of these intervention,[30] policymakers should move quickly towards the provision of NSPs in conjunction with complementary public health interventions such as methadone maintenance treatment and supervised injection facilities in settings marked by ongoing high-risk injection trajectories among drug-using populations.

Table 7. Univariate correlates of injecting cessation among injection drug users in Vancouver, 1996 – 2010 (n = 2,551)*

Characteristic	Injecting Cessation Event**				Unadjusted		
	No N = 17,220		Yes N = 5,849				
	n (%)		n (%)		Odds Ratio	95% CI	p value
Calendar year							
Per Year Later	--	--	--	--	1.22	1.20, 1.24	< 0.001
Age at study baseline							
Median (IQR)	36	(28.3 – 41.8)	35.7	(28.8 – 42.1)	1.00	1.00, 1.01	0.538
Gender							
Male	10,926	(63.4)	3,596	(61.5)			
Female	6,294	(36.6)	2,253	(38.5)	1.17	1.02, 1.32	0.024
Ethnicity							
Non-Aboriginal	11,967	(69.5)	3,889	(66.5)			
Aboriginal	5,253	(30.5)	1,960	(33.5)	1.49	1.27, 1.75	< 0.001
Years injecting at baseline							
Median (IQR)	13.8	(5.9 – 23.5)	13	(4.6 – 24.1)	1.00	0.99, 1.00	0.341
Year of enrolment							
Median (IQR)	1996	(1996 – 2000)	1996	(1996 – 2000)	0.97	0.96, 0.99	0.002
DTES residence							
No	6,060	(35.2)	2,953	(50.5)			
Yes	11,159	(64.8)	2,896	(49.5)	0.60	0.54, 0.66	< 0.001
Incarceration							
No	14,024	(81.4)	5,480	(93.7)			
Yes	3,195	(18.6)	369	(6.3)	0.48	0.42, 0.55	< 0.001
Sexual partner injects							
No	11,431	(66.7)	5,394	(92.9)			
Yes	5,703	(33.3)	414	(7.1)	0.35	0.32, 0.39	< 0.001
Sex trade involvement							
No	14,116	(82.0)	5,527	(94.5)			
Yes	3,098	(18.0)	322	(5.5)	0.36	0.30, 0.43	< 0.001
Homeless							
No	13,235	(76.9)	5,054	(86.4)			
Yes	3,984	(23.1)	795	(13.6)	0.70	0.64, 0.78	< 0.001
Insite access							
No	13,525	(78.7)	5,806	(99.7)			
Yes	3,650	(21.3)	15	(0.3)	0.69	0.63, 0.76	< 0.001
Methadone treatment							
No	11,471	(66.6)	3,744	(64.0)			
Yes	5,749	(33.4)	2,105	(36.0)	2.06	1.87, 2.28	< 0.001
Other addiction treatment							
No	10,755	(62.5)	3,491	(59.7)			
Yes	6,464	(37.5)	2,358	(40.3)	0.96	0.88, 1.05	0.355
Recent heroin injection							
No	6,705	(38.9)	4,791	(81.9)			
Yes	10,514	(61.1)	1,058	(18.1)	0.24	0.22, 0.26	< 0.001
Recent cocaine injection							
No	7,015	(40.7)	4,645	(79.4)			
Yes	10,204	(59.3)	1,204	(20.6)	0.27	0.25, 0.30	< 0.001
Recent speedball injection[†]							
No	9,319	(54.1)	5,018	(85.8)			
Yes	7,900	(45.9)	831	(14.2)	0.42	0.38, 0.46	< 0.001
Recent non-injection crack use							
No	6,155	(35.7)	2,777	(47.5)			
Yes	11,064	(64.3)	3,072	(52.5)	0.85	0.77, 0.95	0.003
Frequent injection[‡]							
No	9,082	(52.7)	4,417	(75.5)			
Yes	8,138	(47.3)	1,431	(24.5)	0.53	0.49, 0.57	< 0.001

Note: CI = Confidence Interval; IQR = Interquartile Range; DTES = downtown eastside; IQR = interquartile range
All behavioural variables refer to behaviours measured in the follow-up survey prior to the first report of cessation;
***Frequencies refer to the number of events throughout study period; [†]Speedball refers to heroin and cocaine in combination; [‡]Frequent refers to at least once daily.*

Table 8. Multivariate generalized estimating equation analysis of correlates of injecting cessation among injection drug users in Vancouver (*n* = 2,551)*

Characteristic	Adjusted Odds Ratio	95% CI	*p* value
Calendar year			
Per Year Later	1.16	1.15, 1.18	< 0.001
Year of enrolment			
Per Year Later	0.88	0.87, 0.90	< 0.001
Female			
Male *vs.* Female	1.12	0.99, 1.30	0.119
Ethnicity			
Non-Aboriginal *vs.* Aboriginal	1.08	0.88, 1.16	0.916
Methadone treatment			
Yes *vs.* No	1.19	1.09, 1.31	< 0.001
DTES residence			
Yes *vs.* No	0.84	0.77, 0.91	< 0.001
Homeless			
Yes *vs.* No	0.95	0.87, 1.05	0.303
Involvement in the sex trade			
Yes *vs.* No	0.70	0.61, 0.79	< 0.001
Incarceration			
Yes *vs.* No	0.91	0.81, 1.01	0.076
Partner is injecting			
Yes *vs.* No	0.74	0.68, 0.81	< 0.001
Accessing Insite			
Yes *vs.* No	0.66	0.58, 0.74	< 0.001
Recent heroin injection			
Yes *vs.* No	0.47	0.43, 0.52	< 0.001
Recent cocaine injection			
Yes *vs.* No	0.53	0.49, 0.59	< 0.001
Recent speedball injection[††]			
Yes *vs.* No	0.72	0.65, 0.79	< 0.001
Recent non-injection crack use			
Yes *vs.* No	0.95	0.90, 1.07	0.612
Frequent injection drug use[°]			
Yes *vs.* No	0.79	0.74, 0.84	< 0.001

Note: CI = Confidence Interval; DTES = downtown eastside.
*All behavioural variables refer to behaviours measured in the follow-up survey prior to the first report of cessation
[†]*Recent refers to the previous six months*
[††]*Speedball refers to heroin and cocaine in combination*
[°]*Frequent refers to at least once daily*
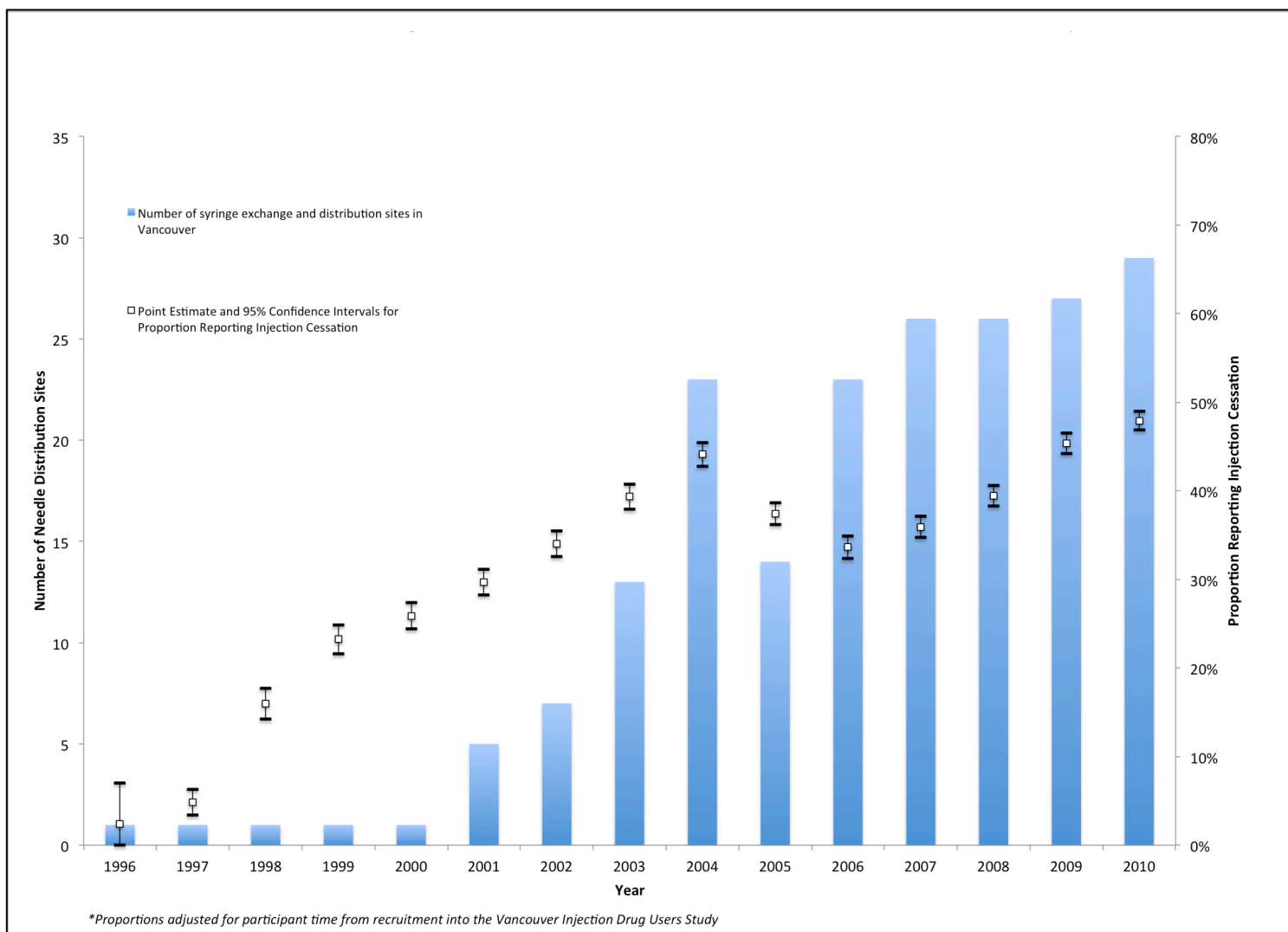
Figure 5. Annual proportion of injection drug users reporting injecting cessation and expansion of needle and syringe programs in Vancouver, 1996 – 2010 (*n* = 2,551)
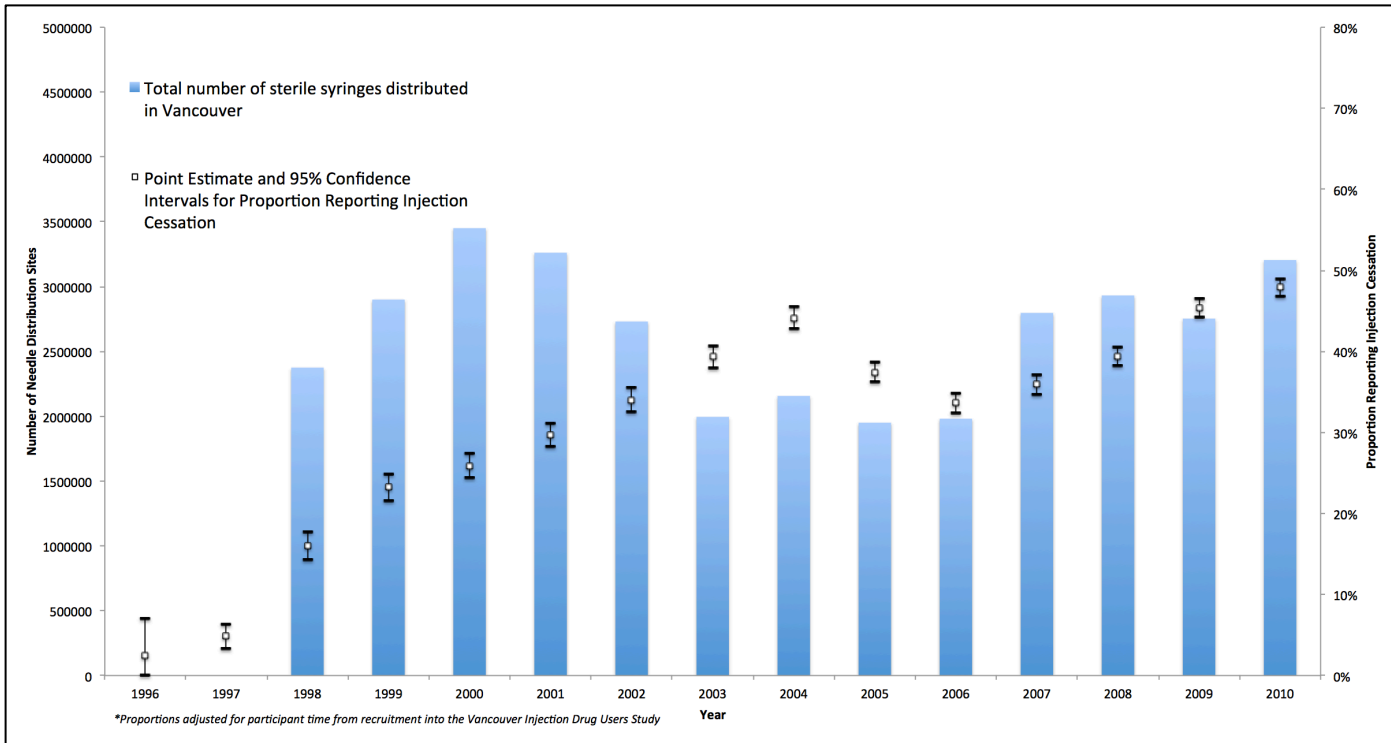
Figure 6. Annual proportion of injection drug users reporting injecting cessation and crude number of sterile syringes distributed in Vancouver, 1996 – 2010 (*n* = 2,551)
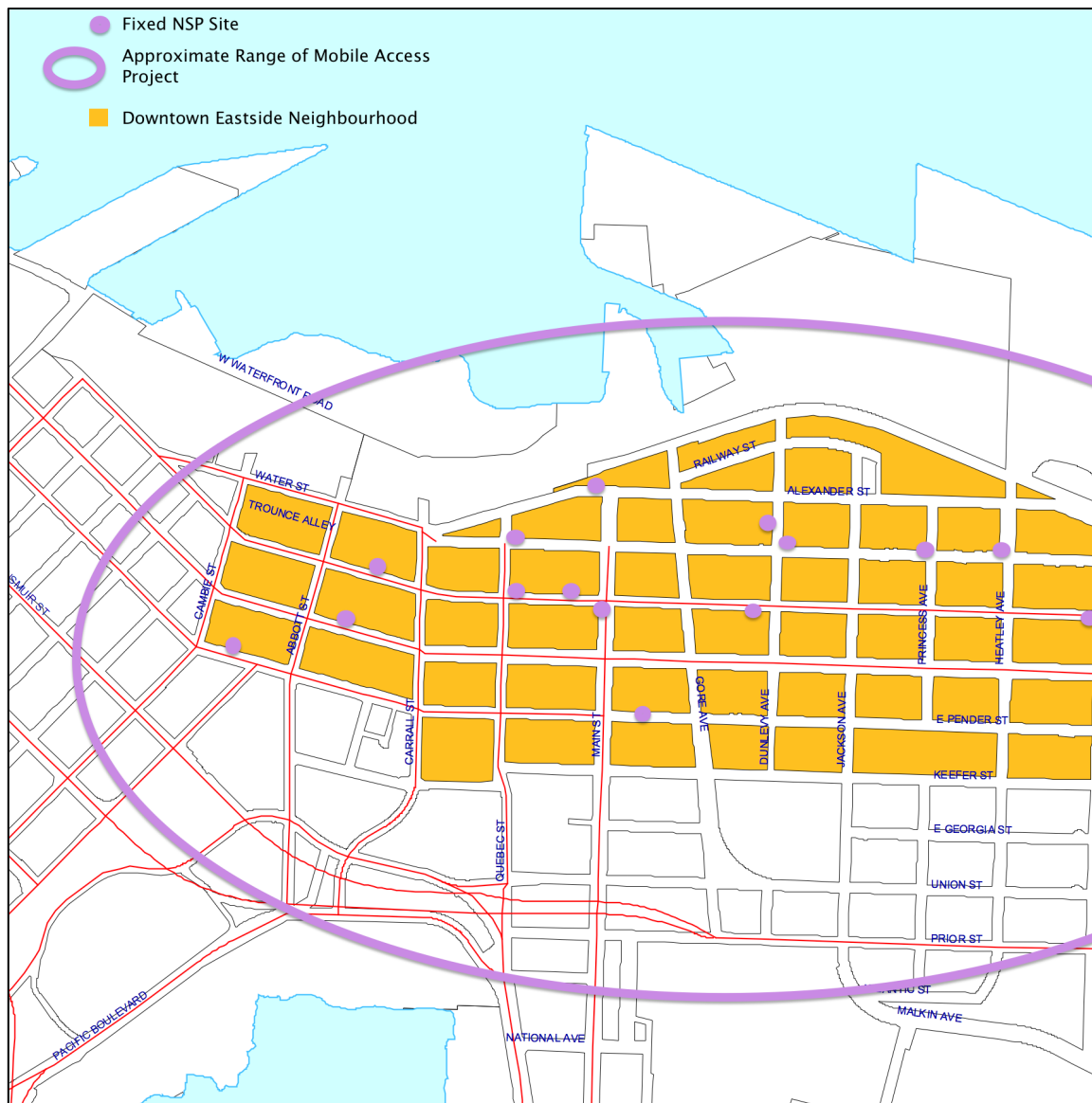
Figure 7. Approximate location of needle and syringe programmes in Vancouver's downtown eastside neighbourhood, 2010

Source: Vancouver Coastal Health

CHAPTER 7: DISCUSSION, FUTURE RESEARCH, CONCLUSIONS

7.1   Summary of findings

As described in Chapters 1 and 2, investigations of the natural history of injection provide insight into how injection-related risks vary over time. Such investigations have also identified key transition events (e.g., initiation and cessation of injection), longitudinal patterns of injecting, and sources of injection-related morbidity and mortality. Given that public health experts have called for the prioritization of interventions to prevent injection drug use,[22] Chapter 3 consists of a systematic review identifying and critically assessing peer-reviewed scientific evaluations of interventions to prevent injecting. Of a total of 384 studies potentially eligible for inclusion in the review, eight met the eligibility criteria,[143-150] which included the presentation of original data and the evaluation of a discrete preventive intervention. While eligible studies varied in methodology, setting, and outcomes, four major types of interventions were identified: social marketing, peer-based behaviour modification, addiction treatment, and drug law enforcement. Of these, peer-based behaviour modification and addiction treatment interventions were found to be the most effective. However, the major finding from this systematic review is that there exists a lack of peer-reviewed evaluations of interventions to prevent initiation into injection drug use. This review therefore highlights the need for research into the development and evaluation of interventions to prevent drug injection. However, results suggest that interventions that reduce the exposure of injection-naïve drug users to injecting environments may have the greatest preventive potential. This is in line with studies identifying exposure to injecting as a key modifier of risk of injection initiation.[38, 42]

In Chapter 4, use of crystal methamphetamine is shown to be independently associated with an increased risk of injection initiation among street-involved youth enrolled in the ARYS cohort in Vancouver, while the drug that cohort participants reported commonly using in injection initiation events was crystal methamphetamine. Further, in a secondary analysis of those that reported ever injecting, almost half of all participants received the injected drug as a gift, and the vast majority reported being injected by someone else.

Chapter 5 investigates the role of the personality trait sensation seeking in modifying individual risk for injection drug use and a variety of other drug-related behaviours identified as predictors of injection initiation, including crystal methamphetamine use, polysubstance use, and binge drug use, among a cohort street-involved youth. For the purposes of this thesis, a modified brief version of the sensation seeking scale (SSS) was developed for use among a sample of street-involved youth. The reliability and validity of the modified brief SSS was then explored using exploratory and confirmatory factor analysis. The hypothesis that participant score on the modified SSS was associated with an increased odds of injecting and risk factors for injection initiation was then tested using self-reported data gathered from a cohort of street-involved youth in Vancouver. In a series of multivariate models, higher SSS score was associated with a higher odds of injecting, of crystal methamphetamine use, of polysubstance use, and of binge drug use during the study period, despite adjustment for a variety of sociodemographic and drug-related factors. While previous studies have identified the role of sensation seeking in modifying the risk of drug use among the general youth population,[98, 296] and while some have employed measures of sensation seeking in investigations of risk

among street-based drug-using populations,[91-93, 198, 297] this is, to our knowledge, the first study to develop a sensation seeking scale for specific use among street-based drug-using populations and to also identify the role of higher sensation seeking in increasing risk of injecting among street-involved youth through a variety of potential causal pathways.

Finally, Chapter 6 sought to examine rates of injection drug use cessation during a period of NSP expansion using data from a cohort of IDU over a 15-year period in Vancouver. Variable selection for the model was guided by the risk environment framework. Specifically, factors such as enrolment in methadone maintenance, access to a supervised injection facility, and incarceration were tested, along with a range of economic, spatial, social network, and policy factors, and the model was adjusted for possible cohort effects. Several factors were associated with ongoing injecting, including residence in Vancouver's downtown eastside, involvement in the sex trade, and having a partner who injects. However, despite the fact that participants reported these risks, the period of NSP expansion was nevertheless associated with increased injection cessation, and enrolment in methadone maintenance therapy was independently associated with an increased likelihood of cessation. This finding supports the conclusion that the implementation of NSPs does not prolong the injection careers of IDU, a finding that has been observed in other settings.[33, 110] It also further suggests that the coordinated implementation of evidence-based treatment, public health, and harm reduction interventions are likely effective in reducing both the harms of drug injecting and in facilitating reductions or cessation of injection drug use.

7.2   Study contributions

Together, the above chapters make several contributions to the literature on the natural history of injection drug use. Primarily, this dissertation includes the adaptation and validation of a psychometric scale to assess the likelihood of drug-related risk-taking among street-involved youth.[32, 298] The development of this modified SSS for the first time provides a culturally appropriate assessment of sensation seeking for a street-involved youth population exhibiting negative drug-related outcomes at a higher rate than other populations in which sensation seeking has previously been studied.[98, 296] Further, the hypothesis testing exercise undertaken in Chapter 5 demonstrates the potential for extending classical epidemiologic models of drug-related risk currently focusing on behavioural, sociodemographic or clinical risk factors to include personality-based risk factors as well. This investigation of personality-based risk factors is consistent with recent calls from the U.S. National Institutes of Health to employ individual-level, neurobiological, and psychological factors in investigations of drug-related risk.[299] In this regard, Chapter 5 represents a preliminary expansion of the scientific literature to articulate the association between sensation seeking and a range of risky drug-related behaviours highly relevant to public health efforts to mitigate drug-related harm, and primarily injection drug use. Additionally, the analyses undertaken in Chapter 4 and Chapter 5 collectively represent a relatively comprehensive investigation of the risks for injection initiation faced by street-involved youth, which remains an understudied phenomenon. These findings are highly relevant given ongoing epidemics of injection drug use globally.[10] Taken together, these suggest an expanded role for research into the role of both crystal

methamphetamine use and sensation seeking in heightening risk of initiation into injection.

This dissertation also includes, in Chapter 3, the first systematic review of interventions to prevent the initiation of injection drug use. Given expert calls for the prioritization of the prevention of injection initiation,[22] this systematic review fills a gap in the scientific literature on this topic, providing researchers and policymakers with what is hoped will be a useful foundational document for future research and intervention development. Of concern, this review highlights the critical dearth of scientifically peer-reviewed evaluations of preventive interventions undertaken to date, and the concomitant need for the development of novel, evidence-based interventions to effectively reduce the incidence of injection initiation.

Collectively, this dissertation identifies a series of factors, such as use of crystal methamphetamine (Chapter 4), exposure to injecting (Chapters 4 and 6), and sensation seeking (Chapter 5), all of which appear to negatively impact the risk of injection transitions. Furthermore, the findings presented in Chapter 6 suggest that current efforts to reduce the harms associated with ongoing high-risk injection trajectories, which include the provision of evidence-based addiction treatment and the expanded distribution of sterile injecting equipment, are unlikely to negatively impact rates of injection cessation among IDU populations for whom these services are made available, despite the fact that the capacity of the sample of IDU under study in Chapter 6 to cease injecting was highly restricted by a range of social, structural, peer-based and policy factors.

7.3   Study strengths and limitations

This dissertation is notable in that all data-driven chapters include longitudinal analyses of drug-related risk undertaken among samples of street-based drug-using populations (e.g., street-involved youth and IDU). In particular, Chapter 6 includes an analysis of 15 years of longitudinal data from the VIDUS cohort. This dissertation also identifies a novel source of increased risk for injection drug use and other risk factors for injection initiation, in the form of high sensation seeking. This thesis also includes the first systematic review identifying and assessing the scientific literature on interventions to prevent the initiation of injection drug use.

With respect to limitations, and as noted elsewhere, the analyses reported here rely on observational data from cohorts of street-based drug-using populations, and behavioural and drug-related data were collected via participant self-report. Given the stigmatized nature of drug use, the potential therefore exists that participants underreported drug-related behaviours.[180, 240] However, all interviewers were trained in a variety of techniques to minimize the possibility of bias resulting from unreliable self-report. These included the use of schedules and cue cards to improve recall, the staging of more sensitive questions later in interviews, and techniques to build trust with study participants. Second, although this thesis employed multivariate analyses, it is possible that unmeasured confounding exists. Finally, given that no population-based registries of street-involved youth or IDU exist, the possibility of constructing probability samples using a comprehensive registry-based system was not available. However, as previously noted, studies have demonstrated that the ARYS and VIDUS cohorts, both of which

employ community-based recruitment techniques such as street-based and snowball sampling, may be generalizable to the broader populations of street-involved youth and IDU residing in Vancouver.[179, 237, 272, 273]

7.4   Recommendations

Several recommendations can be derived from the research presented in this thesis. First, as described in Chapters 3-5, implementing evidence-based interventions to prevent injection initiation among street-involved youth should be a public health priority,[31, 42, 231] given that so few currently exist and only one has been brought to scale. Second, the development of such interventions should seek to identify high-risk individuals from within groups of vulnerable drug-using populations.

In this regard, a focus on the role of established IDU in facilitating injection initiation events is warranted, given the findings of the secondary analysis presented in Chapter 4. There are multiple interventional options for minimizing the exposure of street-involved youth to risk environments for injecting. For example, low-threshold housing should be located in areas inhabited by street-involved youth in order to disrupt their transition into injecting or further entrenchment in a street-based drug-using scene.[71, 72] As well, determining whether current interventions that seek to reduce the incidence of injection (such as the provision of methadone maintenance therapy;[24] the provision of peer-based behavioural interventions;[144] and comprehensive engagement strategies including harm reduction interventions such as NSPs,[4]) also reduce the risk of injection initiation by limiting exposure to injecting and the overall number of IDU peers that non-IDU are exposed to should be prioritized. Supervised injection facilities may be

particularly effective in this regard, given that they disrupt peer influence by reducing exposure to injecting in a number of ways: IDU attending such facilities inject separately from other clients; clients of the supervised injection facility in Vancouver are not allowed to share drugs within the facility (e.g., gifting); injection within such a facility reduces community exposure to injection; and these facilities do not accommodate injection-naïve drug users.[63]

Third, the analysis presented in Chapter 6 found that being exposed to injecting via a sexual partner was associated with a significantly lower likelihood of injection cessation. As described above, supervised injection facilities may modify the risk environment experienced by individuals at varying points along their injection careers by reducing the likelihood of public injecting and thereby potentially mitigating peer influence, with implications for the likelihood, timing, duration, and cessation of injection drug use. However, the intimate nature of sexual relationships may be beyond the capacity of these structural interventions to modify, and complementary approaches are likely therefore required. To that end, multiple studies have found that IDU enrolled in methadone maintenance therapy not only reduce injecting but also report significantly fewer IDU sexual partners,[300, 301] suggesting that this intervention may have the capacity to reduce secondary HIV risk behaviours associated with ongoing injection.

Fourth, the findings presented here reinforce evidence indicating that the implementation and/or expansion of NSPs should be a key part of a comprehensive public health response to drug-related harms in settings characterized by a high prevalence of injection drug use. In short, it is clear that interventions aimed at reducing the incidence of ongoing injecting (e.g., methadone maintenance therapy)

and those that aim to reduce the harms associated with this activity (e.g., NSPs) do not necessarily undermine each other and, as delineated above, may represent a potential area of synergy in treatment and harm reduction efforts. In fact, beyond their demonstrated role in reducing HIV risk among IDU,[62, 295, 302] NSPs have been found to be complementary to efforts to reduce injecting among active IDU in a number of settings.[33, 110, 303] Indeed, it is noteworthy that in a study setting characterized by an intersection of factors, including residency in the downtown eastside, involvement in the sex trade, and having a sexual partner who is injecting, all of which significantly reduce the likelihood of cessation, the period of NSP expansion was nevertheless characterized by an increasing annual proportion of IDU reporting cessation. However, given that previous research has demonstrated that street-level enforcement can reduce the protective effect of NSPs,[304] policymakers should consider alternatives to drug law enforcement in settings characterized by ongoing drug-related health and social harms.[244]

7.5   Future research

The use of psychosocial constructs such as sensation seeking within a risk environment framework provides a starting point for novel research into how personality-based risk factors for injection-related harm may be expressed among street-based drug-using populations experiencing a social and structural context that increases the risk of a range of negative health outcomes. In particular, future testing and refinement of the modified sensation seeking scale presented in Chapter 5 may improve capacity to develop individualized interventions to prevent drug-related harm by identifying those who may be more likely to engage in risky, novel experiences. For example, binge drug use and polysubstance use were associated

with higher sensation seeking score, and both behaviours carry attendant harms and have also been identified as risk factors for injection initiation.[108, 109] More generally, elevated sensation seeking has been shown (in this thesis and elsewhere[305]) to heighten drug-related risk. As such, a promising area of future research may be to undertake intervention studies or addiction treatment trials evaluating the effectiveness of interventions that are specifically designed to aid people who use drugs identified as high sensation seekers to reduce risk-taking behaviours such as crystal methamphetamine use, binge drug use and polysubstance use or to reduce their level of sensation seeking.[191] Additionally, the causal pathways by which sensation seeking and specific types of drug use such as crystal methamphetamine use may impact upon high risk behavior requires further research aiming to identify directions of causality in the association between drug-related risk-taking and sensation seeking. More broadly, the use of psychosocial constructs such as sensation seeking within a risk environment framework may facilitate novel research into how personality-based risk factors for injection-related harm may intersect with social and structural contexts to increase the risk of a range of negative drug-related health and social outcomes.

Additionally, Chapter 6 reconfirms the utility of methadone maintenance therapy in increasing the likelihood of injection cessation among IDU, while also demonstrating that exposure to injecting via a sexual partner appears to decrease the likelihood of cessation. In the context of the findings presented in Chapters 3-5, these results suggest that the provision of methadone maintenance therapy may have both an individual- and community-level impact on injection trajectories. Specifically, along with the direct impact of individual enrolment in methadone

maintenance therapy on injection cessation, such enrolment may also lead to lower community-level exposure to injecting by decreasing a community's number of active injectors. Further investigation of how addiction treatment provision may impact the risk environment experienced by street-level drug-using populations in our study setting – particularly with respect to sexual partnerships among IDU – is warranted.

This dissertation, consistent with previous research, has identified exposure to injecting as a risk factor for initiation and suggests that it may contribute to prolonged injection career trajectories. As such, and consistent with experts calls for research into the social context of injection,[306, 307] future quantitative research should employ network analysis tools[308] in order to determine the extent to which injection transition events are associated with peer behavior. Indeed, while previous research on injection initiation has investigated peer influence,[36, 42, 107, 306] there is a dearth of literature employing formal network analysis tools to assess injection transition events. Future work in this area could therefore expand upon research assessing the impact of social influence on the risk of bloodborne disease transmission among IDU populations.[309]

Finally, future research should explicitly examine the impact of drug policy interventions on the incidence of initiation and cessation of injection drug use among drug-using populations. For example, drug law enforcement interventions negatively impact street-based drug-using populations disproportionately,[252] and previous research has starkly demonstrated how large-scale policy decisions can increase the risk of injection initiation among vulnerable drug-using populations,[310] while also compromising the effectiveness of harm reduction interventions such as

NSPs.[280] Although the results of Chapter 3 of this thesis suggest that drug law enforcement is ineffective in preventing initiation, the association between drug policy and initiation nevertheless remains largely obscure, and more research is thus required. Such research will likely necessitate methodological approaches that employ multilevel modeling to account for the differential impact of drug policies across geographic settings and sociodemographic and structural contexts. This type of research could expand upon the findings presented in Chapters 3, 4 and 6 of this dissertation regarding the potential influence of established injectors in modifying injection trajectories. For example, longitudinal research could be undertaken to investigate the impact of drug policies on the incidence of initiation and cessation of injection as mediated through exposure to other injectors in a drug-using network, types of drugs used, mode of administration, sensation seeking status, intensity of drug law enforcement, and the presence or absence of harm reduction or other public health interventions.

7.6   Conclusions

Despite decades of scientific research on the harms of injection drug use, prevailing drug policies remain largely ineffective in reducing drug-related harm, as evidenced in high ongoing incidence of injection-driven epidemics of blood-borne disease and fatal overdose in a number of settings.[10, 149, 169, 311, 312] This is particularly problematic given that substantial resources to control drug use and supply continue to be allocated towards interventions and policy approaches that lack a scientific evidence base, and that have furthermore been shown to negatively impact injection-related risk through drug law enforcement interventions and the incarceration of people who use drugs.[244, 252, 313] In this context, this thesis found a

relatively limited literature on the natural history of injection drug use, as well as a small number of scientifically-evaluated interventions to prevent injection initiation. Further, using a risk environment framework, findings presented in this thesis suggest that street-involved youth in Vancouver who use crystal methamphetamine are at higher risk of initiating injection drug use, while those that report higher sensation seeking are at higher risk of injection drug use, along with non-injection crystal methamphetamine, polysubstance use and binge drug use – all of which have been shown to contribute to the risk of injection initiation. Additionally, this thesis further confirms that exposure to injecting appears to influence injection transition events, both with respect to initiation and cessation. Finally, during a period of NSP expansion, rates of injection cessation increased substantially, suggesting that this intervention is not associated with reducing injection cessation. It is important to note that this thesis contains limitations typical of observational research, as well as limitations related to the development and preliminary testing of a novel psychometric scale. Nonetheless, the findings presented suggest that the development and implementation of interventions to prevent injection drug use should be considered complementary to efforts to reduce injection-related harms.

Future research into the natural history of injection drug use research that focuses on interactions between a number of potential risk factors holds promise. For example, research investigating the interaction between the individual personality traits of drug users (e.g., level of sensation seeking) and the types of drugs consumed could help identify ways in which these two risk factors impact one another. This is important because research to date has focused almost exclusively on a unidirectional association between sensation seeking and drug use, though

experts have found that adolescent use of drugs such as amphetamines and cannabis may impact brain development and the expression of personality traits.[314] In this way, determining the direction of causation with respect to sensation seeking and drug use may therefore aid in investigations of drug-related risk. Additionally, further investigations of the interaction between drug users at various stages of their injection careers, and on the impact of exposure to injecting, is required in order to further delineate the impact that established injectors may have on modifying the likelihood of injection transition events, and this work may best be undertaken by employing formal network analysis tools. Finally, research pertaining to the interactions between policy decisions and the individual injection career trajectories of people who use drugs would provide insights into how potential policy responses impact drug-related risk-taking.

The global burden of HIV and HCV transmission, fatal overdose, and other health and social harms is overwhelmingly focused on street-based drug-using populations. Within this context, describing the natural history of injection drug use, examining the varying level of drug-related risk that IDU experience, and determining how individuals at different stages of their injection careers impact injection-related risk in others, becomes increasingly important. This is because research of this kind can provide evidence highly relevant to policies that seek to both mitigate ongoing drug-related harms such as blood-borne disease transmission, and reduce the incidence of injection drug use initiation. Given the lack of evidence-based responses that currently exist, and the severity of drug-related harms in a variety of settings, developing comprehensive approaches that can both prevent

injection drug use and reduce injection-related harms represents a critical public

health priority.

References:

1. Mogey GA. Centenary of hypodermic injection. British BMJ. 1953; **2**(4847): 1180-5.

2. Karch SB. Cocaine: history, use, abuse. Journal of the Royal Society of Medicine. 1999; **92**(8): 393.

3. de Ridder M. Heroin: new facts about an old myth. Journal of Psychoactive Drugs. 1994; **26**(1): 65-8.

4. Beyrer C, Malinowska-Sempruch K, Kamarulzaman A, Kazatchkine M, Sidibe M, Strathdee SA. Time to act: A call for comprehensive responses to HIV in people who use drugs. Lancet. 2010; **376**(9740): 551-63.

5. ECOSOC. United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, 1988. Vienna: United Nations Economic and Social Council; 1988.

6. ONDCP. Budget and Performance. 2012. Available from: http://www.whitehouse.gov/ondcp/annual-accounting-report. Washington, D.C.: Office of National Drug Control Policy; 2012. Accessed on January 16th, 2013.

7. West S, O'Neal K. Project D.A.R.E. outcome effectiveness revisited. American Journal of Public Health. 2004; **94**(6): 1027.

8. Werb D, Mills EJ, DeBeck K, Kerr T, Montaner JSG, Wood E. The effectiveness of anti-illicit-drug public-service announcements: A systematic review and meta-analysis. J Epidemiol & Commun Health. 2011; **65**: 7.

9. UNODC. World Drug Report 2012. Vienna: United Nations Office on Drugs and Crime; 2012.

10. Mathers BM, Degenhardt L, Phillips B, Wiessing L, Hickman M, Strathdee SA, et al. Global epidemiology of injecting drug use and HIV among people who inject drugs: A systematic review. Lancet. 2008; **372**(9651): 1733-45.

11. UNAIDS. UNAIDS report on the global AIDS epidemic 2010. Geneva: Joint United Nations Programme on HIV/AIDS; 2010.

12. Backmund M, Reimer J, Meyer K, Gerlach JT, Zachoval R. Hepatitis C virus infection and injection drug users: prevention, risk factors, and treatment. Clin Infect Dis. 2005; **40**(Suppl 5): 330.

13. Darke S, Hall W. Heroin overdose: research and evidence-based intervention. J Urban Health. 2003; **80**(2): 189.

14. Galai N, Safaeian M, Vlahov D, Bolotin A, Celentano DD. Longitudinal patterns of drug injection behavior in the ALIVE Study cohort,1988-2000: description and determinants. Am J Epidemiol. 2003; **158**(7): 695.

15. Murphy DA, Brecht ML, Herbeck D, Evans E, Huang D, Hser YI. Longitudinal HIV risk behavior among the Drug Abuse Treatment Outcome Studies (DATOS) adult sample. Evaluation Review. 2008; **32**(1): 83-112.

16. Binswanger IA, Kral AH, Bluthenthal RN, Rybold DJ, Edlin BR. High prevalence of abscesses and cellulitis among community-recruited injection drug users in San Francisco. Clin Infect Dis. 2000; **30**(3): 579.

17. Lloyd-Smith E, Kerr T, Hogg RS, Li K, Montaner JS, Wood E. Prevalence and correlates of abscesses among a cohort of injection drug users. Harm Reduct J. 2005; **2**(1): 24.

18. Cooper HLF, Wypij D, Krieger N. Police drug crackdowns and hospitalisation rates for illicit-injection-related infections in New York City. Int J Drug Pol. 2005; **16**(3): 150.

19. UNAIDS. UNAIDS World AIDS Day Report 2011. Geneva: Joint United Nations Programme on HIV/AIDS; 2011.

20. Aceijas C, Rhodes T. Global estimates of prevalence of HCV infection among injecting drug users. Int J Drug Pol. 2007; **18**(5): 352-8.

21. Donoghoe M, Verster AD, Mathers B. WHO, UNODC, UNAIDS technical guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users. Geneva: WHO/UNODC/UNAIDS; 2009.

22. Vlahov D, Fuller CM, Ompad DC, Galea S, Des Jarlais DC. Updating the Infection Risk Reduction Hierarchy: Preventing transition into injection. J Urban Health. 2004; **81**(1): 14.

23. Langendam MW, Brussel GHV, Coutinho RA, Ameijden EJV. Methadone maintenance and cessation of injecting drug use: results from the Amsterdam Cohort Study. Addiction. 2000; **95**(4): 591-600.

24. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev. 2009; (2): CD002209.

25. Amato L, Davoli M, Ferri M, Ali R. Methadone at tapered doses for the management of opioid withdrawal. Cochrane Database Syst Rev. 2002; (1): CD003409.

26. Bellin. High dose methadone reduces criminal recidivism in opiate addicts. Addiction research. New York: Harwood Academic Publishers; 1999.

27. Uhlmann S, Milloy MJ, Kerr T, Zhang R, Guillemi S, Marsh D, et al. Methadone maintenance therapy promotes initiation of antiretroviral therapy among injection drug users. Addiction. 2010; **105**(5): 907-13.

28. Roux P, Carrieri MP, Villes V, Dellamonica P, Poizot, Martin I, Ravaux I, et al. The impact of methadone or buprenorphine treatment and ongoing injection on highly active antiretroviral therapy (HAART) adherence: evidence from the MANIF2000 cohort study. Addiction. 2008; **103**(11): 1828-36.

29. Lucas GM, Mullen BA, Weidle PJ, Hader S, McCaul ME, Moore RD. Directly administered antiretroviral therapy in methadone clinics is associated with improved HIV treatment outcomes, compared with outcomes among concurrent comparison groups. Clin Infect Dis. 2006; **42**(11): 1628-35.

30. Mathers BM, Degenhardt L, Ali H, Wiessing L, Hickman M, Mattick RP, et al. HIV prevention, treatment, and care services for people who inject drugs: a systematic review of global, regional, and national coverage. Lancet. 2010; **375**(9719): 15.

31. Roy E, Haley N, Leclerc P, Cedras L, Blais L, Boivin JF. Drug injection among street youths in Montreal: predictors of initiation. J Urban Health. 2003; **80**(1): 92.

32. Wood E, Stolz J-A, Montaner JiSG, Kerr T. Evaluating methamphetamine use and risks of injection initiation among street youth: the ARYS study. Harm Reduct J. 2006; **3**(18): 1.

33. Bruneau J, Brogly SB, Tyndall MW, Lamothe F, Franco EL. Intensity of drug injection as a determinant of sustained injection cessation among chronic drug users: the interface with social factors and service utilization. Addiction. 2004; **99**(6): 727.

34. Chami G, Werb D, Feng C, DeBeck K, Kerr T, Wood E. Neighborhood of residence and risk of initiation into injection drug use among street-involved youth in a Canadian setting. Drug Alc Depend. 2013; **In Press**.

35. Sherman SG, Fuller CM, Shah N, Ompad DV, Vlahov D, Strathdee SA. Correlates of initiation of injection drug use among young drug users in Baltimore, Maryland: the need for early intervention. Journal of Psychoactive Drugs. 2005; **37**(4): 437-43.

36. Fuller CM, Borrell LN, Latkin CA, Galea S, Ompad DC, Strathdee SA, et al. Effects of race, neighborhood, and social network on age at initiation of injection drug use. Am J Pub Health. 2005; **95**: 689-95.

37. Fuller CM, Vlahov D, Latkin CA, Ompad DC, Celentano DD, Strathdee SA. Social circumstances of initiation of injection drug use and early shooting gallery attendance: Implications for HIV intervention among adolescent and young adult injection drug users. J Acquir Immune Defic Syndr. 2003; **32**(1): 86.

38. Harocopos A, Goldsamt LA, Kobrak P, Jost JJ, Clatts MC. New injectors and the social context of injection initiation. Int J Drug Pol. 2009; **20**(4): 317-23.

39. Kermode M, Longleng V, Singh BC, Hocking J, Langkham B, Crofts N. My first time: initiation into injecting drug use in Manipur and Nagaland, north-east India. Harm Reduct J. 2007; **4**(1): 19.

40. Stenbacka M. Initiation into intravenous drug abuse. Acta Psychiatrica Scandinavica. 1990; **81**(5): 459-62.

41. Trenz RC, Harrell P, Scherer M, Mancha BE, Latimer WW. A model of school problems, academic failure, alcohol initiation, and the relationship to adult heroin injection. Subst Use Misuse. 2012; **47**(10): 1159-71.

42. Neaigus A, Gyarmathy VA, Miller M, Frajzyngier VM, Friedman SR, Des Jarlais DC. Transitions to injecting drug use among noninjecting heroin users: Social network influence and individual susceptibility. J Acquir Immune Defic Syndr. 2006; **41**(4): 493.

43. van Ameijden EJ, van den Hoek JA, Hartgers C, Coutinho RA. Risk factors for the transition from noninjection to injection drug use and accompanying AIDS risk behavior in a cohort of drug users. Am J Epidemiol. 1994; **139**(12): 1153.

44. Lynskey M, Hall W. Cohort trends in age of initiation into heroin use. Drug Alc Rev. 1998; **17**(3): 289.

45. Eaves CS. Heroin use among female adolescents: the role of partner influence in path of initiation and route of administration. The Am J Drug Alc Abuse. 2004; **30**(1): 21-38.

46. Crofts N, Louie R, Rosenthal D, Jolley D. The first hit: circumstances surrounding initiation into injecting. Addiction. 1996; **91**(8): 1187-96.

47. Young AM, Havens JR. Transition from first illicit drug use to first injection drug use among rural Appalachian drug users: a cross-sectional comparison and retrospective survival analysis. Addiction. 2012; **107**(3): 587-96.

48. NIDA. Strategic plan: National Institute on Drug Abuse. Bethesda, MD: National Institute on Drug Abuse; 2010.

49. Volkow ND. NIDA's funding priorities in tough fiscal times. Available from: http://www.drugabuse.gov/about-nida/directors-page/messages-director/2012/02/nida%E2%80%99s-funding-priorities-in-tough-fiscal-times. Bethesda, MD: National Institute on Drug Abuse; 2012. Accessed on February 2nd, 2013.

50. Shah NG, Galai N, Celentano DD, Vlahov D, Strathdee SA. Longitudinal predictors of injection cessation and subsequent relapse among a cohort of injection drug users in Baltimore, MD, 1988–2000. Drug Alc Depend. 2006; **83**(2): 147-56.

51. Evans JL, Hahn JA, Lum PJ, Stein ES, Page K. Predictors of injection drug use cessation and relapse in a prospective cohort of young injection drug users in San Francisco, CA (UFO Study). Drug Alc Depend. 2009; **101**(3): 152-7.

52. Global state of harm reduction 2012: Towards an integrated response. London; Harm Reduction International; 2012.

53. Des Jarlais DC. Research, politics, and needle exchange. Am J Pub Health. 2000; **90**(9): 1392.

54. Kaplan EH, Heimer R. HIV incidence among New Haven needle exchange participants: updated estimates from syringe tracking and testing data. J Acquir Immune Defic Syndr Hum Retrovirol. 1995; **10**(2): 175.

55. Vlahov D, Junge B, Brookmeyer R, Cohn S, Riley E, Armenian H, et al. Reductions in high-risk drug use behaviors among participants in the Baltimore needle exchange program. J Acquir Immune Defic Syndr. 1997; **16**(5): 400.

56. Voth EA. Harm reduction drug policy. Lancet Infect Dis. 2008; **8**(9): 528; author reply.

57. Bluthenthal RN, Kral AH, Lorvick J, Erringer EA, Edlin BR. Harm reduction and needle exchange programmes [letter; comment]. Lancet. 1998; **351**(9112): 1333.

58. Urban Health Research Initiative. Drug situation in Vancouver. Vancouver: Urban Health Research Initiative, BC Centre for Excellence in HIV/AIDS; 2013.

59. Tyndall MW, Spittal PM, Laliberte N, Li K, O'Shaughnessy MV, Schechter MT. Intensive injection cocaine use as a primary risk factor of HIV seroconversion among polydrug users in Vancouver. AIDS. 2002; **17**(6): 887.

60. Strathdee SA, Patrick DM, Currie SL, Cornelisse PG, Rekart ML, Montaner JS, et al. Needle exchange is not enough: Lessons from the Vancouver injecting drug use study. AIDS. 1997; **11**(8): F59.

61. Voth EA. Canada's drug problem: Time to get serious [letter; comment]. CMAJ. 1999; **160**(4): 477, 9.

62. Kerr T, Small W, Buchner C, Zhang R, Li K, Montaner J, et al. Syringe sharing and HIV incidence among injection drug users and increased access to sterile syringes. Am J Pub Health. 2010; **100**(8): 1449.

63. Wood E, Tyndall MW, Montaner JS, Kerr T. Summary of findings from the evaluation of a pilot medically supervised safer injecting facility. CMAJ. 2006; **175**(11): 1399.

64. Tyndall MW, Laliberte N, Spittal P, Li K, O'Shaughnessy MV, Schechter MT. Patterns of drug use following the initiation of methadone maintenance treatment. Can J Infect Dis. 2001; **12**(Suppl B): 56B.

65. Gartry CC, Oviedo-Joekes E, Laliberté N, Schechter MT. NAOMI: The trials and tribulations of implementing a heroin assisted treatment study in North America. Harm Reduct J. 2009; **6**(1): 2.

66. Montaner J. HIV treatment to prevent morbidity, mortality, and transmission. American Association for the Advancement of Science Annual Meeting. Vancouver: American Association for the Advancement of Science; 2012.

67. Marshall BDL, Werb D. Health outcomes associated with methamphetamine use among young people: A systematic review. Addiction. 2010; **105**(6): 12.

68. Fairbairn N, Kerr T, Buxton JA, Li K, Montaner JS, Wood E. Increasing use and associated harms of crystal methamphetamine injection in a Canadian setting. Drug Alc Depend. 2007; **88**(2/3): 4.

69. Wood E, Stoltz JA, Zhang R, Strathdee SA. Circumstances of first crystal methamphetamine use and initiation of injection drug use among high-risk youth. Drug Alc Rev. 2008; **27**(3): 270-6.

70. Bungay V, Malchy L, Buxton JA, Johnson J, MacPherson D, Rosenfeld T. Life with jib: A snapshot of street youth's use of crystal methamphetamine. Addiction Research & Theory. 2006; **14**(3): 235-51.

71. Werb D, Kerr T, Fast D, Qi J, Montaner JSG, Wood E. Drug-related risks among street youth in two neighborhoods in a Canadian setting. Health & Place. 2010.

72. Fast D, Small W, Wood E, Kerr T. Coming 'down here': Young people's reflections on becoming entrenched in a local drug scene. Soc Sci Med. 2009; **69**(8): 7.

73. Rhodes T. The 'risk environment': a framework for understanding and reducing drug-related harm. Int J Drug Pol. 2002; **13**(2): 85.

74. Rhodes T, Mikhailova L, Sarang A, Lowndes CM, Rylkov A, Khutorskoy M, et al. Situational factors influencing drug injecting, risk reduction and syringe exchange in Togliatti City, Russian Federation: a qualitative study of micro risk environment. Soc Sci Med. 2003; **57**(1): 39.

75. Rhodes T, Simic M. Transition and the HIV risk environment. BMJ. 2005; **331**(7510): 220-3.

76. Small W, Rhodes T, Wood E, Kerr T. Public injection settings in Vancouver: physical environment, social context and risk. Int J Drug Pol. 2007; **18**(1): 27-36.

77. Hankins CA, Friedman SR, Zafar T, Strathdee SA. Transmission and prevention of HIV and sexually transmitted infections in war settings: Implications for current and future armed conflicts. AIDS. 2002; **16**(17): 2245-52.

78. Friedman SR, Rossi D, Braine N. Theorizing "Big Events" as a potential risk environment for drug use, drug-related harm and HIV epidemic outbreaks. Int J Drug Pol. 2009; **20**(3): 283-91.

79. Rothenberg R, Baldwin J, Trotter R, Muth MS. The risk environment for HIV transmission: Results from the Atlanta and Flagstaff network studies. J Urban Health. 2001; **78**(3): 419-32.

80. Green TC, Grau LE, Blinnikova KN, Torban M, Krupitsky E, Ilyuk R, et al. Social and structural aspects of the overdose risk environment in St. Petersburg, Russia. Int J Drug Pol. 2009; **20**(3): 270-6.

81. Cooper HLF, Bossak B, Tempalski B, Des Jarlais DC, Friedman SR. Geographic approaches to quantifying the risk environment: drug-related law enforcement and access to syringe exchange programmes. Int J Drug Pol. 2009; **20**(3): 217-26.

82. Burris S, Blankenship KM, Donoghoe M. Addressing the "risk environment" for injection drug users: The mysterious case of the missing cop. Milbank Q. 2004; **82**(1): 125.

83. Rhodes T, Lilly R, Fernandez C, Giorgino E, Kemmesis UE, Ossebaard HC, et al. Risk factors associated with drug use: the importance of 'risk environment'. Drugs: Education, Prevention, and Policy. 2003; **10**(4): 303-29.

84. Friedman SR, Aral S. Social networks, risk-potential networks, health, and disease. J Urban Health. 2001; **78**(3): 411-8.

85. Rothenberg R, Muth SQ, Malone S, Potterat JJ, Woodhouse DE. Social and geographic distance in HIV risk. Sexually Transmitted Diseases. 2005; **32**(8): 506-12.

86. Zuckerman M. Behavioral expressions and biosocial bases of sensation seeking. New York: Cambridge University Press; 1994.

87. Hoyle RH, Stephenson MT, Palmgreen P, Lorch EP, Donohew RL. Reliability and validity of a brief measure of sensation seeking. Personality and Individual Differences. 2002; **32**(3): 401-14.

88. Zuckerman M, Donohew L, Sypher HE, Higgins ET. Behavior and biology: Research on sensation seeking and reactions to the media. Communication, Social Cognition, and Affect. 1988: 173-94.

89. Orwin R, Cadell D, Chu A, Kalton G, Maklan D, Morin C, et al. Evaluation of the national youth anti-drug media campaign: 2004 report of findings. Washington, D.C.: National Institute on Drug Abuse; 2004. Report No.: N01DA-8-5063.

90. Harden KP, Tucker-Drob EM. Individual differences in the development of sensation seeking and impulsivity during adolescence: Further evidence for a dual systems model. Developmental Psychol. 2011; **47**(3): 739.

91. Fenaughty AM, Fisher DG. High-risk sexual behavior among drug users: The utility of a typology of alcohol variables. Sexually Transmitted Diseases. 1998; **25**(1): 38-43.

92. Semple SJ, Patterson TL, Grant I. A comparison of injection and non-injection methamphetamine-using HIV positive men who have sex with men. Drug Alc Depend. 2004; **76**(2): 203-12.

93. Brook DW, Brook JS, Whiteman M, Win PT, Gordon-Maloul C, Roberto J, et al. Psychosocial risk factors for HIV transmission in female drug abusers. Am J Addict. 1997; **6**(2): 124.

94. Brook JS, Brook DW, Whiteman M, Roberto J, Masci JR, De Catalogne J, et al. Psychosocial risk factors for HIV transmission in male drug abusers. Genet Soc Gen Psychol Monogr. 1993; **119**(3): 369.

95. Mannheim K. The sociological problem of generations. Essays on the Sociology of Knowledge. 1952: 276-322.

96. Elder GH, Giele JZ. Methods of life course research: Qualitative and quantitative approaches. New York: Sage Publications, Inc.; 1998.

97. Lynch J, Smith GD. A life course approach to chronic disease epidemiology. Annu Rev Public Health. 2005; **26**: 1-35.

98. Zuckerman M. Sensation seeking: The initial motive for drug abuse. Etiological Aspects of Alcohol and Drug Abuse. 1983: 202–20.

99. Vlahov D, Des Jarlais DC, Goosby E, Hollinger PC, Lurie PG, Shriver MD, et al. Needle exchange programs for the prevention of human immunodeficiency virus infection: Epidemiology and policy. Am J Epidemiol. 2001; **154**(12): 70.

100. Strathdee SA, Vlahov D. The effectiveness of needle exchange programs: A review of the science and policy. AIDScience. 2001; **1**(16): 1-31.

101. Warner-Smith M, Lynskey M, Darke S, Hall W. Heroin overdose: Prevalence, correlates, consequences and interventions. Sydney: National Drug and Alcohol Centre; 2000. p. 84.

102. DeBeck K, Kerr T, Li K, Milloy MJ, Montaner JSG, Wood E. Incarceration and drug use patterns among a cohort of injection drug users. Addiction. 2009; **104**: 69.

103. Kerr T, Small W, Johnston C, Li K, Montaner JS, Wood E. Characteristics of injection drug users who participate in drug dealing: Implications for drug policy. J Psychoactive Drugs. 2008; **40**(2): 147-52.

104. Anglin MD, Speckart G. Narcotics use, property crime, and dealing: Structural dynamics across the addiction career. Journal of Quantitative Criminology. 1986; **2**(4): 355-75.

105. Fennema JSA, Ameijden E, Hoek AVD, Coutinho RA. Young and recent-onset injecting drug users are at higher risk for HIV. Addiction. 1997; **92**(11): 1457-66.

106. Ochoa KC, Davidson PJ, Evans JL, Hahn JA, Page-Shafer K, Moss AR. Heroin overdose among young injection drug users in San Francisco. Drug Alc Depend. 2005; **80**(3): 297-302.

107. Fast D, Small W, Krusi A, Wood E, Kerr T. 'I guess my own fancy screwed me over': transitions in drug use and the context of choice among young people entrenched in an open drug scene. BMC Public Health. 2010; **10**(1): 10.

108. Trenz RC, Scherer M, Harrell P, Zur J, Sinha A, Latimer W. Early onset of drug and polysubstance use as predictors of injection drug use among adult drug users. Addictive Behaviors. 2012; **37**(4): 367-72.

109. Miller CL, Strathdee SA, Kerr T, Li K, Wood E. Factors associated with early adolescent initiation into injection drug use: implications for intervention programs. J Adolescent Health. 2006; **38**(4): 462-4.

110. Des Jarlais DC, Arasteh K, McKnight C, Ringer M, Friedman SR. Syringe exchange, injecting and intranasal drug use. Addiction. 2010; **105**(1): 155-8.

111. Doherty MC, Edgar Monterroso MD MPH. Gender differences in the initiation of injection drug use among young adults. J Urban Health. 2000; **77**(3): 396-414.

112. Khalsa M, Anglin M, Paredes A, Potepan P, Potter C. Pretreatment natural history of cocaine addiction: preliminary 1-year follow-up results. NIDA Research Monograph. 1993; **135**: 218.

113. John D, Kwiatkowski CF, Booth RE. Differences among out-of-treatment drug injectors who use stimulants only, opiates only or both: implications for treatment entry. Drug Alc Depend. 2001; **64**(2): 165-72.

114. Latkin CA, Knowlton AR, Hoover D, Mandell W. Drug network characteristics as a predictor of cessation of drug use among adult injection drug users: a prospective study. Am J Drug Alc Abuse. 1999; **25**(3): 463-73.

115. Joe GW, Lehman W, Simpson DD. Addict death rates during a four-year posttreatment follow-up. Am J Pub Health. 1982; **72**(7): 703-9.

116. Joe GW, Simpson DD. Mortality rates among opioid addicts in a longitudinal study. Am J Pub Health. 1987; **77**(3): 347-8.

117. Watterson O, Simpson DD, Sells SB. Death rates and causes of death among opioid addicts in community drug treatment programs during 1970-1973. Am J Drug Alc Abuse. 1975; **2**(1): 99-111.

118. Helpern M. Fatalities from narcotic addiction in New York City: Incidence, circumstances, and pathologic findings. Human Pathology. 1972; **3**(1): 13-21.

119. Degenhardt L, Singleton J, Calabria B, McLaren J, Kerr T, Mehta S, et al. Mortality among cocaine users: a systematic review of cohort studies. Drug Alc Depend. 2011; **113**(2): 88-95.

120. Degenhardt L, Bucello C, Mathers B, Briegleb C, Ali H, Hickman M, et al. Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. Addiction. 2011; **106**(1): 32-51.

121. Singleton J, Degenhardt L, Hall W, Zabransky T. Mortality among amphetamine users: a systematic review of cohort studies. Drug Alc Depend. 2009; **105**(1): 1-8.

122. Charlson F, Degenhardt L, McLaren J, Hall W, Lynskey M. A systematic review of research examining benzodiazepine-related mortality. Pharmacoepidemiology and Drug Safety. 2009; **18**(2): 93-103.

123. Vlahov D, Wang C, Galai N, Bareta J, Mehta SH, Strathdee SA, et al. Mortality risk among new onset injection drug users. Addiction. 2004; **99**(8): 946-54.

124. Davoli M, Perucci CA, Rapiti E, Bargagli AM, D'Ippoliti D, Forastiere F, et al. A persistent rise in mortality among injection drug users in Rome, 1980 through 1992. Am J Pub Health. 1997; **87**(5): 851-3.

125. Wood E, Tyndall MW, Zhang R, Montaner JSG, Kerr T. Rate of detoxification service use and its impact among a cohort of supervised injecting facility users. Addiction. 2007; **102**(6): 916.

126. Christakis NA, Fowler JH. The collective dynamics of smoking in a large social network. NEJM. 2008; **358**(21): 2249-58.

127. Christakis NA, Fowler JH. The spread of obesity in a large social network over 32 years. NEJM. 2007; **357**(4): 370-9.

128. Cohen-Cole E, Fletcher JM. Is obesity contagious? Social networks vs. environmental factors in the obesity epidemic. J Health Econ. 2008; **27**(5): 1382-7.

129. Hall JA, Valente TW. Adolescent smoking networks: The effects of influence and selection on future smoking. Addictive Behaviors. 2007; **32**(12): 3054-9.

130. Oka S. Treatment 2.0 Fact Sheet. Geneva: Joint United Nations Programme on HIV/AIDS; 2010.

131. Dettmer K. Take home naloxone and the prevention of deaths from opiate overdose: two pilot schemes. BMJ. 2001; **322**(7291): 895.

132. Kim D, Irwin KS, Khoshnood K. Expanded access to naloxone: Options for critical response to the epidemic of opioid overdose mortality. Am J PubHealth. 2009; **99**(3): 402.

133. Altice FL, Bruce RD, Lucas GM, Lum PJ, Korthuis PT, Flanigan TP, et al. HIV treatment outcomes among HIV-infected, opioid-dependent patients receiving

buprenorphine/naloxone treatment within HIV clinical care settings: results from a multisite study. J Acquir Immune Defic Syndr. 2011; **56**: S22.

134. Marshall BDL, Milloy MJ, Wood E, Montaner JSG, Kerr T. Reduction in overdose mortality after the opening of North America's first medically supervised safer injecting facility: a retrospective population-based study. Lancet. 2011; **377**(9775): 1429-37.

135. Neaigus A, Friedman SR, Jose B, Goldstein MF, Curtis R, Ildefonso G, et al. High-risk personal networks and syringe sharing as risk factors for HIV infection among new drug injectors. J Acquir Immune Defic Syndr Hum Retrovirol. 1996; **11**(5): 499.

136. Roy E, Alary M, Morissette C, Leclerc P, Boudreau JF, Parent R, et al. High hepatitis C virus prevalence and incidence among Canadian intravenous drug users. Int J STD & AIDS. 2007; **18**(1): 23.

137. Cheung AM, Hwang SW. Risk of death among homeless women: a cohort study and review of the literature. CMAJ. 2004; **170**(8): 1243-7.

138. Boivin JF, Roy E, Haley N, Galbaud du Fort G. The health of street youth. Can J Pub Health. 2005; **96**(6): 432-7.

139. UNODC. HIV prevention among young injecting drug users. Vienna: UN; 2004.

140. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. BMJ. 2009; **339**: b2535.

141. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Commun Health. 1998; **52**(6): 377-84.

142. McCambridge J. A case study of publication bias in an influential series of reviews of drug education. Drug Alc Rev. 2007; **26**(5): 463.

143. Roy E, Denis V, Gutierrez N, Haley N, Morissette C, Boudreau JFÃ. Evaluation of a media campaign aimed at preventing initiation into drug injection among street youth. Drugs: Education, Prevention, and Policy. 2007; **14**(5): 401-14.

144. Des Jarlais CD, Casriel C, Friedman SR, Rosenblum A. AIDS and the transition to illicit drug injection: Results of a randomized trial prevention program. Brit J Addiction. 1992; **87**: 6.

145. Hunt N, Stillwell G, Taylor C, Griffiths P. Evaluation of a brief intervention to prevent initiation into injecting. Drugs: Education, Prevention, and Policy. 1998; **5**(2): 185-94.

146. Gray R. Preventing IDU initiation among drug-curious youth: An attempt to measurably reduce IDU initiation among youth in Central Asia. 19th International Harm Reduction Association Conference. Barcelona, Spain; 2008.

147. Kelley MS, Chitwood DD. Effects of drug treatment for heroin sniffers: a protective factor against moving to injection? Soc Sci Med. 2004; **58**(10): 2083.

148. Friedman SR, Cooper HL, Tempalski B, Keem B, Friedman R, Flom PL, et al. Relationships of deterrence and law enforcement to drug-related harms among drug injectors in US metropolitan areas. AIDS. 2006; **20**(1): 93.

149. Friedman SR, Pouget ER, Chatterjee S, Cleland CM, Tempalski B, Brady JE, et al. Drug arrests and injection drug deterrence. Am J Pub Health. 2011; **101**(2): 344.

150. Day C, Degenhardt L, Hall W. Changes in the initiation of heroin use after a reduction in heroin supply. Drug Alc Rev. 2006; **25**(4): 307-13.

151. Degenhardt L, Day C, Hall W. The causes, course and consequences of the heroin shortage in Australia. Sydney: National Drug and Alcohol Centre; 2004.

152. Wood E, Stoltz J-A, Li K, Montaner JSG, Kerr T. Changes in Canadian heroin supply coinciding with the Australian heroin shortage. Addiction. 2006; **101**(5): 689-95.

153. Weatherburn D, Jones C, Freeman K, Makkai T. Supply control and harm reduction: lessons from the Australian heroin drought. Addiction. 2003; **98**: 83.

154. Neaigus A, Friedman SR, Curtis R, Des Jarlais DC, Furst RT, Jose B, et al. The relevance of drug injectors' social and risk networks for understanding and preventing HIV infection. Soc Sci Med. 1994; **38**(1): 67.

155. Koram N, Liu H, Li J, Luo J, Nield J. Role of social network dimensions in the transition to injection drug use: Actions speak louder than words. AIDS and Behavior. 2011: 1-10.

156. Kermode M, Longleng V, Singh BC, Bowen K, Rintoul A. Killing time with enjoyment: A qualitative study of initiation into injecting drug use in north-east India. Subst Use Misuse. 2009; **44**(8): 1070-89.

157. Bourgois P, Prince B, Moss A. The everyday violence of hepatitis C among young women who inject drugs in San Francisco. Human Organization. 2004; **63**(3).

158. Saunders JB. Publication bias in addiction research. Drug Alc Rev. 2007; **26**: 3.

159. Pearson H. A hard habit to break. Nature. 2004; **430**: 2.

160. Fuller CM, Vlahov D, Arria AM, Ompad DC, Garfein R, Strathdee SA. Factors associated with adolescent initiation of injection drug use. Public Health Rep. 2001; **116 Suppl 1**: 136.

161. UNODC. World Drug Report 2011. Vienna: United Nations Office on Drugs and Crime; 2011.

162. Squeglia LM, Jacobus J, Tapert SF. The influence of substance use on adolescent brain development. Clinical EEG and Neuroscience. 2009; **40**(1): 31-8.

163. Stanwood GD, Levitt P. Drug exposure early in life: functional repercussions of changing neuropharmacology during sensitive periods of brain development. Current Opinion in Pharmacology. 2004; **4**(1): 65-71.

164. Kelly TH, Robbins G, Martin CA, Fillmore MT, Lane SD, Harrington NG, et al. Individual differences in drug abuse vulnerability: d-amphetamine and sensation-seeking status. Psychopharmacology. 2006; **189**(1): 17-25.

165. Berman SM, Kuczenski R, McCracken JT, London ED. Potential adverse effects of amphetamine treatment on brain and behavior: a review. Molecular Psychiatry. 2008; **14**(2): 123-42.

166. Craib KJ, Spittal PM, Wood E, Laliberte N, Hogg RS, Li K, et al. Risk factors for elevated HIV incidence among Aboriginal injection drug users in Vancouver. CMAJ. 2003; **168**(1): 19.

167. Wood E, Montaner JSG, Li K, Zhang R, Barney L, Strathdee SA, et al. Burden of HIV infection among Aboriginal injection drug users in Vancouver, British Columbia. Am J Pub Health. 2008; **98**(3): 515.

168. Mehrabadi A, Craib KJP, Patterson K, Adam W, Moniruzzaman A, Ward-Burkitt B, et al. The Cedar Project: A comparison of HIV-related vulnerabilities amongst young Aboriginal women surviving drug use and sex work in two Canadian cities. Int J Drug Policy. 2008; **19**(2): 159-68.

169. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. Am J Epidemiol. 1993; **138**(11): 14.

170. Fast D, Shoveller J, Shannon K, Kerr T. Safety and danger in downtown Vancouver: Understandings of place among young people entrenched in an urban drug scene. Health & Place. 2010; **16**(1): 10.

171. PHAC. Epi-update: Crystal methamphetamine use among Canadian street-involved youth (1999-2005). Ottawa: Public Health Agency of Canada; 2009.

172. Cretzmeyer M, Sarrazin MV, Huber DL, Block RI, Hall JA. Treatment of methamphetamine abuse: research findings and clinical directions. J Subst Abuse Treat. 2003; **24**(3): 267-77.

173. Zorick T, Sevak RJ, Miotto K, Shoptaw S, Swanson AN, Clement C, et al. Pilot safety evaluation of varenicline for the treatment of methamphetamine dependence. J Experimental Pharmacology. 2009; **2010**(2): 13.

174. Colfax G, Santos G-M, Chu P, Vittinghoff E, Pluddemann A, Kumar S, et al. Amphetamine-group substances and HIV. Lancet. 2010; **376**(9739): 458-74.

175. Colfax G. The methamphetamine epidemic: implications for HIV prevention and treatment. Current HIV/AIDS Reports. 2005; **2**(4): 194-9.

176. Bayoumi A, Strike C, Brandeau ML, Degani N, Fischer B, Glazier R, et al. Report of the Toronto and Ottawa Supervised Consumption Assessment Study. Toronto: St. Michael's Hospital and the Dalla Lana School of Public Health, University of Toronto; 2012.

177. Roy E, Haley N, Leclerc P, Cedras L, Boivin JF. Drug injection among street youth: The first time. Addiction. 2002; **97**: 1003-9.

178. Ouellet LJ, Bailey SL. Drug injection initiation and hepatitis C virus (HCV) infection: An assessment of opportunities for intervention. The 2005 National Viral Hepatitis Prevention Conference. Washington, D.C.; 2005.

179. The McCreary Centre Society. Against the odds: A profile of marginalized and street-involved youth in BC. Report. Vancouver: The McCreary Centre Society; 2007.

180. Macalino GE, Celentano DD, Latkin C, Strathdee SA, Vlahov D. Risk behaviors by audio computer-assisted self-interviews among HIV-seropositive and HIV-seronegative injection drug users. AIDS Educ Prev. 2002; **14**(5): 367.

181. Gudjonsson GH, Sigurdsson JF, Sigfusdottir ID, Young S. An epidemiological study of ADHD symptoms among young persons and the relationship with cigarette smoking, alcohol consumption and illicit drug use. J Child Psychology and Psychiatry. 2012; **53**(3): 304-12.

182. Szobot CM, Rohde LA, Bukstein O, Molina BS, Martins C, Ruaro P, et al. Is attention-deficit/hyperactivity disorder associated with illicit substance use disorders in male adolescents? A community-based case-control study. Addiction. 2007; **102**(7): 1122-30.

183. Volkow ND, Li T-K. Drug addiction: The neurobiology of behaviour gone awry. Nature Reviews Neuroscience. 2004; **5**(12): 963-70.

184. Quinn PD, Harden KP. Differential changes in impulsivity and sensation seeking and the escalation of substance use from adolescence to early adulthood. Development and Psychopathology. 2012; **1**(1): 1-17.

185. Zuckerman M. Item revisions in the Sensation Seeking Scale form V (SSS-V). Personality and Individual Differences. 1996; **20**(4): 515.

186. Zuckerman M. Sexual sensation seeking and sexual compulsivity scales: Reliability, validity, and predicting HIV risk behavior. J Personality Assessment. 1995; **65**(3): 586-601.

187. Patkar AA, Murray HW, Mannelli P, Gottheil E, Weinstein SP, Vergare MJ. Pre-treatment measures of impulsivity, aggression and sensation seeking are associated with treatment outcome for African-American cocaine-dependent patients. Journal of Addictive Diseases. 2004; **23**(2): 109-22.

188. Thombs DL, Beck KH, Mahoney CA, Bromley MD, Bezon KM. Social context, sensation seeking, and teenage alcohol abuse. J School Health. 1994; **64**(2): 73-9.

189. Palmgreen P, Donohew L, Lorch EP, Hoyle RH, Stephenson MT, Hornik RC. Television campaigns and sensation seeking targeting of adolescent marijuana use: A controlled time-series approach. In: Public Health Communication: Evidence for Change; 2002. p. 35.

190. Stephenson M, Palmgreen P. Sensation seeking, perceived message sensation value, personal involvement, and processing of anti-marijuana PSAs. Communication Monographs. 2001; **68**(1): 49-71.

191. Conrod PJ, Stewart SH, Comeau N, Maclean AM. Efficacy of cognitive-behavioral interventions targeting personality risk factors for youth alcohol misuse. J Clinical Child and Adolescent Psychology. 2006; **35**(4): 550-63.

192. Hadland SE, Werb D, Kerr T, Fu E, Wang H, Montaner JS, et al. Childhood sexual abuse and risk for initiating injection drug use during adolescence and young adulthood: A prospective cohort study. J Adolescent Health. 2012; **50**(2): S1-S.

193. Zuckerman M. Experience and desire: A new format for Sensation Seeking Scales. J Behavioral Assessment. 1983; **6**(2): 14.

194. Kalichman SC, Johnson JR, Adair V, Rompa D, Multhauf K, Kelly JA. Sexual sensation seeking: Scale development and predicting AIDS-risk behavior among homosexually active men. J Personality Assessment. 1994; **62**(3): 385-97.

195. Kalichman SC, Rompa D. Sexual Sensation Seeking and Sexual Compulsivity Scales: validity, and predicting HIV risk behavior. J Personality Assessment. 1995; **65**(3): 586-601.

196. Werb D, Kerr T, Lai C, Montane J, Wood E. Nonfatal overdose among a cohort of street-involved youth. Journal of Adolescent Health. 2008; **42**(3): 303-6.

197. Roy É, Boudreau JF, Leclerc P, Boivin JF, Godin G. Trends in injection drug use behaviors over 10 years among street youth. Drug Alc Depend. 2007; **89**(2-3): 170-5.

198. Schafer J, Blanchard L, Fals-Stewart W. Drug use and risky sexual behavior. Psychology of Addictive Behaviors. 1994; **8**(1): 3.

199. Zuckerman M, Kolin EA, Price L, Zoob I. Development of a sensation-seeking scale. J Consulting Psychology. 1964; **28**(6): 477.

200. Preacher KJ, MacCallum RC. Repairing Tom Swift's electric factor analysis machine. Understanding Statistics: Statistical Issues in Psychology, Education, and the Social Sciences. 2003; **2**(1): 13-43.

201. Treiblmaier H, Filzmoser P. Exploratory factor analysis revisited: How robust methods support the detection of hidden multivariate data structures in IS research. Information & Management. 2010; **47**(4): 197-207.

202. Muthén LK, Muthén BO. Mplus User's Guide. Sixth ed. Los Angeles, CA: Muthén & Muthén; 2010.

203. O'Connor BP. SPSS and SAS programs for determining the number of components using parallel analysis and Velicer's MAP test. Behavior Research Methods. 2000; **32**(3): 396-402.

204. Rubinstein RY, Kroese DP. Simulation and the Monte Carlo method. New York: Wiley-Interscience; 2008.

205. Gerbing DW, Anderson JC. An updated paradigm for scale development incorporating unidimensionality and its assessment. J Marketing Research. 1988; **25**: 7.

206. Bollen KA. Structural equations with latent variables. New York: Wiley; 1989.

207. Marsh HW, Hau KT, Wen Z. In search of golden rules: Comment on hypothesis-testing approaches to setting cutoff values for fit indexes and dangers in overgeneralizing Hu and Bentler's (1999) findings. Structural Equation Modeling. 2004; **11**(3): 320-41.

208. Chen F, Curran PJ, Bollen KA, Kirby J, Paxton P. An empirical evaluation of the use of fixed cutoff points in RMSEA test statistic in structural equation models. Sociological Methods & Research. 2008; **36**(4): 462-94.

209. MacCallum RC, Browne MW, Sugawara HM. Power analysis and determination of sample size for covariance structure modeling. Psychological Methods. 1996; **1**(2): 130.

210. Liang KY, Zeger SL. Longitudinal data using generalized linear models. Biometrika. 1986; **73**: 13.

211. Miller CL, Kerr T, Frankish JC, Spittal PM, Li K, Schechter MT, et al. Binge drug use independently predicts HIV seroconversion among injection drug users: implications for public health strategies. Subst Use Misuse. 2006; **41**(2): 199-210.

212. Bulmer MG. Principles of statistics. New York: Dover Publications Inc.; 1979.

213. Balanda KP, MacGillivray HL. Kurtosis: A critical review. American Statistician. 1988; **42**(2): 111-9.

214. Kline P. Handbook of psychological testing. New York: Routledge Inc.; 1999.

215. Nunnally JC, Berstein IH. Psychometric Theory. Third ed. New York: McGraw-Hill; 1994.

216. Hu L, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. Structural Equation Modeling: A Multidisciplinary Journal. 1999; **6**(1): 1-55.

217. Hadland SE, Marshall BDL, Kerr T, Lai C, Montaner JS, Wood E. Ready access to illicit drugs among youth and adult users. Am J Addictions. 2012; **21**(5): 488-90.

218. Krüsi A, Fast D, Small W, Wood E, Kerr T. Social and structural barriers to housing among street-involved youth who use illicit drugs. Health & Social Care in the Community. 2010; **18**(3): 7.

219. Werb D, Kerr T, Li K, Montaner J, Wood E. Risks surrounding drug trade involvement among street-involved youth. Am J Drug Alc Abuse. 2008; **34**(6): 810-20.

220. Behrens DA, Caulkins JP, Tragler G, Haunschmied JL, Feichtinger G. A dynamic model of drug initiation: implications for treatment and drug control. Mathematical Biosciences. 1999; **159**(1): 1-20.

221. Gonzalez R, Vassileva J, Bechara A, Grbesic S, Sworowski L, Novak RM, et al. The influence of executive functions, sensation seeking, and HIV serostatus on the risky sexual practices of substance-dependent individuals. J Int Neuropsychological Society. 2005; **11**(2): 121-31.

222. Dolezal C, Meyer-Bahlburg HFL, Remien RH, Petkova E. Substance use during sex and sensation seeking as predictors of sexual risk behavior among HIV+ and HIV- gay men. AIDS and Behavior. 1997; **1**(1): 19-28.

223. Kalichman SC, Heckman T, Kelly JA. Sensation seeking as an explanation for the association between substance use and HIV-related risky sexual behavior. Archives of Sexual Behavior. 1996; **25**(2): 141-54.

224. Ersche KD, Turton AJ, Pradhan S, Bullmore ET, Robbins TW. Drug addiction endophenotypes: impulsive versus sensation-seeking personality traits. Biological Psychiatry. 2010; **68**(8): 770.

225. Bornovalova MA, Gwadz MA, Kahler C, Aklin WM, Lejuez CW. Sensation seeking and risk-taking propensity as mediators in the relationship between childhood abuse and HIV-related risk behavior. Child Abuse & Neglect. 2008; **32**(1): 99.

226. Strathdee SA, Hogg RS, Martindale SL, Cornelisse PG, Craib KJ, Schilder A, et al. Sexual abuse is an independent predictor of sexual risk-taking among young HIV-negative gay men: results from a prospective study at baseline. Int Conf AIDS. 1996; **11**(Program Supplement): 15 (abstract no. Mo.C.900).

227. Hadland SE, Marshall BDL, Kerr T, Qi J, Montaner JS, Wood E. Suicide and history of childhood trauma among street youth. J Affective Disorders. 2012; **136**(3): 377-80.

228. Brodsky BS, Oquendo M, Ellis SP, Haas GL, Malone KM, Mann JJ. The relationship of childhood abuse to impulsivity and suicidal behavior in adults with major depression. Am J Psychiatry. 2001; **158**(11): 1871-7.

229. Zlotnick C, Shea MT, Pearlstein T, Simpson E, Costello E, Begin A. The relationship between dissociative symptoms, alexithymia, impulsivity, sexual abuse, and self-mutilation. Comprehensive Psychiatry. 1996; **37**(1): 12-6.

230. Norberg MM, Kezelman S, Lim-Howe N. Primary prevention of cannabis use: A systematic review of randomized controlled trials. PLoS ONE. 2013.

231. Staiger PK, Kambouropoulos N, Dawe S. Should personality traits be considered when refining substance misuse treatment programs? Drug Alc Rev. 2007; **26**(1): 17-23.

232. Pollack MH, Penava SA, Bolton E, Worthington JJ, Allen GL, Farach FJ, et al. A novel cognitive-behavioral approach for treatment-resistant drug dependence. J Subst Abuse Treat. 2002; **23**(4): 335-42.

233. Kanters S, Richardson C. Substance use risk personality profiles as predictors of substance use and intentions: A latent profile analysis in young adolescents. Lost in Translation: Exploring the early origins of addiction. Vancouver, BC; 2013.

234. DeBeck K, Buxton J, Kerr T, Qi J, Montaner J, Wood E. Public crack cocaine smoking and willingness to use a supervised inhalation facility: implications for street disorder. Subst Abuse Treat Prev Pol. 2011; **6**(1): 4.

235. Strathdee SA, Navarro JR. Commentary on Salmon et al.(2010): The case for safer inhalation facilities: Waiting to inhale. Addiction. 2010; **105**(4): 684-5.

236. Slocum-Gori SL, Zumbo BD. Assessing the unidimensionality of psychological scales: Using multiple criteria from factor analysis. Social Indicators Research. 2011; **102**(3): 443-61.

237. PHAC. Street youth in Canada. Ottawa: Public Health Agency of Canada; 2006.

238. Fendrich M, Xu Y. The validity of drug use reports from juvenile arrestees. Int J Addiction. 1994; **29**(8): 971.

239. Magura S. Validating self-reports of illegal drug use to evaluate National Drug Control Policy: A reanalysis and critique. Evaluation and Program Planning. 2010; **33**(3): 234-7.

240. Des Jarlais DC, Paone D, Milliken J, Turner CF, Miller H, Gribble J, et al. Audio-computer interviewing to measure risk behaviour for HIV among injecting drug users: a quasi-randomised trial. Lancet. 1999; **353**(9165): 5.

241. Cochrane Collaborative Review Group on HIV Infection and AIDS. Structural interventions to increase needle/syringe access for preventing HIV and hepatitis C in injection drug users. San Francisco: University of California; 2010.

242. Cohen DA, Wu SY, Farley TA. Comparing the cost-effectiveness of HIV prevention interventions. J Acquir Immune Defic Syndr. 2004; **37**(3): 1404.

243. UNAIDS. Joint UNAIDS statement on HIV prevention and care strategies for drug users. Geneva: Joint United Nations Programme on HIV/AIDS; 2005.

244. Global Commission on Drug Policy. The War on Drugs and HIV/AIDS: How the criminalization of drug use fuels the global pandemic. Rio de Janeiro: Global Commission on Drug Policy; 2012 June 26.

245. Bruneau J, Lamothe F, Franco E, Lachance N, Desy M, Soto J, et al. High rates of HIV infection among injection drug users participating in needle exchange programs in Montreal: results of a cohort study. Am J Epidemiol. 1997; **146**(12): 994.

246. Wood E, Lloyd-Smith E, Li K, Strathdee SA, Small W, Tyndall MW, et al. Frequent needle exchange use and HIV incidence in Vancouver, Canada. Am J Med. 2007; **120**(2): 172-9.

247. Degenhardt L, Mathers B, Vickerman P, Rhodes T, Latkin C, Hickman M. Prevention of HIV infection for people who inject drugs: why individual, structural, and combination approaches are needed. Lancet. 2010; **376**: 16.

248. Cao W, Treloar C. Comparison of needle and syringe programme attendees and non-attendees from a high drug-using area in Sydney, New South Wales. Drug Alc Rev. 2006; **25**(5): 439-44.

249. Rhodes T, Judd A, Mikhailova L, Sarang A, Khutorskoy M, Platt L, et al. Injecting equipment sharing among injecting drug users in Togliatti City, Russian Federation: Maximizing the protective effects of syringe distribution. J Acquir Immune Defic Syndr. 2004; **35**(3): 293.

250. Maher L, Dixon D. The cost of crackdowns: Policing Cabramatta's heroin market. Current Issues in Criminal Justice. 2001; **13**(1): 5.

251. Rhodes T, Singer M, Bourgois P, Friedman SR, Strathdee SA. The social structural production of HIV risk among injecting drug users. Soc Sci Med. 2005; **61**(5): 1026.

252. Wood E, Werb D, Kazatchkine M, Kerr T, Hankins C, Gorna R, et al. Vienna Declaration: a call for evidence-based drug policies. Lancet. 2010; **6736**(10): 2.

253. Bluthenthal RN, Kral AH, Lorvick J, Watters JK. Impact of law enforcement on syringe exchange programs: A look at Oakland and San Francisco. Med Anthropol. 1997; **18**(1): 61.

254. Gostin LO. The legal environment impeding access to sterile syringes and needles: the conflict between law enforcement and public health. J Acquir Immune Defic Syndr Hum Retrovirol. 1998; **18**(Suppl 1): S60.

255. Kerr T, Small W, Wood E. The public health and social impacts of drug market enforcement: A review of the evidence. Int J Drug Pol. 2005; **16**(4): 210.

256. Maher L, Dixon D. Policing and public health: Law enforcement and harm minimization in a street-level drug market. Brit J Criminol. 1999; **39**(4): 488.

257. Horton R, Das P. Rescuing people with HIV who use drugs. Lancet. 2010; **376**(9737): 207-8.

258. Kasperowicz P. DC delegate: Congress has 'killed' with needle exchange prohibition. The Hill. 2011 April 4.

259. Cooper HLF, Des Jarlais DC, Ross Z, Tempalski B, Bossak B, Friedman SR. Spatial access to syringe exchange programs and pharmacies selling over-the-counter syringes as predictors of drug injectors' use of sterile syringes. Am J Pub Health. 2011; **101**(6): 1118.

260. Haber PS, Demirkol A, Lange K, Murnion B, Womack H, Parfitt T. The future of harm reduction programmes in Russia. The Lancet. 2009; **374**(9697): 1284-93.

261. Matichon. วุ่นแล้ว ! สนับสนุนใช้เข็ม อุปกรณ์ฉีดที่สะอาด ป้องกันการติดเชื้อ เอชไอวี ส่อผิดกฎหมาย Matichon Online. 2011.

262. PEPFAR. Comprehensive HIV Prevention for People Who Inject Drugs, Revised Guidance. Washington, DC: President's Emergency Plan for AIDS Relief; 2010 July.

263. A bill making appropriations for the Department of State, foreign operations, and related programs for the fiscal year ending September 30, 2012, and for other purposes. 112. United States Congress:1st Session ed; 2011.

264. Werb D, Wood E, Small W, Strathdee S, Li K, Montaner J, et al. Effects of police confiscation of illicit drugs and syringes among injection drug users in Vancouver. Int J Drug Pol. 2008; **19**(4): 332.

265. Kerr T, Fairbairn N, Tyndall M, Marsh D, Li K, Montaner J, et al. Predictors of non-fatal overdose among a cohort of polysubstance-using injection drug users. Drug Alc Depend. 2007; **87**(1): 39.

266. Vancouver Coastal Health. 2011; Available from: http://www.vch.ca/. Accessed on November 27th, 2012.

267. Keyes KM, Utz RL, Robinson W, Li G. What is a cohort effect? Comparison of three statistical methods for modeling cohort effects in obesity prevalence in the United States, 1971-2006. Soc Sci Med. 2010; **70**(7): 1100-8.

268. Nelson KE, Galai N, Safaeian M, Strathdee SA, Celentano DD, Vlahov D. Temporal trends in the incidence of human immunodeficiency virus infection and risk behavior among injection drug users in Baltimore, Maryland, 1988-1998. Am J Epidemiol. 2002; **156**(7): 641.

269. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. Biometrics. 1986; **42**(1): 121.

270. Diggle PJ, Heagerty PJ, Liang K-Y, Zeger SL. Time-dependent covariates. Analysis of Longitudinal Data. Oxford: Oxford University Press; 2002. p. 245-81.

271. Janssen PA, Gibson K, Bowen R, Spittal PM, Petersen KL. Peer support using a mobile access van promotes safety and harm reduction strategies among sex trade workers in Vancouver's Downtown Eastside. J Urban Health. 2009; **86**(5): 804-9.

272. Public Health Agency of Canada. I-Track: Enhanced surveillance of risk behaviours among people who inject drugs. Phase I Report, August 2006. Report. Ottawa: Surveillance and Risk Assessment Division, Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada; 2006.

273. Buxton J, Mehrabadi A, Preston E, Tu A. Vancouver site report for the Canadian Community Epidemiology Network on Drug Use. Report. Vancouver: City of Vancouver; 2007.

274. Remis RS, Strathdee SA, Millson M, Leclerc L, Degani N, Palmer RWH, et al. Consortium to characterize injection drug users in Montreal, Toronto and Vancouver, Canada. Report. Ottawa: Bureau of HIV/AIDS, STD and TB, Health Canada; 1998.

275. Buchanan AS, Latkin CA. Drug use in the social networks of heroin and cocaine users before and after drug cessation. Drug Alc Depend. 2008; **96**(3): 286.

276. Nandi A, Glass TA, Cole SR, Chu H, Galea S, Celentano DD, et al. Neighborhood poverty and injection cessation in a sample of injection drug users. Am J Epidemiol. 2010; **171**(4): 391-8.

277. Skelton C. Is Vancouver's Downtown Eastside really 'Canada's poorest postal code?'. Vancouver Sun. 2010 February 10.

278. Rockwell R, Jarlais DCD, Friedman SR, Perlis TE, Paone D. Geographic proximity, policy and utilization of syringe exchange programmes. AIDS Care. 1999; **11**(4): 437-42.

279. Wood E, Tyndall MW, Spittal P, Li K, Hogg RS, O'Shaughnessy M, et al. Needle exchange and difficulty with needle access during an ongoing HIV epidemic. Int J Drug Pol. 2002; **13**(2): 95.

280. Cooper HL, Des Jarlais DC, Tempalski B, Bossak BH, Ross Z, Friedman SR. Drug-related arrest rates and spatial access to syringe exchange programs in New York City health districts: Combined effects on the risk of injection-related infections among injectors. Health & Place. 2012; **18**(2): 218-28.

281. Degenhardt L, Chiu W-T, Sampson N, Kessler RC, Anthony JC, Angermeyer M, et al. Toward a global view of alcohol, tobacco, cannabis, and cocaine use: Findings from the WHO World Mental Health Surveys. PLoS Med. 2008; **5**(7): 1053-67.

282. Reuter P, Stevens A. An analysis of UK drug policy. 2007.

283. Nosyk B, Marsh DC, Sun H, Schechter MT, Anis AH. Trends in methadone maintenance treatment participation, retention, and compliance to dosing guidelines in British Columbia, Canada: 1996-2006. J Subst Abuse Treat. 2010; **39**(1): 22-31.

284. Drach L, Guernsey J, Maher JE, Rumptz M, Stark M, Pranian K, et al. Should we move from syringe exchange to distribution? Am J Pub Health. 2011; **101**(3): 389.

285. Broadhead RS, Heckathorn DD, Weakliem DL, Anthony DL, Madray H, Mills RJ, et al. Harnessing peer networks as an instrument for AIDS prevention: Results from a peer-driven intervention. Public Health Rep. 1998; **113 Suppl 1**: 42.

286. Grund JP, Blanken P, Adriaans NF, Kaplan CD, Barendregt C, Meeuwsen M. Reaching the unreached: targeting hidden IDU populations with clean needles via known user groups. J Psychoactive Drugs. 1992; **24**(1): 41.

287. Latkin CA. Outreach in natural settings: the use of peer leaders for HIV prevention among injecting drug users' networks. Public Health Rep. 1998; **113 Suppl 1**: 151.

288. Genberg BL, Gange SJ, Go VF, Celentano DD, Kirk GD, Mehta SH. Trajectories of injection drug use over 20 years (1988-2008) in Baltimore, Maryland. Am J Epidemiol. 2011; **173**(7): 829-36.

289. Leonard L, DeRubeis E, Pelude L, Medd E, Birkett N, Seto J. "I inject less as I have easier access to pipes": Injecting, and sharing of crack-smoking materials, decline as safer crack-smoking resources are distributed. Int J Drug Pol. 2008; **19**(3): 255-64.

290. Chettiar J, Shannon K, Wood E, Zhang R, Kerr T. Survival sex work involvement among street-involved youth who use drugs in a Canadian setting. J Pub Health. 2010; **32**(3): 322-7.

291. Werb D, Kerr T, Small W, Li K, Montaner J, Wood E. HIV risks associated with incarceration among injection drug users: implications for prison-based public health strategies. J Pub Health. 2008.

292. Heimer R, Eicher A, Eno R, Greaves S, Kamina A, Singh M, et al. Needle exchange programs as a conduit to drug treatment: the New Haven experience. Int Conf AIDS. 1996; **11**(2): 155 (abstract no. We.C.3561).

293. Klee H, Morris J. The role of needle exchanges in modifying sharing behaviour: cross-study comparisons 1989-1993. Addiction. 1995; **90**(12): 1635.

294. Lurie PG, Drucker E, Knowles A. Still working after all these years: increasing evidence of needle exchange program (NEP) effectiveness in studies published since 1993. Int Conf AIDS. 1998; **12**: 670 (abstract no. 33403).

295. Des Jarlais DC. Structural interventions to reduce HIV transmission among injecting drug users. AIDS. 2000; **14**(Suppl 1): S41.

296. Palmgreen P, Donohew L, Lorch EP, Hoyle RH, Stephenson MT. Television campaigns and adolescent marijuana use: Tests of sensation seeking targeting. Am J Pub Health. 2001; **91**(2): 292.

297. Schaefer M, Schmidt F, Folwaczny C, Lorenz R, Martin G, Schindlbeck N, et al. Adherence and mental side effects during hepatitis C treatment with interferon alfa and ribavirin in psychiatric risk groups. Hepatology. 2003; **37**: 443.

298. Goldsamt LA, Harocopos A, Kobrak P, Jost JJ, Clatts MC. Circumstances, pedagogy and rationales for injection initiation among new drug injectors. J Community Health. 2010; **35**(3): 258-67.

299. Bucardo J, Brouwer KC, Magis-RodrÃ-guez C, Ramos R, Fraga M, Perez SG, et al. Historical trends in the production and consumption of illicit drugs in Mexico: implications for the prevention of blood borne infections. Drug Alc Depend. 2005; **79**(3): 281-93.

300. Wells EA, Calsyn DA, Clark LL, Jackson TR, Saxon AJ. Retention in methadone maintenance is associated with reductions in different HIV risk behaviors for women and men. Am J Drug Alc Abuse. 1996; **22**(4): 509-21.

301. Williams AB, McNelly EA, Williams AE, D'Aquila RT. Methadone maintenance treatment and HIV type 1 seroconversion among injecting drug users. AIDS Care. 1992; **4**(1): 35-41.

302. Bluthenthal RN, Kral AH, Gee L, Erringer EA, Edlin BR. The effect of syringe exchange use on high-risk injection drug users: a cohort study. AIDS. 2000; **14**(5): 605.

303. Huo D, Bailey SL, Ouellet LJ. Cessation of injection drug use and change in injection frequency: the Chicago Needle Exchange Evaluation Study. Addiction. 2006; **101**(11): 1606-13.

304. Wood E, Kerr T, Small W, Jones J, Schechter MT, Tyndall MW. The impact of police presence on access to needle exchange programs. J Acquir Immune Defic Syndr. 2003; **34**(1): 116.

305. Arnett J. Sensation seeking: A new conceptualization and a new scale. Personality and Individual Differences. 1994; **16**(2): 289-96.

306. Galea S, Nandi A, Vlahov D. The social epidemiology of substance use. Epidemiologic Reviews. 2004; **26**(1): 36-52.

307. Goldsamt L, Neaigus A, Welle DL. The social course of drug injection and sexual activity among YMSM and other high-risk youth: an agenda for future research. J Urban Health. 2003; **80**(3): iii26-iii39.

308. Scott J, Carrington PJ. The SAGE handbook of social network analysis. New York: SAGE publications; 2011.

309. Wylie JL, Shah L, Jolly A. Incorporating geographic settings into a social network analysis of injection drug use and bloodborne pathogen prevalence. Health & Place. 2007; **13**(3): 617-28.

310. Strathdee SA, Zafar T, Brahmbhatt H, Baksh A, ul Hassan S. Rise in needle sharing among injection drug users in Pakistan during the Afghanistan war. Drug Alc Depend. 2003; **71**(1): 17.

311. Ferri M, Davoli M, Perucci CA. Heroin maintenance treatment for chronic heroin-dependent individuals: a Cochrane systematic review of effectiveness. J Subst Abuse Treat. 2006; **30**(1): 63-72.

312. Brouwer KC, Lozada R, Weeks JR, Magis-Rodriguez C, Firestone M, Strathdee SA. Intraurban mobility and its potential impact on the spread of blood-borne infections among drug injectors in Tijuana, Mexico. Subst Use Misuse. 2012; **47**(3): 244-53.

313. Wolfe D, Malinowska-Sempruch K. Illicit drug policies and the global HIV epidemic: Effects of UN and national government approaches. Report. New York: Open Society Institute; 2004.

314. Degenhardt L, Coffey C, Moran P, Carlin JB, Patton GC. The predictors and consequences of adolescent amphetamine use: findings from the Victoria Adolescent Health Cohort Study. Addiction. 2007; **102**(7): 1076-84.