SPECIFIC AIMS

This application proposes novel investigations into the natural history of injection drug use, from initiation to cessation or death, as well as studies of trends in morbidity and mortality. We propose to undertake this work in Vancouver, Canada, where, as in the US, the emergence of prescription opioid (PO) misuse is a growing concern. Accordingly, we also seek to evaluate the impact of PO misuse on the natural history of injection drug use in an environment with an active heroin market.

Members of our multidisciplinary team have more than two decades of experience conducting NIDA-funded cohort-based research, including through studies of injection drug users (IDU) participating in the Vancouver Injection Drug Users Study (VIDUS), which is one of the longest-running IDU cohort studies in the world, and street-involved drug-using youth enrolled in the At-Risk Youth Study (ARYS). VIDUS, assembled in 1996, currently involves more than 1000 HIV-negative IDU and has led to more than 200 peer-reviewed publications in the areas public health, HIV/AIDS and injection drug use. Established in 2005, ARYS has followed more than 700 young street-involved drug users and has generated more than 70 peer-reviewed publications on various topics. Importantly, ARYS is one of the only cohort studies to successfully follow high-risk youth up to and beyond the time of initiation into injection drug use. To take advantage of considerable efficiencies, both academic and financial, we propose merging the ARYS and VIDUS cohorts into the Vancouver Drug Users Study (V-DUS), enabling a critical additional five years of investigation into the natural history of injection drug use.

Vancouver is ideally suited for the proposed study for several reasons. First, the city was home to one of the most explosive HIV epidemics ever documented among IDU in the developed world, with HIV incidence peaking at 18 per 100 person-years in 1997. A total of 174 HIV seroconversions have been documented. Second, Vancouver is a port of entry for illicit drugs that are trafficked across North America and, like many US cities, is now experiencing a PO misuse epidemic. Notably, heroin, cocaine, crack and methamphetamine remain widely available locally, which allows for investigations of the impacts of different types of drugs on the initiation and cessation of injecting and associated morbidity and mortality. Third, Vancouver continues to observe high rates of injecting, despite the emergence of crack and methamphetamine use. Fourth, under the province of British Columbia's universal healthcare plan, we are able to link survey and biological data to a range of administrative databases, permitting assessments of barriers to care that are free of the confounding effects of medical insurance schemes. Fifth, our well-established multidisciplinary team and other NIDA investigators use this platform to undertake diverse work in the areas of clinical epidemiology, social, spatial and basic science, as well as modeling and cost-effectiveness studies. Lastly, Vancouver has been the site of the development of a range of innovative programs for IDU, such as supervised injection facilities and Seek, Test, Treat and Retain Initiatives; we therefore hope to continue to use this cohort infrastructure to build on our track record of evaluating highly innovative programs for IDU, as well as other naturally occurring events. Herein, we propose the following aims, consistent with the NIDA U01 cohort program that calls for the creation of cohort platforms to facilitate a broad set of scientific activities focused on HIV and drug use:

1. To examine the impact of prescription opioid misuse on injecting initiation and cessation, risk behaviors for HIV and other viruses, and non-fatal and fatal overdose in a setting with an active heroin market;
2. To characterize early injecting careers, with a focus on the individual and social–structural factors that shape initiation, risk behaviors for HIV and other viruses, early cessation and sustained injecting;
3. To characterize established injecting careers, with a focus on the individual, social–structural and environmental factors that shape cessation of and relapse into injecting, morbidity and mortality;
4. To continue to operate a NIDA-funded cohort that serves as a platform for:
    a. Comparisons between HIV-positive and HIV-negative IDU in analyses examining morbidity, mortality, and addiction- and HIV-related treatment outcomes;
    b. Observational evaluation of interventions, including structural interventions and "naturally occurring" events that cannot be assessed through randomized controlled trials;
    c. Application of phylogenetic and bioinformatic methods to study the evolution and dynamics of acute/early infections in HIV seroconverters, with a focus on host genetic, immunologic and virologic factors associated with transmission and evolution, including drug-resistant strains;
    d. Ethnographic, qualitative and spatial research on the natural history of injection drug use;
    e. Mathematical modeling and cost-effectiveness studies of drug use, the HIV epidemic and the impact of Seek, Test, Treat and Retain initiatives.

Through the Vancouver Drug Users Study (V-DUS), we propose to follow 1800 illicit drug users, including new recruits. Participants provide behavioral information and biological specimens for testing and repository, and use by our team and other NIDA investigators. Through this work, we aim to address several urgent global health issues and inform the development of policies and interventions that address illicit drug use.

3. RESEARCH STRATEGY

3.A. SIGNIFICANCE

Injection drug use remains a major driver of the global HIV/AIDS pandemic.[1] Currently, many of the fastest growing HIV epidemics are driven by injection drug use, and people who inject drugs (IDU) remain a key bridge population within generalized epidemics through transmission to sex partners.[2,3] However, IDU remain among those most vulnerable to social and structural forces that condition HIV-related risks and determine access to HIV-focused prevention and treatment programs.[3,4] In light of these ongoing challenges, we seek to address a range of significant issues specific to the natural history of injection drug use.

Initiation into injection drug use and early injecting careers remain under-studied and significant public health challenges.[5-7] Little is known about initiation into injecting and early injecting careers.[6,7] Interventions to prevent initiation into injecting are lacking,[8] including potential social, structural and environmental interventions that may address this problem.[6,9] In part, this is because few research groups have succeeded in following high-risk youth up to and beyond initiation into injecting. Even less is known about factors that predict early cessation versus sustained injecting among recent initiates.[10] Our team recently produced a number of key longitudinal studies on injecting initiation[11-15] that opened up several second-generation questions (3.C.1). Our proposed research plan is highly significant, as we will build on and extend our work on the initiation of injecting by identifying social–structural drivers of injection initiation and focusing on early cessation and sustained injecting among those early in their injecting careers.

Prescription opioid misuse is the most significant substance abuse problem facing North America, and its impact on the natural history of addiction is unknown. Among the most alarming drug use trends in North America is the rapidly increasing misuse of prescription opioids (PO).[16,17] North Americans currently consume roughly 80% of the world's supply of POs;[18] between 1999 and 2009, US treatment admissions for PO misuse among those 12 years of age or older increased by more than 400%.[19] In 2011, the US Centers for Disease Control and Prevention declared deaths from PO overdoses to be a public health epidemic.[20] A few recent qualitative and cross-sectional studies suggest that PO misuse may promote transition into heroin use and initiation into injecting, thereby drastically increasing the risk of other drug-related harms, including HIV and hepatitis C (HCV) infection and overdose.[21-23] In light of recent calls for more research on the impact of PO misuse on trajectories to heroin use, injection drug use and associated harms,[24,25] our proposed plan will examine the impact of PO misuse on injecting initiation and cessation, levels of risk behaviors for blood-borne diseases, and the likelihood of overdose.[26]

Chronic pain among substance users is prevalent, associated with PO misuse, and under-studied. Nearly four years after the US Congress heralded a "decade of pain control and research" (2001-2010), chronic pain management remains a mounting public health concern worldwide.[27 28,29] Globally, more than 1.5 billion people suffer from chronic pain.[30] In the US, pain is the most common reason for seeking medical care;[31-33] 100 million Americans suffer from chronic pain—more than the number of Americans with diabetes, heart disease, stroke and cancer combined.[34-36] Further, the escalating problem of chronic pain parallels a distinct rise in PO misuse. A recent systematic review and meta-analysis found a 48% pooled prevalence of pain among PO misusers.[25] Studies revealed a positive association between chronic pain and PO misuse,[37,38] particularly among individuals with a history of substance misuse,[39,40] who are significantly more likely to receive inadequate pain management.[41,42] However, there remains a paucity of high quality research on the role that chronic pain plays in driving PO misuse among IDU, as well as the role untreated pain might play in shaping the natural history of injection drug use.[24,25] Accordingly, we aim to assess relationships between untreated chronic pain and PO misuse, as well as injection drug use initiation, relapse and cessation.

In light of important advances in the treatment of HIV disease, parallel investigations of HIV-infected and -uninfected IDU are highly significant. With recent advances in the treatment of HIV disease, long-term outcomes for HIV-infected IDU are changing dramatically.[43] As a result, there is growing interest in HIV-associated non-AIDS (HANA) comorbidities, which increasingly account for a greater proportion of morbidity and mortality among HIV-positive individuals.[44,45] Many of these HANA comorbidities, such as various cancers and chronic/end-stage liver, cardiovascular and renal disease,[43,46-48] are often seen as age-related. However, questions remain as to whether HIV infection can lead to premature aging via compromised immune functioning,[49] in part because studies of HANA have often lacked appropriate controls (i.e., HIV-negative individuals). Accordingly, as we have done in the past,[50-54] we will continue to harmonize our data collection instruments across our parallel studies of HIV-negative and -positive individuals, allowing for rigorous combined analyses that adjust for HIV status in studies of risk behavior, service access, morbidity and mortality among IDU.

Longitudinal cohort studies of HIV-negative drug users are unique, valuable resources. VIDUS is now one of the longest-running community-recruited IDU cohort studies in the world.[55] Since its inception in 1996, it

has made landmark contributions to our understanding of the natural history of injection drug use,[56-61] policies and interventions that seek to address injection drug use and HIV risks,[50,62-67] and the various social and structural factors that shape health among IDU.[68-73] Likewise, ARYS, begun in 2005, has significantly contributed to our understanding of young high-risk drug users[10,74-76] and is one of the only cohort studies of young drug users to undertake longitudinal evaluations of injection initiation.[11,12,14] Our fully harmonized cohorts support a range of complementary studies in the areas of basic,[77-83] social[84-90] and spatial research,[62,91] modeling and cost-effectiveness studies,[92-95] and evaluation of naturally occurring experiments (3.C.1).[58,66,96,97] These cohorts have also served as a platform for training; in the past five years, more than 70 of our publications have been led by more than 30 trainees. This cohort infrastructure is a key component of Canada's first American Society of Addiction Medicine accredited fellowship program (R25DA037756). Hence, the maintenance of this exceptional and unique resource is itself highly significant, and its continuation has high potential to promote ongoing multidisciplinary research and training focused on HIV/AIDS and injection drug use.

3.B. INNOVATION

Vancouver offers an ideal setting for studies of the natural history of injection drug use. Unlike other North American cities, despite the emergence of crack cocaine, Vancouver continues to experience high availability and rates of use of injection heroin, cocaine and methamphetamine.[26] This offers a unique natural laboratory in which to study the impacts of different and emerging drugs on the trajectories associated with injection drug use, including those drugs prescribed and often misused (e.g., hydromorphone, oxycodone),[98,99] as well as new illicit drugs (e.g., DOC).[100] We have recently observed a dramatic increase in the availability of diverted POs,[26] and given our track record and existing infrastructure, we are exceptionally well positioned to examine the impact of PO misuse on injection drug use initiation, relapse and cessation. Further, by incorporating rigorous assessments of pain, we seek to bring innovation to research on PO misuse by carefully considering the impacts of pain and untreated pain on PO misuse and injecting trajectories. Our approach is also innovative in that our combined cohort infrastructure includes high-risk youth with a high rate of injection drug use initiation, as well as established injectors. The inclusion of high-risk youth will allow us to study the complete natural history of injection drug use from initiation to cessation or death. Further, we will be well positioned to characterize early injecting careers and identify potential points for intervention. By following those who initiate injecting, we will be able to refresh our pool of injectors and thus ensure that our sample of IDU continues to represent those in the early, middle and late stages of their injecting careers.

Vancouver remains a site of ongoing innovation with respect to novel interventions. We have previously used our cohort studies to evaluate a range of unique interventions (Vancouver's supervised injection site, decentralized syringe distribution programs, peer-driven interventions)[63,97,101,102] and naturally occurring experiments (e.g., policing during the 2010 Winter Olympics, heroin seizures and droughts, an aggressive HIV Seek, Test, Treat and Retain program).[50,96,103-106] A further unique feature is our universal healthcare system, which confers opportunities to assess barriers to treatment and care (e.g., addiction treatment, hospital care) without the confounding effects of medical insurance schemes. As well, all residents in the province of British Columbia have a personal health number, an identifier that allows us to link participant data to a range of external databases and thus reduce our reliance on self-reported health care use.[107,108]

Limitations of individually-focused interventions have prompted the development of ecologically-focused approaches that emphasize the influence of social, structural and environmental factors on health,[4,109] as well as interventions targeting structural, social or environmental change—an area of research given high priority in the 2013 NIH Office of AIDS Research Trans-Plan.[110] Interactions among individual, social, structural and environmental drivers of health exert great influence on the distribution of morbidity and mortality among IDU.[3,4] Although we have made various contributions to understanding ecological drivers of health and the impact of structural and environmental interventions,[57,65,73,111-117] we seek to build on our past work by exploring the role that various social–structural and environmental exposures (e.g., drug scene involvement, incarceration, unstable housing) play in shaping early and established injecting careers, as well as morbidity and mortality. In doing so, we hope to continue to contribute to the refinement of the Risk Environment Framework, which has been widely adopted in studies of injection drug use and HIV/AIDS.[3,4]

3.C. APPROACH

3.C.1. Progress/Preliminary Studies: VIDUS began in May 1996 as an HIV outbreak investigation. It was subsequently funded by NIDA in 1998 (R01DA11591) and included HIV-positive and HIV-negative IDU. In 2004, VIDUS was re-funded and extended to include street-involved drug-using youth, and all HIV-positive participants were moved into ACCESS, a sister cohort of HIV-positive drug users (R01DA021525).[116,117] In 2009–10, NIDA supported a division of the original cohort into distinct cohorts of HIV-negative IDU (VIDUS, R01DA011591) and street-involved, non-injecting, drug-using youth (ARYS, R01DA028532), although data

collection procedures and instruments remained harmonized. At this time we are seeking to reunite VIDUS and ARYS into the Vancouver Drug Users Study (V-DUS) and enhance it through ongoing recruitment to maximize and take advantage of a range of scientific, practical and fiscal efficiencies, as described below (3.C.5).

The enrollment, follow-up and outcome data for VIDUS are presented in Table 1. As shown, since 1996 VIDUS has enrolled 2240 unique individuals. As mentioned, while HIV-positive individuals were followed in VIDUS initially, when the ACCESS cohort was funded in 2005, HIV-positive individuals were moved into that cohort. Of the remaining HIV-negative individuals who are alive and eligible to be followed (n=1362), 1028 (75.47%) are currently under active follow-up (i.e., 75% of those enrolled since 1996 who are currently eligible to be followed). Over the 16-year period (1996–2013), our median annual rate of loss to follow-up was <7%. We have succeeded in maintaining high rates of follow-up through efforts by the front-line staff (3.C.6), coupled with low migration rates and the high concentration of study participants in a small geographic area. The enrollment, follow-up and outcome data for ARYS are presented in Table 2. As shown, since 2005 ARYS has enrolled 1051 unique individuals. Of the remaining HIV-negative individuals who are alive, still 26 years of age or younger and therefore eligible to be followed (n=898), 707 (78.77%) are currently under active follow-up (i.e., 78% of those eligible to be followed since 2005). Over the 8-year period (2005–13), our median annual rate of loss to follow-up was <7%. The basic characteristics of those lost to follow-up have not differed in significant ways from those retained, leaving both cohorts representative of the local drug-using population. The characteristics of the combined cohort currently under follow-up is shown in section 3.C.5. We plan to enroll 180 new participants in each year to ensure a cohort of 1800 individuals. Recruitment efforts will focus primarily on non-injecting youth to ensure the follow-up of 800 non-injectors.

Table 1. VIDUS Enrollment, Follow-up and Outcomes 1996–2013

Number enrolled	2240
Median number of months followed (IQR)	78.13 (IQR: 44.37–108.58)
HIV serconversions **Incidence density per 100 person-years**	174 1.50 (95% CI: 1.29–1.75)
HCV serconversions **Incidence density per 100 person-years**	130 8.73 (95% CI: 7.11–10.71)
Number who ceased injecting* **Incidence density per 100 person-years**	1178 19.36 (95% CI: 18.38–20.40)
Number of deaths **Incidence density per 100 person-years**	271 1.89 (95% CI: 1.68–2.12)
Total person-years of observation	14,074.55

* Cessation of injecting for a period of 6 months

Table 2. ARYS Enrollment, Follow-up and Outcomes 2005–2013

Number enrolled	1051
Median number of months followed (IQR)	26.17 (IQR: 16.69–44.16)
Number of HIV serconversions **Incidence density per 100 person-years**	12 0.65 (95% CI: 0.37–1.14)
Number of HCV serconversions **Incidence density per 100 person-years**	66 4.30 (95% CI: 3.36–5.50)
Number who reached 27 years of age	134
Number of deaths **Incidence density per 100 person-years**	12 0.64 (95% CI: 0.36–1.12)
Number of initiates into injecting **Incidence density per 100 person-years**	89 8.88 (95% CI: 7.16–11.02)
Total person-years of observation	1866.99

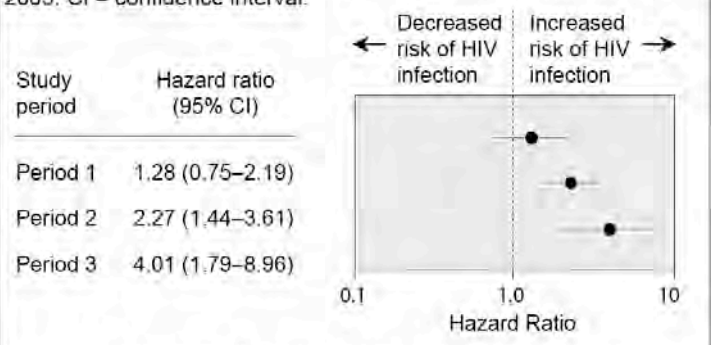
The overarching objectives of VIDUS and ARYS in the past funding cycle were to evaluate the impact of evolving drug use patterns and ecological factors on injecting initiation, HIV risk behavior and incidence, morbidity and mortality. During this time, we published more than 80 peer-reviewed papers in such high impact journals as *Addiction,*[57] *BMJ,*[50] *Lancet*[62] and the *American Journal of Public Health,*[59,63] and the training of more than 30 medical residents, graduate students and postdoctoral fellows was supported. Below, we describe our progress and present new, innovative research aims building on our progress and other developments in the understanding of the natural history of injection drug use.

We have made key contributions to understanding the impact of emerging drug use trends. We described large increases in crack cocaine use among IDU and revealed a new, strong, independent association between crack cocaine smoking and HIV incidence (hazard ratio: 2.74; 95% CI: 1.06–7.11; fig. 1).[56,118] We showed a steep rise in crystal methamphetamine use and injecting locally,[11,119-121] and demonstrated the relationship between methamphetamine use and injection initiation,[11] violence,[122] HCV infection,[123] malnutrition, incarceration,[124] emergency room use,[125] overdose,[126] suicide attempts[127] and syringe sharing.[128]

We are responsive to new and emerging drug use patterns. Given the emergence of PO misuse as one of the most pressing drug use problems in North America,[16,19] we recently began research into this significant issue. In a 2012 *Drug and Alcohol Dependence* paper that combined VIDUS and ARYS data, we identified trends in the availability of six POs (aspirin/oxycodone, hydromorphone, oxycodone, morphine, acetaminophen/codeine and methadone).[26] As shown (fig. 2), after controlling for individual characteristics hypothesized to influence availability, significant increases in PO availability were seen during a time when the availability of traditional drugs of abuse remained constant, with the adjusted odds of delayed availability *vs.* unavailability being between 34% (hydromorphone) and 71% (acetaminophen/codeine) greater in each year.

A pressing concern related to the rise in PO misuse is the potential for PO users to transition to heroin injecting.[21,24] While a few qualitative and retrospective quantitative studies have examined such transitions,[21,23,129] we know of no studies that have longitudinally assessed transitions from PO misuse to heroin injecting. The impacts of transitioning from non-injecting PO use to injecting of POs have also not been characterized, nor have the associated effects on HIV risk behaviors and overdose. Accordingly, we seek to build on our past work and address these key gaps by examining the impact of prescription opioid misuse on injecting initiation and cessation, risk behaviors for HIV and other viruses, and non-fatal and fatal overdose in a setting with an active heroin market. In doing so, we recognize recent research showing that PO users often have complex risk profiles[21,130] distinct from those who primarily use heroin and cocaine. Specifically, the reluctance of PO users to engage with conventional addiction treatment, possibly because of the stigma associated with illicit drug use,[130-134] might extend to other health programs such as syringe exchange programs and supervised injection facilities. There is recent evidence suggesting that, among PO users, individual outcomes can differ according to whether individuals initiated PO use through a legal prescription or through illicit sources[135]—although calls for more research on this topic have been made.[25] Accordingly, we will seek to confirm and extend this work by considering whether barriers to health programs and the means through which PO use is initiated shape adverse outcomes associated with PO injecting.

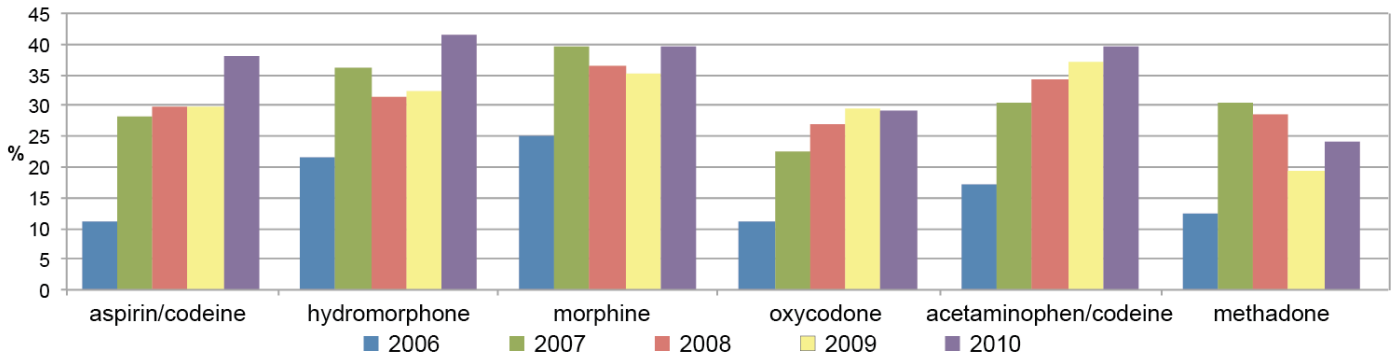
Figure 1. Association between daily smoking of crack cocaine and HIV seroconversion. A hazard ratio above 1.0 indicates an increased risk of HIV seroconversion. Period 1 = May 1, 1996 to Nov. 30, 1999; period 2 = Dec. 1, 1999 to Nov. 30, 2002; period 3 = Dec. 1, 2002 to Dec. 31, 2005. CI = confidence interval.



Adapted from DeBeck K, Kerr T, Li K, Fischer B, Buxton J, Montaner JS, Wood E. Smoking of crack cocaine as a risk factor for HIV infection among people who use injection drugs. *Canadian Medical Association Journal*, 2009; 181(9): 585-589.

Given the relationship between PO, heroin use and chronic pain[25,135,136] and the high rates of pain among IDU,[137] we have begun investigating these issues and aim to extend this work. We recently published a study in *Pain Management* showing high rates of pain and pain self-management among adult IDU.[137] We have also seen an independent association between pain self-management and having been refused pain medications by a physician.[137] Consistent with recent calls by our group and others,[136] we now seek to examine the impact of chronic pain and untreated chronic pain on various outcomes associated with PO misuse.[24,25] Consistent with past aims, we produced several novel works focused on injecting initiation[11-15] and succeeded in following high-risk youth through and beyond initiation into injecting. As shown (fig. 3), we recently found a strong, independent relationship between crystal methamphetamine use and initiation of injecting.[11] We also reported on the relationship between injection initiation and childhood trauma,[14] homelessness,[13] neighborhood of residence[15] and gender.[12] We completed one study on early injecting careers,[10] revealing that 72% of those who tried injecting became regular injectors; although we had limited power to detect differences, we identified diverse trajectories leading to regular injecting, as some soon became regular injectors while others did not begin injecting regularly for more than a year. These differences point to opportunities for intervention to promote early cessation of injecting. Through this proposal, we seek to build on our past work and address gaps in research on early injecting careers. Accordingly, our second aim is to characterize early injecting careers, with a focus on the individual and social–structural factors that shape initiation, risk behaviors for HIV and other viruses, early cessation, and sustained injecting. With regard to social–structural and environmental factors, we produced a number of works showing

Figure 2. Percentage of ever-users of each drug indicating immediate availablity*



* Immediately available = available within 10 minutes. Data are derived from baseline interviews of participants entering the cohorts each year.

Adapted from Nosyk B, Marshall BDL, Fischer B, Montaner JSG, Wood E, Kerr T. Increases in the availability of prescribed opioids in a Canadian setting. *Drug Alcohol Depend*, 2012; 126: 7-12.

that unstable housing,[71,74] incarceration[57,138] and drug scene involvement (e.g., drug dealing, sex work, hours spent in the drug scene each day)[73,75,112,139,140] are strongly associated with various risks and adverse outcomes. However, we have not examined how these exposures affect early injecting careers and associated HIV risks. Likewise, while we have produced various works demonstrating strong independent relationships between childhood trauma, injecting initiation and suicide,[14,59,114,141] we have not yet examined how trauma in adulthood (which is common among IDU)[68,142] affects early injecting careers and associated risks and outcomes. Therefore, we have developed specific methods and hypotheses to address these issues.

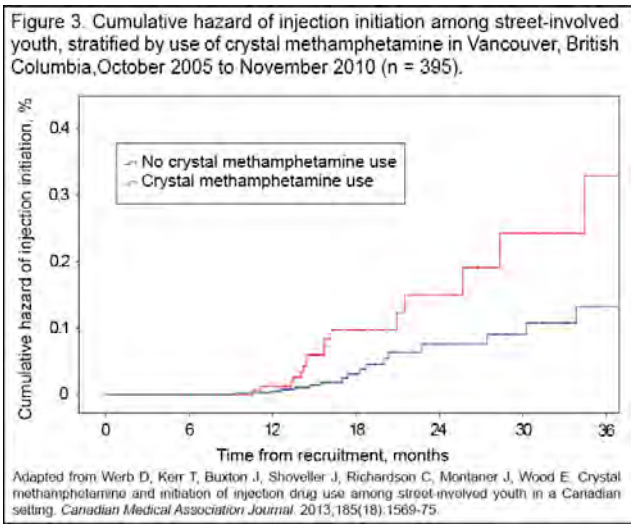


Figure 3. Cumulative hazard of injection initiation among street-involved youth, stratified by use of crystal methamphetamine in Vancouver, British Columbia,October 2005 to November 2010 (n = 395).

Adapted from Werb D, Kerr T, Buxton J, Shoveller J, Richardson C, Montaner J, Wood E. Crystal methamphetamine and initiation of injection drug use among street-involved youth in a Canadian setting. *Canadian Medical Association Journal*. 2013;185(18):1569-75.

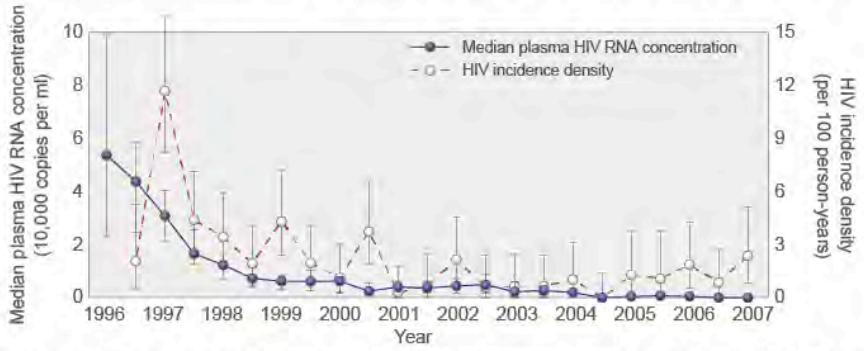
During the past cycle, we studied established injectors, and in *Addiction*[57] showed that incarceration was negatively associated with cessation of injecting in linear growth curve analyses. We also showed that rates of injection cessation were unaffected by dramatic increases in sterile syringe distribution.[58] While our work has shown that many IDU cease injecting, these periods are often short-lived. We therefore aim to expand our work in this area by examining relapse into injecting among those who cease injecting for both short and long periods. Given our ongoing work on the adverse health impacts of various social–structural and environmental factors, such as incarceration,[57,143] drug scene involvement[73,112,139] and unstable housing,[71,74,115] as well our interest in untreated chronic pain,[136,137] we have developed specific hypotheses to explore the effects of these factors on relapse into injecting. Further, since Vancouver is home to a large number of stimulant injectors,[144,145] we will examine the impact of distinct poly-drug use patterns on cessation of injecting.

During the past cycle we continued to produce works focused on morbidity among established IDU, showing high levels of community-associated methicillin-resistant *Staphylococcus aureus* (MRSA),[146,147] cutaneous infections,[143,148,149] suicide,[59,127,150] depression,[151] overdose,[62,152] sexually transmitted infections,[74,115] HCV[123,153,154] and violence.[68,122] Taking advantage of our ability to link cohort data to a variety of external databases, we also described the epidemiology of emergency department and acute hospital bed use among IDU.[125,155,156] Although a few studies indicate that HCV-associated liver disease is accounting for an increasing burden of morbidity and mortality,[157,158] to our knowledge none of these studies has focused on IDU. Further, using 15 years of data from the VIDUS and ACCESS cohorts, we recently found that HCV seropositivity was not significantly associated with liver-related mortality (adjusted hazard ratio [AHR]: 0.45; 95% CI: 0.15–1.37), but HIV seropositivity was (AHR: 2.67; 95% CI: 1.27–5.63).[159] Therefore, in collaboration with our sister cohort of HIV-positive drug users,[116] we aim to conduct combined analyses focused on assessing the impact of HCV-associated liver disease, relative to HIV, on hospitalization and mortality, as new HCV direct-acting antiretrovirals are rolled out under our universal healthcare system. Given our aging HCV-infected population, we anticipate that HCV-associated liver disease will account for an increasing burden of hospitalization and mortality (the liver-related mortality rate is currently low at 2.10 per 1000 person-years in our cohorts), but with our universal healthcare system, the high penetration of antiretroviral therapy[160] and the arrival of once-daily antivirals for HCV, it will not surpass HIV-related causes. Lastly, we have shown that homicide is a leading cause of death among female IDU in our cohort.[161] Vancouver has been the site of the mass disappearance and murder of women involved in sex work.[162] In response, a commission of inquiry has prompted policy changes designed to protect vulnerable women, and the Supreme Court of Canada recently ruled the nation's sex work laws unconstitutional.[163] However, given the ongoing circumstances surrounding sex work,[164] housing[74] and gender-based violence within drug scenes,[165,166] we will continue to investigate mortality from homicide and will seek to determine the factors driving homicide among vulnerable women in this setting.

Consistent with the spirit of this U01 mechanism, we will continue to use our cohort infrastructure as a platform for a diverse set of research activities. Perhaps most importantly, the cohort described herein will serve as a key HIV-negative comparison cohort for combined analyses involving HIV-positive drug users. As shown (fig. 4), we used a combined cohort analysis to develop the concept of "community viral load" and successfully undertook the first observational studies showing an impact of HIV treatment on prevention of HIV infection among IDU.[50] While we recently found that HIV seropositivity remained independently associated with all-cause mortality among local IDU (AHR: 3.13; 95% CI: 2.58–3.80), causes of death among HIV-positive persons have shifted over time from AIDS-related causes to chronic illnesses.[167] Our cohort infrastructure was

also used to evaluate new interventions and naturally occurring experiments, including novel syringe distribution programs,[97,102] supervised injection facilities,[65,101,108,168-171] Seek, Test, Treat and Retain initiatives,[50,105,106,160] peer-driven interventions[97,102,172] and policing activities.[103,173,174] We will continue to be responsive to these and other emerging developments (e.g., HCV treatment) and undertake related evaluations. Our cohort infrastructure is also a key component of an ongoing NIDA-funded program of ethno-spatial epidemiology (R01DA033147) which includes a range of innovative ethnographic, qualitative and spatial research (qualitative and quantitative) activities.[87-89,91,175,176] Through V-DUS we will continue to collect geocoded data, and our qualitative team will continue to query our cohort database to identify individuals with unique exposures so as to recruit them for qualitative interviews. As well, the biological material collected from cohort participants has been used extensively by basic scientists in the US and Canada.[77,78,81-83] We will continue to make this material available to individuals at and outside our center, where several leading experts are applying phylogenetic and bioinformatic methods to study the evolution and dynamics of acute/early infections in HIV seroconverters, including host genetic, immunologic and virologic factors associated with transmission and evolution, such as drug-resistant strains.[77-79,81-83] Lastly, we have used our cohort data to support a range of mathematical modeling and cost-effectiveness studies focused on drug use and the HIV epidemic among IDU,[92,93] and our IDU cohort participants are critical to an ongoing Avant-Garde study (R01DA036307) of Seek, Test, Treat and Retain initiatives in our province. **While V-DUS is an invaluable research platform, the diverse activities described above are funded entirely through other sources and accordingly we do not provide hypotheses and methods specific to them in the following sections.**

Figure 4. Estimated community plasma HIV-1 RNA concentrations and HIV incidence density.



Adapted from Wood E, Kerr T, Marshall B, Li K, Zhang R, Harrigan P, Hogg R, Montaner JS. Longitudinal community plasma HIV-1 RNA levels and HIV-1 incidence among injection drug users. *British Medical Journal*, 2009; 338: B1649.

3.C.2. Investigators and Environment: In light of our success to date, we will keep our core leadership and add emerging researchers with complementary expertise to help inform the investigation of novel aims. Our team spans expertise in social and clinical epidemiology, public health, psychology, sociology, health economics and modeling, gender and sexuality, virology, addiction and HIV medicine. The study will continue to be led by Dr. Thomas Kerr (PI), a psychologist with extensive experience in epidemiology and public health specific to drug use and HIV who has authored more than 380 peer-reviewed publications. He will be supported by two productive junior co-PIs, Drs. Kora DeBeck and Kanna Hayashi, who will assist with study management. Senior members of our team, in particular Drs. Evan Wood and Julio Montaner, will continue to provide support to the core study leadership. We will continue to involve key consultants Drs. Steffanie Strathdee (first VIDUS PI) and Tom Patterson and to use the committee structure that has been key to our success, which includes *Steering*, *Measurement*, *Analytic*, and *Clinical Outcomes* committees (see budget justification and biosketches for individual roles). We will continue to hold quarterly investigator meetings to provide progress reports and discuss plans. Further, an active *Community Advisory Board* that includes members of the affected community is in place and will continue to advise investigators on community concerns and aid in results dissemination.

Our study environment is ideal for pursuing our proposed aims. Study investigators, research staff and graduate students are located in Canada's largest HIV treatment and research center at the British Columbia Centre for Excellence in HIV/AIDS (CfE) at St. Paul's Hospital, Vancouver. The CfE is well equipped with all the required technical, human and laboratory resources. Recruitment, follow-up, and community outreach activities take place in a purpose-built 6000 sq. ft. field office in the Downtown Eastside inner-city neighborhood and a second office in the Downtown South. The study also benefits from the faculty appointments held by investigators at the University of British Columbia and Simon Fraser University, fostering involvement of graduate students and postdoctoral trainees. Of note, as indicated in the budget, the majority of investigator salaries are covered by other sources (e.g., Canadian university salaries).

3.C.3. Research Overview & Hypotheses: Guided by Rhodes' Risk Environment Framework (3.C.4),[109,177] we will pursue analyses that account for individual characteristics and the social and structural factors that shape the natural history of injection drug use. We will focus on PO misuse, early injecting careers, established injecting careers, and morbidity and mortality. We will also build a platform for ongoing evaluation of naturally

occurring and future structural interventions. Our interdisciplinary team will refine, expand and harmonize methods across our existing cohort studies and bring significant innovation to HIV-focused research on injection drug use. Our proposed study is directly responsive to the 2013 NIH Office of AIDS Research's call for *"multidisciplinary research that investigates… sociobehavioral determinants of injection drug use and the transition from noninjection to injection drug use as they relate to HIV transmission."*

Hypotheses: Select study hypotheses, linked to our specific study aims, are presented here. As data collection, analysis and evaluation continue iteratively, we expect to continue our track record of innovation; as in past funding cycles, additional hypotheses will be developed and tested over the life of the project.

H.1.1: PO use will be independently associated with elevated rates of initiation into heroin injecting after adjustment for other individual characteristics and social–structural exposures known to be associated with injection initiation.

H.1.2: PO injection will be independently associated with syringe sharing and non-fatal and fatal overdose; these relationships will be mediated by lower access to syringe exchange programs, supervised injection facilities and opioid substitution treatment (OST).

H.1.3: Reporting inadequate treatment of chronic pain will be independently associated with increased initiation of injection of heroin among PO users who are injection-naïve at baseline, independent of age.

H.1.4: Injection cessation among PO injectors will be higher among those who initiated PO use via legal prescription and those who exclusively inject POs and not heroin, after adjustment for inadequate treatment of chronic pain.

H.2.1: Intensity of engagement in drug scenes (sex work, drug dealing) and frequency of incarceration will be independently associated with initiation of injecting after adjustment for known individual and social–structural risks for injection initiation.

H.2.2: Stimulant injecting, binge drug use and engagement in drug scenes will be independently associated with syringe sharing, independent of access to syringe distribution programs, and unprotected sex.

H.2.3: There will be a dose-dependent relationship between sustained injecting and frequency of incarceration exposures, engagement in drug scenes, and duration in unstable housing.

H.2.4: Trauma during adulthood will be independently associated with a reduced likelihood of early cessation of injecting after adjustment for untreated chronic pain and childhood trauma.

H.3.1: Unstable housing and incarceration will be independently associated with relapse into injecting after adjustment for inadequate treatment of chronic pain and other potential confounders.

H.3.2: Cessation of injecting will be positively associated with addiction treatment exposure among opioid but not stimulant injectors, and will be negatively associated with drug scene involvement after adjustment for inadequate treatment of chronic pain.

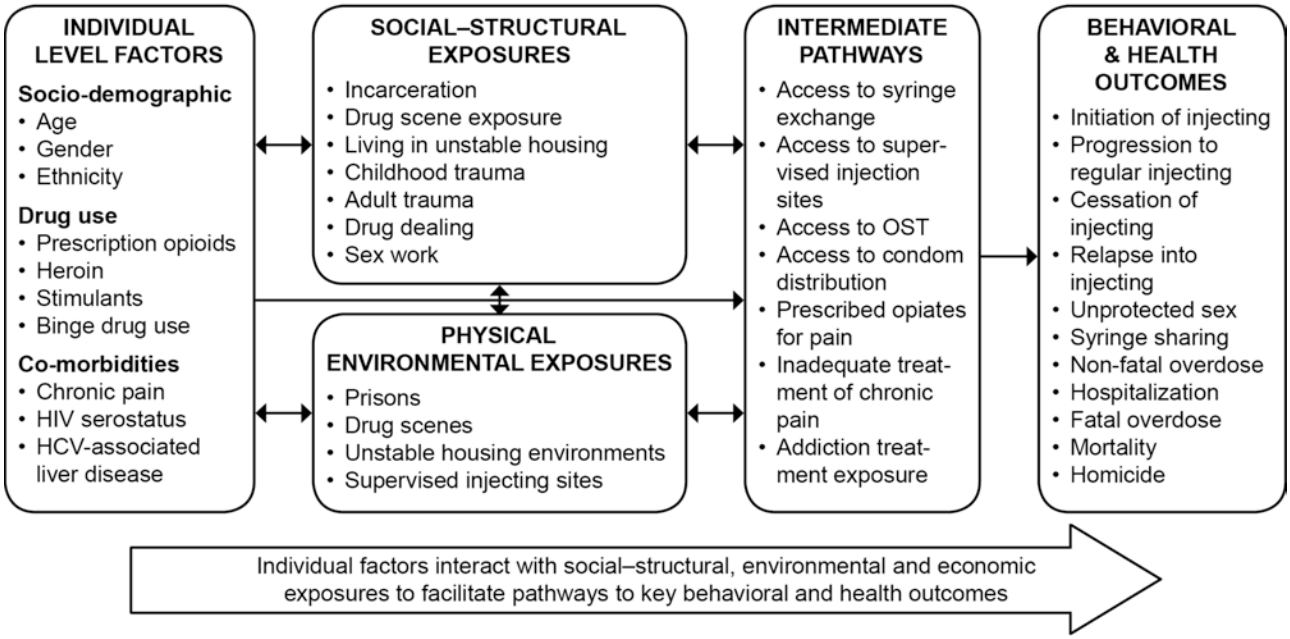
H.3.3: In combined analyses involving HIV-positive and HIV-negative IDU and adjustment for HIV status, hepatitis C–associated chronic liver disease will not surpass HIV-related illnesses as a primary cause of hospitalization and mortality.

H.3.4: Mortality rates from homicide will be higher among women and will be predicted by sex work involvement, stimulant injection and unstable housing.

3.C.4. Conceptual Framework: The proposed research will be informed by Rhodes' Risk Environment Framework,[4,109,177] which holds that the health of people who use drugs is not simply defined by individual-level factors, such as HIV knowledge; rather, behaviors are largely defined by the broader risk environment, imposing constraints and opportunities that shape both risks and access to services. Focusing on the risk environment will enable an investigation of the interactions between processes at the individual level, along with social–structural and environmental exposures.[178] Our team has extensive experience applying and refining the Risk Environment Framework in our NIDA-funded work, and through the work proposed we aim to contribute to its ongoing development.[86,115,117,121] Potential causal connections and pathways are elucidated in fig. 5.

3.C.5. Study Population: Over the past five years, we have recruited and followed approximately 1000 HIV-negative IDU and 700 street-involved drug-using youth from the open drug scene, single-room occupancy hotels, low-barrier health and social services, and other hang-outs and service venues in the Downtown Eastside and Downtown South neighborhoods of Vancouver. Our cohorts are therefore recruited from a range of community settings and avoid selection bias associated with treatment settings or clinics. Projected enrollment will involve maintaining a cohort of 1800 individuals under active follow-up, including 1000 active adult IDU and 800 non-injecting drug users under the age of 26. This will require enrolling approximately 180 new participants each year. Individuals are eligible to participate if they are 14 years of age or older, have used illicit drugs other than cannabis at least once in the previous month, are HIV-negative, and provide written informed consent. Contacted individuals are asked to visit one of our study offices, where the study is

Figure 5. Conceptual model to examine the natural history of injection drug use



Adapted from the Risk Environment Framework (Rhodes, 2002, 2009)

explained, and are offered $10 to undergo a rapid HIV test. Socio-demographic and behavioral characteristics of individuals currently under follow-up are detailed in Table 3.

At this time we are seeking to merge our adult HIV-negative and street youth cohorts into one cohort: the ***Vancouver Drug Users Study (V-DUS)***. We propose the reunification of these cohorts for several reasons. First, the cohorts are already harmonized in terms of recruitment, follow-up and data collection methods, allowing for both retrospective and prospective analyses. Second, there are analytic advantages to merging these cohorts, as many analyses focus on key events (e.g., cessation of drug use) and behaviors (e.g., PO misuse) that cut across cohorts. Merging these cohorts at this time would create efficiencies in terms of data storage, management and analysis. Third, there are financial and practical advantages to combining the cohorts, as we would function with one academic and front-line leadership/management structure, rather than two.

Table 3: Baseline characteristics of 1735 individuals currently followed in the V-DUS.

Characteristic	*n* (%)
Socio-demographic characteristics	
Female gender	540 (31.1%)
Race (Hispanic)	23 (1.3%)
Ethnicity	
Caucasian	1081 (62.3%)
Black	44 (2.5%)
Aboriginal	428 (24.7%)
Other	182 (10.5%)
Age (median, range)	31 (14–66)
Behavioral characteristics[a]	
Any drug use	
Heroin	868 (50.0%)
Cocaine	835 (48.1%)
Crystal methamphetamine	523 (30.1%)
Crack cocaine	1201 (69.2%)
Prescription opioids	432 (24.9%)
Injection drug use	1133 (65.3%)
Heroin[b]	753 (66.5%)
Cocaine[b]	510 (45.0%)
Crystal methamphetamine[b]	283 (25.0%)
Crack cocaine[b]	31 (2.7%)
Prescription opioids[b]	358 (31.6%)
Syringe sharing[b]	187 (16.5%)
Unprotected sex	627 (36.1%)

[a] Refers to the six months prior to the baseline interview.
[b] Percentages are based on n/N=1133 (individuals who reported injection drug use during the previous six months at baseline).

3.C.6. Cohort Methods & Data Linkages: At baseline and at 6-month follow-up visits, participants provide blood samples for HIV and HCV antibody testing, and respond to a harmonized interviewer-administered questionnaire that captures information concerning demographics, behaviors, health status, healthcare use, and social–structural and environmental exposures. As well, a nurse administers a second questionnaire that captures more detailed health and personal information (e.g., medication use, pain, suicidality). At baseline, the main instrument measures historic and recent characteristics, behaviors and exposures, including: socio-demographic information (age, gender, ethnic background, migration, education, income); drug-using behaviors (injection and non-injection drug use frequency, drug type, and public and binge use, including use of POs); and social–structural, environmental and health service exposures, including unstable housing and homelessness, incarceration and criminal justice system contacts, access to treatment for alcohol and drug use, sex work participation, and health and social service use. The questionnaire incorporates a number of standardized instruments, including the Centers for Epidemiologic Studies Depression Inventory,[179] the Addiction Severity Index–Lite (drug and alcohol section), the Childhood Trauma Questionnaire,[180] the Self-efficacy for Limiting

HIV Risk Behavior Scale,[181] and an HIV Knowledge Scale.[182] We will also be adding new scales to facilitate our proposed analyses focused on pain. Chronic pain will be ascertained using the Brief Pain Inventory (BPI).[183] The BPI is a self-reported pain instrument that has been extensively shown to be valid and reliable,[184-187] and it has been widely used with substance-using populations.[42,188,189] In addition to measuring pain severity and interference, the BPI includes questions about pain location, prescribed pain medications, insufficient pain relief from prescribed medications, and self-management of pain outside of prescribed medications. These questions will be used to ascertain under-treated pain in combination with various Pain Management Indexes (PMIs)[190-192] that have been used previously to quantify adequacy of pain management among substance-using populations based on the BPI's pain severity scales and the strength of analgesic prescribed.[42,188] For analyses focused on adult trauma, we will use various existing items specific to violence, accidents and morbidity, but will also include the Trauma History Screen.[193] Our follow-up instrument focuses on analogous characteristics, behaviors and exposures in the previous 6 months. Since the study's inception, we have devoted significant energy to ensuring sound and valid variable measurement; the measures and scales we employ are identical to those used in our ongoing work with HIV-positive IDU and were largely derived from instruments used among US IDU cohorts.

To minimize response biases, we also use each participant's personal health number (PHN), a unique and persistent government-provided identifier, to confidentially link to participant information held in various administrative databases.[108,194] These include: hospital linkages, which provide information on emergency department and acute bed admissions and discharges; PARIS, which provides details (date, type, location, etc.) on uptake of social services such as public housing and addiction treatment; PRIME, held by the Royal Canadian Mounted Police, which details incarceration episodes, including date, location, and offense; and a subset of the PharmaNet database, held by the College of Pharmacists of British Columbia, which provides details (date, dosage, location, etc.) of dispensations of methadone maintenance therapy and other non-antiretroviral medications.[195,196] Our setting also has a robust system of low-threshold access to opioid agonist therapy, including methadone and suboxone, that can be prescribed from physicians' offices and dispensed directly from a network of pharmacies rather than through dedicated methadone clinics. Study staff have experience building confidential linkages, using PHNs, to harmonized participant information held in government administrative databases,[108,117,194] and more than 95% of cohort participants consent to these linkages. For example, we established a confidential linkage to the British Columbia Coroners Service and Vital Statistics Agency to gather information on deaths, including date, location and underlying causes of death according to the 10th edition International Classification of Diseases (ICD-10) codes.[62,197-199]

We will employ the same follow-up procedures that we have successfully used to date and are consistent with IDU cohort studies in other Canadian and US cities. These include: (1) maintaining a tracking database of updated contact information; (2) giving participants a reminder card after each interview; (3) providing honoraria for study visits; (4) obtaining contact information for two persons who know but do not live with the participant; (5) contacting agencies (e.g., social services) to remind participants; (6) conducting regular outreach to areas frequented by participants; (7) maintaining a toll-free number so that participants may phone the study office long distance or from jail; (8) flagging study ID numbers at the supervised injection facility as a means of reminding participants to return for study visits; (9) maintaining regular communications with police and jails, prisons and treatment centers to allow for participants to be interviewed while in such settings; (10) conducting semi-annual linkages with the province's Vital Statistics Agency to determine if the participant has died and, if so, the cause of death. We have used these methods to maintain high annual follow-up rates (3.C.1).

3.C.7. Data Analysis Plan: For **Aim 1**, we will examine impacts of PO misuse on drug use patterns and drug-related harm. Outcomes of interest will be consistent with previous studies and include: (1) time to initiation of heroin injecting; (2) injection drug use cessation, defined as reporting no injection drug use during the past 6 months;[58] (3) receptive and distributive syringe sharing;[63,200] (4) non-fatal overdose;[201] and (5) time to fatal overdose. As in the past analyses,[199] we will ascertain causes of death through PHN linkage with the BC Vital Statistics Agency. Consistent with previous studies,[190,202] ICD-10 codes for fatal overdose will include accidental poisoning by and exposures to noxious substances (X40–49). Primary explanatory variables include PO misuse and inadequate treatment of chronic pain, assessed via validated measures such as BPI and PMIs (3.C.6). PO misuse will be defined as using (or injecting) any POs (including codeine, morphine, tramadol, hydrocodone, oxycodone, hydromorphone, OxyNeo, Percocet, Methadone, Methadose, Fentanyl and Tylenol 3) only for the experience or feeling they cause. Selection of secondary explanatory variables will be informed by the Risk Environment conceptual framework (3.C.4). Such variables will include individual characteristics (e.g., age, gender) and social–structural and environmental exposures (e.g., unstable housing, incarceration). For initial analyses of time to first heroin injection and fatal overdose (outcomes 1 & 5), we will use Kaplan-

Meier (KM) methods and the log-rank test to estimate survival probabilities from first heroin injection and fatal overdose and compare them between those who did or did not misuse POs. Next, we will assess univariable relationships between these outcomes and explanatory variables using Cox regression. For analyses of other outcomes (2, 3, 4), we will assess univariable relationships using generalized linear mixed effects models (GLMMs) with a logit-link function to account for repeated measurements within individuals. To evaluate specific hypotheses, we will employ an *a priori*–defined confounding model procedure outlined by Maldonado and Greenland[203] to fit multivariable regression models that consider both time-invariant (e.g., gender, ethnicity) and time-varying (e.g., age, incarceration) variables. We will fit a full model and then use a stepwise approach to fit reduced models, dropping variables with less relative influence on the relationship between the primary explanatory variable and the outcome. The final model will be selected when the minimum relative change exceeds 5%. These methods have been utilized extensively in our previous work.[116,139,204,205]

For mediation analyses, we will employ a strategy we have used previously,[206-208] based on the approach described by Baron and Kenny.[209] In brief, we will fit four multivariable regression models according to the hypothesized relationships between the independent variable (i.e., PO injection [the exposure]), potential mediators (i.e., lower access to syringe exchange programs, supervised injection facilities and OST) and the dependent variables (i.e., syringe sharing and non-fatal and fatal overdose [the outcomes]). With these models, we will estimate the effect of PO injection on each potential mediator (path *a*); the effect of each potential mediator on each dependent variable (path *b*); the effect of PO injection on each dependent variable without adjusting for each potential mediator (path *c*); and the effect of PO injection on each dependent variable adjusted for each potential mediator (path *c′*). We will use directed acyclic graphs to identify variables that need to be controlled for, including confounders with respect to the exposure–outcome and mediator–outcome relationships.[210,211] We will examine the magnitude and significance of coefficients in each path and assess the presence of full or partial mediation. Additionally, we will conduct a Sobel test to determine the statistical significance of the hypothesized mediation pathway.[212]

For analyses of injection cessation among PO users, rates of cessation and 95% CIs will be calculated using Poisson regression and examined graphically by calendar time, stratified by select characteristics. Multivariable GLMMs will be used to determine associations of cessation among individuals with and without specific exposures, including sources of POs (legitimate prescription *vs.* obtained without prescription) and concurrent injection of POs and heroin. Confounder adjustment will follow the procedures described above.[203]

To characterize early injecting careers (**Aim 2**), we will first restrict the sample to individuals who have never injected drugs or never injected drugs at least once per week for a total of 12 months or more. Further restrictions will be applied for specific outcomes. We will examine the relationships between individual and social–structural factors and a range of outcomes. The outcomes of interest will include: (1) initiation into drug injecting; (2) sustained injecting, defined as reporting at least weekly injection drug use during the previous 6 months;[10] (3) early cessation of injecting, defined as reporting no injection drug use during the past 6 months after having injected drugs at least on a weekly basis for a minimum of 6 months; (4) receptive and distributive syringe sharing; and (5) unprotected sex, defined as reporting not always using a condom during vaginal and/or anal intercourse.[115] The primary explanatory variables of interest will include individual factors (e.g., injecting stimulants [methamphetamine, cocaine], binge drug use) and social–structural exposures (e.g., engagement in drug dealing and/or sex work). As in the past,[116,213] we will also measure the intensity, frequency and/or duration of these behaviors and exposures to examine dose-dependent relationships between the primary explanatory variables and outcomes. Guided by our conceptual framework, we will consider other relevant individual characteristics (e.g., childhood trauma) and social–structural exposures (e.g., access to syringe distribution programs) as secondary explanatory variables. For the analysis of the time to first drug injection (outcome 1), we will employ KM methods and the log-rank test to compare the cumulative survival probabilities from first drug injection stratified by select characteristics, and then use Cox regression to examine univariable relationships with time-invariant and time-varying variables. For analyses of other outcomes (2, 3, 4, 5), we will assess univariable relationships using GLMMs. To estimate the independent relationships between select explanatory variables and outcomes, we will fit multivariable regression models adjusted for confounding variables identified using the aforementioned confounding model-building protocol.[203]

To characterize established injecting careers (**Aim 3**), we will identify individual and social–structural factors that shape cessation and relapse into drug injecting, as well as morbidity and mortality among participants with established injecting careers (i.e., individuals who have ever injected drugs at least once per week for a total of 12 months or more). Injection drug use cessation will be defined as above,[58] and relapse will be defined as reporting injection drug use during the past 6 months while having reported no injection drug use during the past 6 months in the previous assessment. For analyses focusing on these outcomes, key explanatory

variables of interest will include: unstable housing, defined as living in single-room occupancy hotels, shelters, other transitional housing, or on the street;[214] incarceration; inadequate treatment of chronic pain; addiction treatment exposure;[71] and engagement in drug dealing and/or sex work. As previous studies indicate that the natural history of injection drug use typically involves recurrent episodes of cessation and relapse,[215,216] we will use time-updated measurements of cessation and relapse as our outcome measures. First, rates of cessation and relapse will be estimated using Poisson regression and graphically shown by calendar time, stratified by select individual characteristics (e.g., stimulant injection) and social–structural exposures (e.g., incarceration). We will then identify factors independently associated with cessation and relapse using univariable and multivariable GLMMs. Further, the analysis of injection cessation will be stratified by the primary drug injected immediately prior to cessation (i.e., opioids *vs.* stimulants).

For analyses focusing on the impact of chronic liver disease among both HIV-positive and HIV-negative IDU, we will take advantage of data from ACCESS, our NIDA-funded parallel cohort of HIV-positive drug users, and conduct analyses stratified by HIV serostatus. Data specific to hospitalization will be derived through a confidential record linkage to hospital databases. The hospital records provide detailed information concerning reasons for admissions. Using Poisson regression, we will estimate and graphically display the incidence rates of hospitalization due to HIV-related illnesses and chronic liver disease. Rates of HIV- and liver-related mortality (ICD-10 codes: B20–24 for HIV; B15–19, B942, C22 and K70–77 for liver-related[217,218]) will be calculated for the entire study period as well as for each calendar year. The same technique will be applied to the analyses focusing on mortality rates from homicide (ICD-10 codes: X85–Y09 and Y871), although analyses will be stratified by gender. KM methods and the log-rank test will also be used to compare the survival function between male and female participants. To identify predictors of death from homicide, we will use multivariable Cox regression and consider a range of individual, social–structural and environmental factors (e.g., sex work involvement, stimulant injection, unstable housing) as independent variables.

3.C.8. Statistical Power: The estimation of person-years to be accumulated during the study period is shown in Table 4. During the most recent funding cycles of VIDUS and ARYS, attrition rates due to HIV seroconversion, death and loss to follow-up were 6–8.5% per year. Assuming that 10% of participants will be lost from V-DUS annually, approximately 180 individuals will have to be recruited every year to ensure that approximately 1800 participants are retained under active follow-up. Given our prior experience, we are confident in our ability to follow and recruit the target number. In the following sections, we present power calculations for hypotheses that warrant careful consideration of statistical power. All calculations, performed using PASS software, were based on a two-sided test and an alpha level of 0.05. Where possible, we have used observations from the ongoing studies to inform the parameters used below. **H.1.1.** posits that PO use will be associated with initiation of heroin injection. The power calculations are based on the following assumptions: (a) the number of individuals with no history of heroin injection at baseline will be 725 based on preliminary data; (b) the proportion (*P*) of individuals reporting recent PO use (i.e., in the 6 months prior to interview) at baseline will be between 5% and 15% based on preliminary data; (c) the rate of initiation of heroin injection among individuals not reporting recent PO use at baseline will be 7.5 per 100 person-years based on preliminary data; and (d) the two rates will follow a Poisson distribution. As shown in Table 5, we will have ≥80% power to detect a relative incidence of 1.75 after 3 years. **H.2.1.** posits that engagement in drug scenes will be associated with higher rates of initiation of injection drug use. The power calculations are based on the following assumptions: (a) the number of individuals with no history of illicit drug injection at baseline will be 488 based on preliminary data;[10] (b) the proportion (*P*) of individuals reporting recent engagement in drug scenes at baseline will be between 30% and 40% based on preliminary data; (c) the rate of initiation of injection among individuals not engaged in drug scenes at baseline will be 10.1 per 100 person-years based on preliminary data;[219] and (d) the two rates will follow a Poisson distribution. As shown in Table 6, we will have ≥90% power to detect a relative incidence of 1.75 after 3 years. **H.3.1.** posits that living in unstable housing will

Table 4. Estimated person-years of observation in the V-DUS cohort.

Year	1	2	3	4	5	Total
Pop. at start	1800	1800	1800	1800	1800	
Attrition	180	180	180	180	180	900
New recruit	180	180	180	180	180	900
Total person-years	1800	1800	1800	1800	1800	9000

Note: Estimates assume a 10% per annum rate of attrition as a result of HIV seroconversion, death and loss to follow-up, with an average of 0.5 person-years of observation for the first year of each new recruit and for the year a participant is lost.

Table 5. Power to detect associations between PO use and initiation of heroin injection (n = 725)

Relative incidence	Power (%)					
	P = 0.05		P = 0.10		P = 0.15	
	3Y	5Y	3Y	5Y	3Y	5Y
1.50	37.6	45.0	56.5	66.8	69.3	79.8
1.75	60.4	69.1	82.6	89.8	92.3	96.7
2.00	77.3	84.4	94.4	97.5	98.6	99.6

Table 6. Power to detect associations between drug scene exposure and initiation of illicit drug injection (n = 488)

Relative incidence	Power (%)					
	P = 0.30		P = 0.35		P = 0.40	
	3Y	5Y	3Y	5Y	3Y	5Y
1.50	74.4	83.9	77.4	86.6	79.4	88.4
1.75	95.4	98.3	96.7	98.9	97.5	99.3
2.00	99.5	99.9	99.8	99.9	99.9	99.9

be associated with relapse into injecting among individuals with established injecting careers. The power calculations are based on a time-averaged difference on the logit-link scale between two proportions in a repeated measures design and the following assumptions: (a) the number of individuals who have ever injected drugs at least once per week for a total of ≥12 months and who report injection drug use cessation during the past 6 months at baseline will be 380 based on preliminary data; (b) the proportion (P) of individuals reporting recent unstable housing will be between 40% and 50% based on preliminary data; (c) the proportion of individuals who do not report recent unstable housing but who report relapse into injecting during each 6-month study follow-up will be 16% based on preliminary data; and (d) the correlation between the repeated measurements and a compound symmetry covariance structure will be 0.5.[220] As shown in Table 7, we will have ≥80% power to detect an odds ratio of 1.75 after 3 years.

Table 7. Power to detect associations between unstable housing and relapse into injecting (n = 380)

Odds ratio	Power (%)					
	P = 0.40		P = 0.45		P = 0.50	
	3Y	5Y	3Y	5Y	3Y	5Y
1.50	49.2	51.8	50.9	53.5	51.8	54.4
1.75	78.1	80.6	80.0	82.4	81.0	83.4
2.00	93.1	94.5	94.2	95.4	94.8	95.9

3.C.9. Data Management: Data will be centrally located and managed at the BC Centre for Excellence in HIV/AIDS (CfE) at St. Paul's Hospital in Vancouver, Canada. The investigators and study staff have extensive experience with data entry, management, linkage and analysis. Data management, including quality control and security, is overseen by a full-time data manager based at the CfE. We also have extensive experience performing linkages to external government-operated administrative databases. The CfE operates a state-of-the-art computer system with a network of approximately 200 connected clients, including networked servers, Apple OSX and Windows desktop computers, and printers. Applications on the internal network include file exchange, Oracle databases, a research server containing RNA sequence data, and Lotus Notes Domino with QSI, SOPs, calibration records, and form control documents. Wired Ethernet connections are available in all study offices. See the Data and Safety Monitoring section for additional details.

3.C.10. Limitations: As there are no registries or censuses of HIV-negative IDU or high-risk youth, the V-DUS cohort may not be representative of all local drug users. However, we have used extensive community-based methods to recruit individuals both in and out of clinical care and, through aggressive follow-up, maintained a retention rate >85%. The use of self-report, especially for socially stigmatized and criminalized behaviors, can introduce errors of recall and social-desirability bias. However, in addition to using various safeguards to optimize self-report, we obtain many key measures (incarceration, methadone use, etc.) via database linkages.

3.C.11. Summary of Significance & Innovation: The proposed cohort study has significant potential to inform the understanding of the natural history of injection drug use, including early and established injecting careers, and the effects of PO misuse and chronic pain on various health outcomes. Our community-recruited cohort is unique as it is linked to and harmonized with an ongoing NIDA-funded cohort study of HIV-positive drug users and therefore a key control/comparison in work focused on HIV/AIDS among substance users, including ongoing evaluations of Seek, Test, Treat and Retain initiatives.[50,105,106] Our cohort already serves as a platform for innovative work in basic science,[77-79,81-83] qualitative, ethnographic and spatial research,[84,87,88,90,91,172,176,221,222] and modeling and cost-effectiveness studies,[26,92,93,223] and has been used extensively to study naturally occurring interventions and novel programs.[65,66,87,97,200,225] Further, Vancouver is a unique setting in which to study the effects of a diverse set of drugs, including POs, and continues to be the site of innovative policies and programs specific to illicit drug use.[26,56,145,224] Our setting's universal healthcare system allows us to study barriers to treatment and care free of the confounding effects of insurance schemes and financial status, and to use a unique personal health number to link cohort data to various administrative databases.[108,156,225] Our adult cohort of HIV-negative IDU is one of the oldest of its kind in the world, and our youth cohort is one of the only cohorts to succeed in longitudinally following individuals through to and beyond injection initiation.[11-14] Combining these cohorts will make for a powerful and unique cohort infrastructure globally. We believe it is well suited to the current U01 mechanism, has great potential to be a useful addition to the existing participating studies, and could be a valuable resource to NIDA investigators working in various areas of research. Given our track record to date, including our innovative work on social–structural and environmental drivers of health,[57,73,86,112,114,139] we feel we are well positioned to undertake significant and innovative research specific to the natural history of injection drug use, and thereby make important contributions to policy and program development throughout North America and globally.

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