BMJ Open

The Involvement of People Who Inject Drugs in Injection Initiation Events: Identifying Similarities and Differences Across Three North American Settings

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-046957
Article Type:	Original research
Date Submitted by the Author:	13-Nov-2020
Complete List of Authors:	Marks, Charles; University of California San Diego, Medicine Meyers, Stephanie; University of California San Diego, Medicine Jain, Sonia; University of California San Diego, Biostatistics Research Center Sun, Xiaoying; University of California San Diego, Biostatistics Research Center Hayashi, Kanna; Simon Fraser University, Health Sciences Gonzalez-Zuniga, Patricia; University of California San Diego, Medicine Strathdee, Steffanie; University of California San Diego, School of Medicine, Division of Infectious Disease and Global Public Health Garfein, Richard; University of California San Diego, Family Medicine and Public Health Milloy, M; British Columbia Centre on Substance Use, DeBeck, Kora; British Columbia Centre on Substance Use Cummins, Kevin; University of California San Diego, Medicine Werb, Dan; Unity Health Toronto, Centre on Drug Policy Evaluation; University of California San Diego, Division of Global Infectious Diseases and Global Public Health
Keywords:	Substance misuse < PSYCHIATRY, PUBLIC HEALTH, EPIDEMIOLOGY, Public health < INFECTIOUS DISEASES, STATISTICS & RESEARCH METHODS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title: **The Involvement of People Who Inject Drugs in Injection Initiation Events: Identifying Similarities and Differences Across Three North American Settings**

Charles Marks[1,2,3], Stephanie A. Meyers[1,2,3], Sonia Jain[4], Xiaoying Sun[4], Kanna Hayashi[5,6], Patricia Gonzalez-Zuniga[2], Steffanie A. Strathdee[2], Richard S. Garfein[7], M-J Milloy[6,8], Kora DeBeck[6,9], Kevin Cummins[1,2,3], Dan Werb[2,10,*]

[1] Interdisciplinary Research on Substance Use Joint Doctoral Program, San Diego State University & University of California, San Diego

[2] Department of Medicine, University of California, San Diego, USA

[3] School of Social Work, San Diego State University, USA

[4] Biostatistics Research Center, Department of Family Medicine and Public Health, University of California, San Diego, USA

[5] Faculty of Health Sciences, Simon Fraser University

[6] British Columbia Centre on Substance Use, Vancouver, Canada

[7] Department of Family Medicine and Public Health, University of California San Diego, La Jolla, CA, USA

[8] Department of Medicine, University of British Columbia, Vancouver, Canada

[9] School of Public Policy, Simon Fraser University, Vancouver, Canada

[10] Centre on Drug Policy Evaluation, St. Michael's Hospital, Toronto, Canada

[*] Corresponding Author: dwerb@ucsd.edu

Key Words: Injection drug use, injection initiation, San Diego, Tijuana, Vancouver

Tables: 2

Word Count: 4,163

Abstract

Objectives: People who inject drugs (PWID) play an integral role in facilitating the entry of others into injection drug use (IDU). We sought to assess factors influencing PWID in providing IDU initiation assistance across three distinct North American settings and to generate pooled measures of risk.

Design: We employed data from three PWID cohort studies participating in *PReventing Injecting by Modifying Existing Responses* (PRIMER), for this cross-sectional analysis.

Setting: Tijuana, Mexico; San Diego, United States; Vancouver, Canada.

Participants: A total of 2,944 participants were included in this study (Tijuana: n = 766, San Diego: n = 353, Vancouver: n = 1,825).

Measurements: The outcome was defined as recently (i.e. past 6 months) assisting in an IDU initiation event. Independent variables of interest were identified from previous PRIMER analyses. Site-specific multiple modified Poisson regressions were fit. Pooled relative risks were calculated and heterogeneity across sites was assessed via linear random effects models.

Results: Evidence across all three sites indicated that having a history of providing IDU initiation assistance (Pooled Relative Risk [pRR]: 4.83, 95% Confidence Interval [CI]: 3.49-6.66) and recently being stopped by law enforcement (pRR: 1.49, 95% CI: 1.07-2.07) were associated with a higher risk of providing assistance with IDU initiation; while recent opioid agonist treatment enrollment (pRR: 0.64, 95% CI: 0.43-0.96) and no recent IDU (pRR: 0.21, 95% CI: 0.07-0.64) were associated with a lower risk. We identified substantial differences across site in the association of age (I^2: 52%), recent housing insecurity (I^2: 39%), and recent non-injection heroin use (I^2: 78%).

Conclusion: We identified common and site-specific factors related to PWID's risk of assisting in IDU initiation events. Interventions and harm reduction strategies aimed at reducing the harms of IDU should incorporate context-specific approaches to reduce the initiation of IDU.

Word Count: 291

Strengths and Limitations of This Study

- This is the first study to assess common and differential risk factors for assisting injection drug use initiation across different geographic sites.
- By applying Zou's modified regression, the results may be readily applied to mathematical modeling studies looking at the initiation of injection drug use.
- Due to the cross-sectional nature of this study, our ability to evaluate the causal relationship between identified risk factors and assisting injection initiation is limited.
- Due to the small number of sites (three), our ability to quantiatively identify heterogeneity across sites is also limited.

Funding Statement

PRIMER and Dan Werb are supported by a US National Institute on Drug Abuse Avenir Award (DP2-DA040256-01), the Canadian Institutes of Health Research via a New Investigator Award, and the Ontario Ministry of Research, Innovation and Science via an Early Researcher Award. El Cuete IV was supported through NIDA grant R37 DA019829. STAHR II was supported through NIDA grant R01DA031074. VDUS is supported by NIDA grant U01DA038886, and the ACCESS Study is supported by NIDA grant U01DA021525.

Competing Interests

We have no competing interests to disclose.

Author Contributions

CM contributed to project conceptualization, analytic design, data analysis, and original manuscript writing. SM contributed to project conceptualization, analytic design, and manuscript editing. SJ contributed to analytic design and manuscript editing. XS contributed to analytic design and manuscript editing. KH contributed to data collection and manuscript editing. PGZ contributed to data collection and manuscript editing. SAS contributed to data collection and manuscript editing. RSG contributed to data collection and manuscript editing. MJM contributed to data collection and manuscript editing. KD contributed to data collection and manuscript editing. KC contributed to analytic design and manuscript editing. DW contributed to project conceptualization, project supervision, funding acquisition, data collection, and manuscript editing.

Data Availability Statement

The data for this study cannot be made public due to human subjects protections.

Background

North America is currently facing an opioid overdose epidemic, causing the United States Department of Health and Human Services to declare a public health emergency in 2017.[1] As of January 2019, it was estimated that over 130 people died each day the previous year as a result of opioid-related overdose in the United States.[1–3] Given the increased presence of potent synthetic opioids such as fentanyl and carfentanil in illicit drug markets in North America, people who inject drugs (PWID) are exposed to a greater risk of overdose. There are an estimated 2.6M PWID in North America,[4]among whom 45% (>1M) have experienced an overdose.[5]This implies that injection drug use (IDU) is a key driver of overdose, and that **preventing IDU is key to reducing population-level overdose mortality.** PWID who practice unsafe injection drug use (IDU) are also at high risk of HIV and hepatitis B and C transmission, and are especially vulnerable to these infections within the first few years of initiating IDU.[4,6,7] Given the increase in the intensity of these risks in the months immediately after IDU initiation events, as well as the difficulty in preventing IDU-related causes of morbidity and mortality once people begin to inject, experts have suggested that efforts to prevent IDU-related harms should be focused upstream towards preventing IDU initiation.[8,9]

To that end, a large and growing evidence base has established that PWID play an integral role in the process of IDU initiation, with at least 75% of PWID across a variety of settings reporting being assisted in their IDU initiation events by another person experienced with drug injecting.[10] The *PReventing Injecting by Modifying Existing Responses* (PRIMER) study has identified a range of factors placing PWID at increased likelihood of providing IDU initiation assistance to injection-naïve individuals across differing North American contexts (Vancouver, Canada; Tijuana, Mexico; and, San Diego, United States).[8] These include age,[11] gender,[11] injection frequency, the use of particular drug types (e.g., opioids, crystal methamphetamine), non-injection drug use,[12] criminal justice system involvement,[13,14] and access to opioid agonist treatment (OAT).[15–17] While these findings reveal important similarities and differences, no effort has yet been made to pool findings across settings to assess heterogeneity in risk factors for IDU initiation assistance provision.

We therefore sought to pool findings to assess the heterogeneity of factors related to assisting IDU initiation in San Diego, Tijuana, and Vancouver in order to establish a baseline understanding of common and site-specific factors influencing the process of IDU initiation.

Methods

Setting. PRIMER is a cohort consortium study seeking to identify factors influencing the provision of IDU initiation assistance among PWID, and to investigate whether interventions to reduce HIV risk among PWID may also be effective in preventing this behavior.[18] The methods used in the PRIMER study have been previously described in full.[18] In brief, PRIMER includes quantitative data collected beginning in August 2014 from existing prospective community-recruited open cohort studies of PWID including the Proyecto El Cuete IV (ECIV) cohort (Tijuana, Mexico), the Study of Tuberculosis, AIDS, and Hepatitis C Risk (STAHR II) cohort (San Diego, US), and the linked Vancouver Drug Users Study (VDUS) and AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS). All of these cohort studies sought to investigate HIV risk behaviors among PWID living in urban settings, and ECIV and STAHR II were specifically designed as a linked binational study mechanism with highly comparable survey items.[19] ECIV inclusion criteria were that participants be 18 years or older, report IDU in the prior month, speak Spanish or English, currently be living in Tijuana with no plans to relocate, and not be participating in intervention studies.[18] STAHR II inclusion criteria were that participants be 18 years or older, report IDU in the past month, speak English or Spanish, and had no plans to move away in the next 24 months.[18] For Vancouver: VDUS is comprised of two merged cohorts, the Vancouver Injection Drug Users Study (VIDUS) and the At-Risk Youth Study (ARYS). Inclusion criteria for the VIDUS cohort were that participants be 18 years or older, report injection drug use in the prior month, and be HIV negative. Inclusion criteria for the ARYS cohort were that participants be between the ages of 14 and 26 at baseline, report illicit drug use in the past month, and either have experienced homelessness or accessed services aimed at aiding youth experiencing homelessness in the prior month. The other linked Vancouver based cohort, ACCESS, included participants 18 years or older at baseline, living with HIV, and reporting illicit drug use other than or in addition to cannabis in the prior month.[18] For the current study, only those who had reported a history of IDU were included for analysis. PRIMER

interviews collected data on the involvement of PWID in providing IDU initiation assistance as well as participants' self-reported socio-demographic information, substance use, incarceration history, OAT enrollment, and other related factors. Baseline PRIMER data from ECIV (n = 766), STAHR II (n = 353), and VDUS/ACCESS (n = 1,825) will be the focus for the present study. Since PRIMER involves linking distinct and pre-existing cohort studies, the baseline PRIMER data does not correspond necessarily to baseline cohort data.

Measures. All data are self-reported. For this study, the outcome of interest was reporting having recently (i.e., past 6 months) assisted at least one person with IDU initiation in the prior six months, coded dichotomously (yes/no). Independent variables of interest were chosen based on findings from published peer-reviewed PRIMER studies identifying site-specific factors associated with IDU initiation assistance provision. These include the following: age (in years)[11,12]; gender (male/female)[11–13]; years since first IDU[11]; recent IDU (yes/no)[17]; having ever assisted an IDU initiation prior to the past six months (yes/no) [17]; recent housing insecurity (yes/no: defined in Vancouver as recently experiencing homelessness; in San Diego and Tijuana defined as whether or not participants reported living in at least one of the following places in the prior 6 months: on the streets, in an abandoned building, at their place of work, in a migrant worker camp, in a vehicle, at a shooting gallery, or in a homeless shelter)[15]; having recently been stopped by law enforcement (yes/no)[13]; having recently been incarcerated (yes/no)[20]; recent enrollment in OAT (yes/no)[15–17]; recent methamphetamine injection (yes/no)[15,17]; recent speedball (heroin and cocaine combined) injection (yes/no)[15,17]; any recent non-injection use of heroin, cocaine, or methamphetamine (yes/no), as well as any non-injection use of heroin, cocaine, or methamphetamine (yes/no, for each).[12] Five individuals in the STAHR cohort identified as "Transgender," though further information on their gender identity was not recorded. In-line with past research, and due to shared vulnerabilities between the two groups,[21] these five individuals were included in the "Female" gender category for all analyses.

Statistical Analyses. For each of the three sites, modified Poisson regression models were fit to assess the relationship between identified variables and recently assisting IDU initiation. Age (by 10 year increment), gender, years since first injection, recent IDU, and history of assisting IDU initiation were chosen as control variables across all three sites. These five variables were chosen as controls because they address: 1)

demographics; 2) injection drug use behaviors; and 3) long-term history of having provided injection drug use assistance. Distinct regression models were fit to assess the relationship between each identified factor and their relationship with providing IDU initiation assistance, controlling for the five noted variables. Models assessing recent methamphetamine IDU and recent speedball IDU did not include recent IDU as a control variable to protect from the effects of confounding.

The modified Poisson regression returns log-relative risk point estimates, which we presented as relative risks.[22] Given recent publications aimed at predictive modelling of population patterns of IDU initiation,[17,23] we determined that calculating relative risks (as opposed to using logistic regression to calculate odds ratios) would provide greater utility to future modelling efforts while still applying appropriate statistical rigor. This is because the modified Poisson regression with robust variance estimation (i.e., a "sandwich" estimator) provides a statistically consistent estimate of relative risk and its estimation variance.[22] The modified Poisson regression model is preferable to the use of logistic regression where an estimate of relative risk is sought, as logistic regression does not provide an unbiased estimation of relative risk except in the special case of case-control studies.[24]

Once modified Poisson models were fit, a meta-analytic approach using participant data from across all sites was used to assess heterogeneity and to compute pooled relative risks for each predictor. This is consistent with the definitions laid out by Blettner et al.,[25] where meta-analysis is used to assess site heterogeneity and compute pooled relative risks. This approach was preferable to pooling data from all three sites into a single model because each of the parent studies was designed and implemented independent of each other with separate protocols which may have led to variations in population sampling and covariate data collection for PRIMER. Specifically, log-relative risks extracted from the modified Poisson regression models were assessed for heterogeneity using a restricted maximum-likelihood estimator and pooled by fitting linear random effects models, applying log-standard errors to establish study weight. Higgins I^2 were generated to assess site heterogeneity for each variable (excluding those included in a syringe-related risk behavior subanalysis restricted to data from participants in San Diego and Tijuana, as outlined below).[26] I^2 presents the percentage of estimated

variance that can be attributed to site heterogeneity; an I^2 of 0% indicates that the differences across study are explained entirely by sampling error, while an I^2 of 100% indicates that the differences across study are explained entirely by site heterogeneity. All analyses were performed in R, with meta-analysis performed by applying the *rma* function in the *metafor* package.[27]

We present the results stratified by whether a given variable's association with providing IDU initiation assistance was homogenous or heterogenous across site. Due to low power to assess heterogeneity, and to ensure conservative thresholds of hetereogeneity, variables with an I^2 greater than 0% are presented as heterogenous. We assessed associations as homogeneous if they were in the same direction across all three sites (given the absence of tests to assess homogeneity). For all variables, we present site-specific and pooled relative risks along with their respective confidence intervals, p-values, and I^2 values.

Subanalysis: The association between IDU risk behaviors and IDU initiation assistance across sites. IDU-related risk behaviors were assessed in San Diego and Tijuana, but not Vancouver, as a result of limited data access. These behaviors were: recently providing a used syringe to another person to inject with (yes/no); recently injecting with a used syringe (yes/no); recently injecting shared drugs via frontloading or backloading (i.e. when drugs are divvied out between PWID by using one syringe to fill another syringe; yes/no); and, recently sharing drug preparation equipment (such as cookers, water, or cotton swabs) prior to IDU (yes/no). In addition to these four categorical variables, an IDU-related risk score, ranging from 0-4, was calculated by summing together all positive responses to the four IDU-related risk behavior variables, in line with previous studies.[28] The same meta-analytic approach as described above was used to calculate site-specific and pooled relative risks, though we do not present an assessment of site heterogeneity for the subanalysis.

Results Evaluation Framework. Consistent with emerging statistical recommendations in the field calling for an end to reliance on brightline significance testing,[29–31] we opt to report study findings by applying the Post-Significance Communication Structure (POCS).[32] Instead of relying on null hypothesis significance testing to evaluate study findings, through POCS we make an evaluation of point estimates, confidence intervals, and corresponding *p*-values in relation to the underlying scientific questions to make study conclusions.[32] As such,

we consider *p*-values as continuous rather than dichotomous variables and refrain from denoting significance based on a bright-line value, α.

Patient and Public Involvement. Neither patients nor the public were involved in the design, conduct, reporting, or dissemination plans of our research. The full protocol of the PRIMER study has been described elsewhere.[18]

Results

Participant Characteristics

Overall, 766, 353, and 1,825 participants contributed data for this study from Tijuana, San Diego, and Vancouver, respectively (total *n* = 2,944; see **Table 1**). Of these participants, 41 (5.4%), 18 (5.1%), and 88 (4.8%) reported recently providing IDU initiation assistance, respective to each site (total *n* = 147; 4.9%). Average age of participants was 40 years old in Tijuana (Interquartile Range [IQR]: 34-47), 47 years old in San Diego (IQR: 38-55), and 42 years old in Vancouver (IQR: 31-53). Those reporting recently assisting IDU initiation in Vancouver were, on average, younger (32 years old, IQR: 23-40), which is potentially explained by the inclusion of young adults (ages 14-26) in the VDUS cohort. Recent IDU prevalence ranged by site (86% in Tijuana, 65% in San Diego, 67% in Vancouver). Of those reporting recently assisting IDU initiation, however, 93% in Tijuana, 94% in San Diego, and 97% (in Vancouver) reported recent IDU. While most participants reported never having assisted IDU initiation prior to the past six months (87% in Tijuana, 66% in San Diego, 79% in Vancouver), approximately half of those who provided recent assistance had a history of doing so (46% in Tijuana, 56% in San Diego, 60% in Vancouver).

<<Table 1>>

While a minority of participants reported recent housing insecurity across site (17% in Tijuana, 26% in San Diego, and 27% in Vancouver), a greater proportion of those who had recently assisted IDU initiation reported housing insecurity (24% in Tijuana, 33% in San Diego, and 42% in Vancouver). Similarly, a greater proportion of those who had recently assisted IDU initiation reported recently being stopped by law enforcement (63% in Tijuana, 61% in San Diego, 65% in Vancouver) as compared to those who had not (45% in Tijuana, 46%

in San Diego, 37% in Vancouver). A minority of participants reported recent incarceration (27% in Tijuana, 21% in San Diego, 9% in Vancouver) and, of those reporting recently assisting IDU initiation, 22% in Tijuana, 39% in San Diego, and 14% in Vancouver reported recent incarceration. Only 3% of participants in Tijuana reported recent enrollment in OAT, likely reflective of lack of access to available services in the region, though OAT enrollment was higher in both San Diego (20%) and Vancouver (49%). Pf those reporting recently assisting IDU initiation, only 6% in San Diego and 35% in Vancouver reported recent OAT enrollment.

Homogeneity Across Sites in Reporting Recently Providing IDU Initiation Assistance

Having not recently injected drugs was associated with at least a 36% reduced likelihood of having recently assisted IDU initiation across all three sites (Pooled Relative Risk [pRR]: 0.21, 95% Confidence Interval [CI]: 0.07-0.64, see **Table 2**). Similarly, strong evidence across all three sites indicated that having a history of assisting IDU initiation increased the likelihood of recently assisting initiation by at least 249% (pRR: 4.83, 95% CI: 3.49-6.66). Identifying as male was associated with an increased likelihood of recently assisting initiation, though the point estimate of the pooled effect and the range of the confidence interval (pRR: 1.29, 95% CI: 0.93-1.79) indicate that male gender may be associated with a 7% decrease up to a 79% increase in likelihood of recently assisting IDU initiation. Being recently stopped by law enforcement was associated with an 8% to 107% increased likelihood of having recently assisted initiation across all three sites (pRR: 1.49, 95% CI: 1.08-2.07). Evidence across sites indicated that recent methamphetamine IDU (pRR: 2.77, 95% CI: 1.92-3.98) and recent speedball IDU (pRR: 2.11, 95% CI: 1.35-3.31) were associated with a higher likelihood of having recently assisted initiation. Recent non-injection drug use (heroin, cocaine, and/or methamphetamine) was associated with an increased likelihood of assisting IDU initiations, though the pooled effect and confidence interval (pRR: 1.30, 95% CI: 0.93-1.81) indicate that recent non-IDU may be associated with a 7% decrease up to an 81% increase in the likelihood of recently assisting IDU initiation.

<<**Table 2>>**

Heterogeneity Across Site in Reporting Recently Providing IDU Initiation Assistance

The association of age with recently assisting initiation was heterogenous across site (I^2=51.73%). Specifically, a 10-year increase in age being associated with a decreased likelihood of recently assisting in both Tijuana (RR: 0.54, 95% CI: 0.31-0.90) and Vancouver (RR: 0.66, 95% CI: 0.43-0.90), while the direction of effect could not be confidently determined for San Diego (RR: 1.02, 95% CI: 0.96-1.08). The association of years since first injection and recently assisting initiation was barely heterogenous across site (I^2=0.20%), though the direction of effect could not be confidently determined for any of the three sites. The effect of housing insecurity was also heterogeneous across site (I^2=40.11%). In Tijuana, while recent housing insecurity was associated with between a 14% decrease to a 233% increase in likelihood (RR: 1.69, 95% CI: 0.86-3.33), the existence and direction of effect could not be determined for San Diego (RR: 1.25, 95% CI: 0.46-3.38) or Vancouver (RR: 0.84, 95% CI: 0.56-1.29). Additionally, the association of recent incarceration and recently assisting initiation was heterogenous across site (I^2=56.99%), with evidence that the risk associated with recent incarceration on having recently assisted in San Diego could range from having no impact to a 478% increase in the likelihood of recently assisting IDU initiation (RR: 2.40, 95% CI: 1.00-5.78). While the direction of the effect of recent IDU on assisting IDU initiation was consistent across site, we found the magnitude of effect to be heterogenous across site (I^2=50.40%). This is likely because not recently injecting had a weaker inverse association with assisting initiation in Tijuana (RR: 0.52) compared with San Diego (RR: 0.14) and Vancouver (RR: 0.11). The association of recent non-injection heroin use with recently assisting IDU initiation was heterogenous across site (I^2=78.36%); in Tijuana, the increased likelihood of recently assisting initiation in Tijuana associated with this factor ranged from 28% to 381% (RR: 2.49, 95% CI: 1.28-4.81).

Risk Behavior Sub-Analysis of San Diego and Tijuana

The effect of recent IDU-related risk behaviors was assessed for the Tijuana and San Diego cohorts only (see **Table 1**). Across both sites, strong evidence indicated that recent piggybacking (sharing drugs via front- or back-loading) (pRR: 1.98, 95%CI: 1.10-3.55) and recently sharing IDU preparation equipment (i.e., cookers, cotton, water) (pRR: 2.44, 95%CI: 1.18-5.02) were associated with an increased likelihood of recently assisting initiation. As above, a risk score, between 0 and 4, was calculated for each participant by summing the number

of risk behaviors participants indicated they had recently performed. Across both sites, an increased score was associated with a 23% to 48% increase likelihood of recently assisting initiation (pRR: 1.23, 95%CI: 1.02-1.48).

Discussion

This is the first study to pool findings across distinct cohort studies to assess factors associated with IDU initiation events. The findings presented indicate that, like other dynamic population-level health phenomena such as infectious disease epidemics, the dissemination of IDU initiation assistance across vulnerable populations is driven by both shared and setting-specific factors. For example, we found that a history of assisting IDU initiation, recently being stopped by law enforcement, and recent methamphetamine and speedball injection were associated with an increased likelihood of recently assisting IDU initiation across all three sites. Further, we found that reporting abstinence from recent IDU and recent OAT enrollment were associated with a decreased likelihood of assisting IDU initiation across all three sites. These results have implications for efforts to prevent or delay transitions to IDU and other injection-related harms, in a range of sociocultural and geographic settings.

The current study highlights the considerable heterogeneity in the influence of factors on recently assisting IDU initiation—including recent non-injection heroin and cocaine use, recent incarceration, and recent housing insecurity—which we found were influential in only specific settings. For example, recent non-injection heroin use was positively associated with recently assisting IDU initiation in Tijuana but, within the study sample in San Diego (a contiguous metropolitan setting), was negatively associated with recently assisting. This may be explained by a historically high geographic concentration of non-injection drug use and IDU in the Tijuana River canal, where up to 1,000 people were recently believed to have resided,[33] whereas San Diego does not have a location with a similarly dense concentration of PWID and people who use drugs (PWUD) through other routes of administration cohabitating. Thus, we may consider one source of site-specific heterogeneity as the presence of geographically concentrated public injecting such as that found both in the Tijuana River canal and Vancouver's Downtown Eastside neighborhood, which has a disproportionately dense and stable population of PWID.[33,34] Locations with higher concentrations of public IDU may facilitate interactions between PWID and injection-naïve PWUD and thereby increase the likelihood of IDU initiation assistance occurring.[35,36] However,

future research is required to further examine the factors that may explain site-specific outcomes. In the case of public IDU, we hypothesize that a threshold for visibility may exist (i.e., a sufficient number of injection-naïve individuals observing IDU events) beyond which the provision of IDU initiation assistance by observed PWID becomes more likely.

This study implies directions for future research and interventions aimed at disrupting IDU transition events and related harms. Break the Cycle (BTC) and the adapted Change the Cycle, for example, are behavioral interventions aimed at reducing the likelihood that PWID assist IDU initiation in the future.[37,38] The interventions use motivational interviewing, role playing, and resource education to empower PWID to not assist IDU initiation.[37,38] Recent preliminary evidence from New York City, USA and Tallinn, Estonia[38] as well as Toronto, Canada[37] indicate potential efficacy of this program. Our findings indicate that, across settings, engaging current PWID who inject methamphetamine and/or speedball, are not enrolled in OAT, and/or with a history of assisting IDU initiation may lead to improved efficacy of BTC. Further, they indicate that factors such as incarceration and housing insecurity should be incorporated into sampling strategies on a context-specific basis.

With respect to other interventional approaches, we found that recent OAT enrollment is associated with a decreased likelihood of assisting IDU initiation, even though we had insufficient power to assess the direction and magnitude of this relationship in Tijuana (as only 3% of our Tijuana sample reported recent OAT enrollment). This is likely explained in large part by the lack of available OAT treatment in Tijuana, the prohibitive cost of OAT,[39] stigma related to OAT,[33] as well as restrictions on OAT provision,[40] and suggests a critical limitation of the use of OAT in under-resourced settings as a mode to reduce IDU initiation assistance among PWID. This is in juxtaposition to US and Canadian settings, where policies promoting a highly regulated expansion of OAT services in response to the current opioid crisis continue to expand.[41] It is noteworthy, though, that OAT regulatory environments in the US (which are stricter and controlled by federal policy) and Canada (which are more relaxed and subject to provincial policy),[41] create unique contexts which may influence the efficacy and collateral health effects of OAT on the incidence of IDU initiation assistance provision. It is clear that future

research that seeks to assess the potential use of OAT as an IDU initiation prevention intervention in other contexts must account for setting-specific policies surrounding the provision of substance use treatment.[42]

Limitations

This study has limitations inherent to exploratory analysis of observational data from multiple distinct cohort studies. For instance, our ability to assess heterogeneity between sites was limited by two factors: limited statistical power to analyze site-specific data (particularly for Tijuana and San Diego); and the limited number of sites (n = 3) from which we pooled data. These findings must therefore be interpreted in light of this uncertainty. In particular, because of the low power that we have to detect heterogeneity we can be confident in the presence of heterogeneity among those variables identified as such given the magnitude of heterogeneity required to generate signal. We also caution that an I^2 of 0% for a given factor does not mean that that factor is homogenous across sites, but, more likely, that we were not powered to detect heterogeneity.

In addition, this study has limitations that are typical of observational cross-sectional research. For example, non-probability sampling was employed, and thus the participants sampled may not be representative of the broader PWID population in each study setting. The population under study is also highly mobile and the high degree of human traffic between San Diego and Tijuana opens up the possibility that some of the IDU initiation assistance events reported by San Diego participants may have occurred in Tijuana, and vice versa. Furthermore, providing IDU initiation assistance is highly stigmatized and sensitive in nature.[43] As a result, relying on self-report within the current study likely led to underreporting of this behavior. If patterns of underreporting are not explained by the factors explored in this study, this bias would likely skew results towards the null. Further research is needed to determine if underreporting is explained by any of these factors.

Conclusion

The current study is the first to pool cross-national data to assess commonality and heterogeneity in factors influencing IDU initiation assistance provision across distinct settings. These findings can inform interventions and policies seeking to prevent IDU initiation across distinct sociocultural contexts. Furthermore, our results

imply that interventions targeting transitions into IDU and injection-related harms will need to move past a "one size fits all" approach and be adapted to address unique factors specific to each geographic and sociocultural context.

References

1. United States Department of Health and Human Services. What is the U.S. Overdose Crisis? https://www.hhs.gov/opioids/about-the-epidemic/index.html. Published 2019.
2. National Institute on Drug Abuse. Opioid Overdose Crisis. https://www.drugabuse.gov/drugs-abuse/opioids/opioid-overdose-crisis. Published 2019. Accessed March 12, 2019.
3. Haskins J. Suicide, opioids tied to ongoing fall in US life expectancy: Third year of drop. *Nation's Heal*. 2019;49(1):1 LP - 10.
4. Degenhardt L, Peacock A, Colledge S, et al. Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. *Lancet Glob Heal*. 2017;5(12):e1192-e1207. doi:10.1016/S2214-109X(17)30375-3
5. Colledge S, Peacock A, Leung J, et al. The prevalence of non-fatal overdose among people who inject drugs: A multi-stage systematic review and meta-analysis. *Int J Drug Policy*. 2019;73:172-184. doi:10.1016/j.drugpo.2019.07.030
6. 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):258-267. doi:10.1007/s10900-010-9231-z
7. Garfein RS, Doherty MC, Monterroso ER, Thomas DL, Nelson KE, Vlahov D. Prevalence and Incidence of Hepatitis C Virus Infection Among Young Adult Injection Drug Users. *JAIDS J Acquir Immune Defic Syndr*. 1998;18.
8. Werb D, Buxton J, Shoveller J, Richardson C, Rowell G, Wood E. Interventions to prevent the initiation of injection drug use: A systematic review. *Drug Alcohol Depend*. 2013;133(2):669-676. doi:10.1016/j.drugalcdep.2013.08.017
9. Vlahov D, Fuller CM, Ompad DC, Galea S, Jarlais DC Des. Updating the Infection Risk Reduction Hierarchy : Preventing Transition into Injection. *J Urban Health*. 2004;81(1):14-19.
10. Gicquelais RE, Werb D, Marks C, et al. Prevalence and Correlates of Providing and Receiving Assistance with the Transition to Injection Drug Use. *Epidemiol Rev*. 2020;In Press.
11. Meyers SA, Scheim A, Jain S, et al. Gender differences in the provision of injection initiation assistance: A comparison of three North American cities. *Harm Reduct J*. 2018;(Under Rev.
12. Ben Hamida A, Rafful C, Jain S, et al. Non-injection Drug Use and Injection Initiation Assistance among People Who Inject Drugs in Tijuana, Mexico. *J Urban Heal*. 2018;95(1):83-90. doi:10.1007/s11524-017-0188-4
13. Melo JS, Garfein RS, Hayashi K, et al. Do law enforcement interactions reduce the initiation of injection drug use? An investigation in three North American settings. *Drug Alcohol Depend*. 2018;182(24):67-73. doi:10.1016/j.drugalcdep.2017.10.009

14. Bouck Z, Jain S, Sun X, Milloy M-J, Werb D, Hayashi K. Recent incarceration and risk of first-time injection initiation assistance: A prospective cohort study of persons who inject drugs. *Drug Alcohol Depend*. 2020;212:107983. doi:10.1016/j.drugalcdep.2020.107983

15. Mittal ML, Jain S, Sun S, et al. Opioid agonist treatment and the process of injection drug use initiation. *Drug Alcohol Depend*. 2019;197(January):354-360. doi:10.1016/j.drugalcdep.2018.12.018

16. Mittal ML, Vashishtha D, Sun S, et al. History of medication-assisted treatment and its association with initiating others into injection drug use in San Diego, CA. *Subst Abuse Treat Prev Policy*. 2017;12(42). doi:10.1186/s13011-017-0126-1

17. Marks C, Borquez A, Jain S, et al. Opioid agonist treatment scale-up and the initiation of injection drug use: A dynamic modeling analysis. Tsai AC, ed. *PLOS Med*. 2019;16(11):e1002973. doi:10.1371/journal.pmed.1002973

18. Werb D, Garfein R, Kerr T, et al. A socio-structural approach to preventing injection drug use initiation: rationale for the PRIMER study. *Harm Reduct J*. 2016;13(25). doi:10.1186/s12954-016-0114-1

19. Robertson AM, Garfein RS, Wagner KD, et al. Evaluating the impact of Mexico's drug policy reforms on people who inject drugs in Tijuana, B.C., Mexico, and San Diego, CA, United States: a binational mixed methods research agenda. *Harm Reduct J*. 2014;11(4). doi:10.1186/1477-7517-11-4

20. Rafful C, Melo J, Medina-Mora ME, et al. Cross-Border Migration and Initiation of Others into Drug Injecting in Tijuana, Mexico. *Drug Alcohol Rev*. 2018;37(3):S277-S284. doi:10.1111/dar.12630

21. Shannon K, Kerr T, Strathdee SA, Shoveller J, Montaner JS, Tyndall MW. Prevalence and structural correlates of gender based violence among a prospective cohort of female sex workers. *BMJ*. 2009;339:b2939-b2939. doi:10.1136/bmj.b2939

22. Zou G. A Modified Poisson Regression Approach to Prospective Studies with Binary Data. *Am J Epidemiol*. 2004;159(7):702-706. doi:10.1093/aje/kwh090

23. Tan J, Altice FL, Madden LM, Zelenev A. Effect of expanding opioid agonist therapies on the HIV epidemic and mortality in Ukraine: a modelling study. *Lancet HIV*. December 2019. doi:10.1016/S2352-3018(19)30373-X

24. Knol MJ, Le Cessie S, Algra A, Vandenbroucke JP, Groenwold RHH. Overestimation of risk ratios by odds ratios in trials and cohort studies: alternatives to logistic regression. *Can Med Assoc J*. 2012;184(8):895-899. doi:10.1503/cmaj.101715

25. Blettner M, Sauerbrei W, Schlehofer B, Scheuchenpflug T, Friedenreich C. Traditional reviews, meta-analyses and pooled analyses in epidemiology. *Int J Epidemiol*. 1999;28(1):1-9. doi:10.1093/ije/28.1.1

26. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558. doi:10.1002/sim.1186

27. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. *J Stat Softw*. 2010;36(3). doi:10.18637/jss.v036.i03

28. Rafful C, Jain S, Sun X, et al. Identification of a Syndemic of Blood-Borne Disease Transmission and Injection Drug Use Initiation at the US–Mexico Border. *JAIDS J Acquir Immune Defic Syndr*. 2018;79(5):559-565. doi:10.1097/QAI.0000000000001858

29. Wasserstein RL, Schirm AL, Lazar NA. Moving to a World Beyond " p < 0.05." *Am Stat*. 2019;73(sup1):1-19. doi:10.1080/00031305.2019.1583913

30. Hurlbert SH, Levine RA, Utts J. Coup de Grâce for a Tough Old Bull: "Statistically Significant" Expires.

Am Stat. 2019;73(sup1):352-357. doi:10.1080/00031305.2018.1543616

31. Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. *Nature*. 2019;567(7748):305-307. doi:10.1038/d41586-019-00857-9

32. Cummins KM, Marks C. Farewell to Bright-Line: A Guide to Reporting Quantitative Results Without the S-Word. *Front Psychol*. 2020;11. doi:10.3389/fpsyg.2020.00815

33. Rafful C, Medina-Mora ME, González-Zúñiga P, et al. "Somebody Is Gonna Be Hurt": Involuntary Drug Treatment in Mexico. *Med Anthropol*. May 2019:1-14. doi:10.1080/01459740.2019.1609470

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 Alcohol Depend*. 2013;132(3):486-490. doi:10.1016/j.drugalcdep.2013.03.011

35. Tobin KE, Davey-Rothwell M, Latkin CA. Social-Level Correlates of Shooting Gallery Attendance: A Focus on Networks and Norms. *AIDS Behav*. 2010;14(5):1142-1148. doi:10.1007/s10461-010-9670-7

36. Mazhnaya A, Tobin KE, Owczarzak J. Association between injection in public places and HIV/HCV risk behavior among people who use drugs in Ukraine. *Drug Alcohol Depend*. 2018;189:125-130. doi:10.1016/j.drugalcdep.2018.04.036

37. Strike C, Rotondi M, Kolla G, et al. Interrupting the social processes linked with initiation of injection drug use: Results from a pilot study. *Drug Alcohol Depend*. 2014;137:48-54. doi:10.1016/j.drugalcdep.2014.01.004

38. Des Jarlais D, Uuskula A, Talu A, et al. Implementing an Updated "Break the Cycle" Intervention to Reduce Initiating Persons into Injecting Drug Use in an Eastern European and a US "opioid epidemic" Setting. *AIDS Behav*. 2019;23(9):2304-2314. doi:10.1007/s10461-019-02467-y

39. Burgos JL, Cepeda JA, Kahn JG, et al. Cost of provision of opioid substitution therapy provision in Tijuana, Mexico. *Harm Reduct J*. 2018;15(1):28. doi:10.1186/s12954-018-0234-x

40. Goodman-Meza D, Medina-Mora ME, Magis-Rodríguez C, Landovitz RJ, Shoptaw S, Werb D. Where Is the Opioid Use Epidemic in Mexico? A Cautionary Tale for Policymakers South of the US–Mexico Border. *Am J Public Health*. 2019;109(1):73-82. doi:10.2105/AJPH.2018.304767

41. Priest KC, Gorfinkel L, Klimas J, Jones AA, Fairbairn N, McCarty D. Comparing Canadian and United States opioid agonist therapy policies. *Int J Drug Policy*. 2019;74:257-265. doi:10.1016/j.drugpo.2019.01.020

42. Vashishtha D, Mittal ML, Werb D. The North American opioid epidemic: current challenges and a call for treatment as prevention. *Harm Reduct J*. 2017;14(7). doi:10.1186/s12954-017-0135-4

43. Guise A, Horyniak D, Melo J, McNeil R, Werb D. The experience of initiating injection drug use and its social context: a qualitative systematic review and thematic synthesis. *Addiction*. 2017;112(12):2098-2111. doi:10.1111/add.13957

Table 1. Recent Injection Initiation Assistance Provision and Related Factors Among People Who Inject Drugs in San Diego, USA; Tijuana, Mexico; and Vancouver, Canada, 2014-2018 (n = 2,944)

Variable	Tijuana		San Diego		Vancouver	
	Did not recently assist injection initiation (n=725)	Recently assisted injection initiation (n=41)	Did not recently assist injection initiation (n=335)	Recently assisted injection initiation (n=18)	Did not recently assist injection initiation (n=1737)	Recently assisted injection initiation (n=88)
Age (mean (SD))	40.72 (9.13)	38.25 (8.10)	46.87 (11.19)	46.61 (12.70)	42.86 (12.64)	32.44 (10.65)
Gender						
Female	289 (39.9)	12 (29.3)	94 (28.1)	4 (22.2)	657 (37.9)	31 (35.6)
Male	436 (60.1)	29 (70.7)	234 (70.3)	14 (77.8)	1078 (62.1)	56 (64.4)
Transgender	0 (0.0)	0 (0.0)	5 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Years Since First Injection (mean (SD))	19.68 (9.97)	19.23 (8.85)	23.98 (13.19)	23.06 (12.53)	21.05 (13.50)	12.06 (10.60)
Recent Active IDU						
Yes	625 (86.2)	38 (92.7)	231 (69.0)	17 (94.4)	1133 (65.2)	85 (96.6)
No	100 (13.8)	3 (7.3)	104 (31.0)	1 (5.6)	604 (34.8)	3 (3.4)
History of Having Assisted IDU Initiation						
No	645 (89.0)	22 (53.7)	222 (66.3)	8 (44.4)	1399 (80.5)	35 (39.8)
Yes	80 (11.0)	19 (46.3)	113 (33.7)	10 (55.6)	338 (19.5)	53 (60.2)
Recent Housing Insecurity						
No	605 (83.4)	31 (75.6)	250 (74.6)	12 (66.7)	1287 (74.1)	51 (58.0)
Yes	120 (16.6)	10 (24.4)	85 (25.4)	6 (33.3)	449 (25.9)	37 (42.0)
Recently Stopped by Law Enforcement						
No	397 (54.8)	15 (36.6)	182 (54.3)	7 (38.9)	1097 (63.2)	31 (35.2)
Yes	328 (45.2)	26 (63.4)	153 (45.7)	11 (61.1)	640 (36.8)	57 (64.8)
Recently Incarcerated						
No	532 (73.4)	32 (78.0)	267 (79.7)	11 (61.1)	1584 (91.6)	76 (86.4)
Yes	193 (26.6)	9 (22.0)	68 (20.3)	7 (38.9)	146 (8.4)	12 (13.6)
Recent OAT Enrollment						
No	704 (97.1)	40 (97.6)	267 (79.7)	17 (94.4)	873 (50.3)	57 (64.8)
Yes	21 (2.9)	1 (2.4)	68 (20.3)	1 (5.6)	864 (49.7)	31 (35.2)
Recent Methamphetamine Injection						
No	617 (85.1)	27 (65.9)	183 (54.6)	6 (33.3)	1147 (66.0)	20 (22.7)
Yes	108 (14.9)	14 (34.1)	152 (45.4)	12 (66.7)	590 (34.0)	68 (77.3)
Recent Speedball Injection						
No	703 (97.0)	38 (92.7)	314 (93.7)	16 (88.9)	1626 (93.6)	74 (84.1)
Yes	22 (3.0)	3 (7.3)	21 (6.3)	2 (11.1)	111 (6.4)	14 (15.9)
Recent Non-Injection Use of Heroin, Cocaine, or Methamphetamine						
No	419 (57.8)	17 (41.5)	108 (32.2)	3 (16.7)	758 (43.6)	28 (31.8)
Yes	306 (42.2)	24 (58.5)	227 (67.8)	15 (83.3)	979 (56.4)	60 (68.2)
Recent Non-Injection Use of Heroin						
No	665 (91.7)	33 (80.5)	258 (77.0)	16 (88.9)	1494 (86.0)	64 (72.7)
Yes	60 (8.3)	8 (19.5)	77 (23.0)	2 (11.1)	243 (14.0)	24 (27.3)
Recent Non-Injection Use of Methamphetamine						
No	441 (60.8)	18 (43.9)	127 (37.9)	5 (27.8)	1256 (72.3)	45 (51.1)

Yes	284 (39.2)	23 (56.1)	208 (62.1)	13 (72.2)	481 (27.7)	43 (48.9)
Recent Non-Injection Use of Cocaine						
No	693 (95.6)	35 (85.4)	286 (85.4)	15 (83.3)	1013 (58.3)	44 (50.0)
Yes	32 (4.4)	6 (14.6)	49 (14.6)	3 (16.7)	724 (41.7)	44 (50.0)
Risk Behaviors Sub-Analysis						
Recent Risk Behaviors: Gave Used Syringe To Other PWID						
No	288 (40.7)	12 (29.3)	237 (71.0)	9 (50.0)	--	--
Yes	419 (59.3)	29 (70.7)	97 (29.0)	9 (50.0)	--	--
Injected with Used Syringe						
No	293 (41.4)	12 (29.3)	213 (67.6)	7 (38.9)	--	--
Yes	414 (58.6)	29 (70.7)	102 (32.4)	11 (61.1)	--	--
Front- or Back-Loaded						
No	288 (40.7)	11 (26.8)	231 (69.0)	6 (33.3)	--	--
Yes	419 (59.3)	30 (73.2)	104 (31.0)	12 (66.7)	--	--
Shared Injection Equipment						
No	251 (35.5)	6 (14.6)	199 (59.4)	5 (27.8)	--	--
Yes	456 (64.5)	35 (85.4)	136 (40.6)	13 (72.2)	--	--
Recent Risk Behavior Score* (mean (SD))	2.36 (1.73)	3.00 (1.38)	1.31 (1.52)	2.50 (1.65)	--	--

*Recent Risk Behavior Score is the sum of how many of the four individual risk behaviors participants responded recently having performed, resulting in a score between 0 and 4.
SD: Standard Deviation, IDU: Injection Drug Use, PWID: People Who Inject Drugs, OAT: Opioid Agonist Treatment

Table 2. Multiple Modified Poisson Regressions and Pooled Relative Risks Assessing the Association Between Related Factors and Assisting IDU Initiation Across San Diego, USA, Tijuana, Mexico, and Vancouver, Canada, 2014-2018 (n = 2,944).

	Tijuana		San Diego		Vancouver		Pooled		I^{2****}
	RR (95%CI)*	p	RR (95%CI)	p	RR (95%CI)	p	RR (95%CI)	p	
Age (10 Year Increment)	0.54 (0.31 - 0.90)	0.028	1.22 (0.66 – 2.16)	0.597	0.66 (0.43 - 0.90)	0.023	0.74 (0.48 - 1.10)	0.116	51.73%
Gender**									
Male	1.47 (0.77-2.82)	0.243	1.41 (0.48 - 4.19)	0.532	1.21 (0.80 - 1.82)	0.368	1.29 (0.93 - 1.79)	0.131	0.00%
Years Since First Injection	1.03 (0.97-1.08)	0.309	0.98 (0.94-1.03)	0.460	0.99 (0.95-1.03)	0.588	1.00 (0.97-1.02)	0.795	0.20%
Recent Active IDU									
No	0.52 (0.17-1.57)	0.246	0.14 (0.02 - 1.02)	0.052	0.11 (0.04-0.34)	<0.001	0.21 (0.07-0.64)	0.006	50.40%
History of Having Assisted IDU Initiation									
Yes	5.4 (2.95-9.90)	<0.001	2.48 (1.00-6.19)	0.052	5.26 (3.46-8.00)	<0.001	4.83 (3.49-6.66)	<0.001	0.00%
Recent Housing Insecurity									
Yes	1.69 (0.86-3.33)	0.127	1.25 (0.46-3.38)	0.657	0.84 (0.56-1.29)	0.432	1.13 (0.70-1.83)	0.621	40.11%
Recently Stopped by Law Enforcement									
Yes	1.66 (0.91-3.03)	0.096	1.52 (0.62-3.76)	0.362	1.40 (0.91-2.16)	0.125	1.49 (1.08-2.07)	0.017	0.00%
Recently Incarcerated									
Yes	0.85 (0.41-1.77)	0.67	2.40 (1.00-5.78)	0.051	0.81 (0.44-1.47)	0.483	1.11 (0.59-2.10)	0.740	56.99%
Recently Enrolled in OAT									
Yes	1.03 (0.14 - 7.71)	0.974	0.28 (0.04 - 1.99)	0.201	0.65 (0.43 - 1.00)	0.048	0.64 (0.43-0.96)	0.032	0.00%
Recent Methamphetamine Injection***									
Yes	2.27 (1.22-4.22)	0.009	2.15 (0.81-5.72)	0.124	3.38 (2.04-5.62)	<0.001	2.77 (1.92-3.98)	<0.001	0.00%
Recent Speedball Injection***									
Yes	2.16 (0.81-5.76)	0.122	2.36 (0.47-11.96)	0.300	2.07 (1.22-3.53)	0.007	2.11 (1.35-3.31)	0.001	0.00%
Recent Non-Injection Use of Heroin, Cocaine, or Meth									
Yes	1.68 (0.90 - 3.13)	0.105	1.27 (0.32-4.96)	0.734	1.16 (0.77-1.76)	0.479	1.30 (0.93-1.81)	0.127	0.00%
Recent Non-Injection Use of Heroin									
Yes	2.49 (1.28-4.81)	0.007	0.32 (0.07-1.53)	0.152	1.16 (0.73-1.82)	0.530	1.19 (0.46-3.07)	0.726	78.36%
Recent Non-Injection Use of Methamphetamine									
Yes	1.76 (0.96-3.23)	0.067	0.93 (0.31-2.75)	0.895	1.17 (0.79-1.73)	0.435	1.28 (0.94-1.76)	0.123	0.00%
Recent Non-Injection Use Of Cocaine									
Yes	2.43 (1.08-5.44)	0.031	0.91 (0.23-3.67)	0.899	1.30 (0.88-1.91)	0.183	1.46 (0.96-2.21)	0.078	15.07%
Recent Risk Behaviors: Gave Used Syringe to Other PWID									
Yes	1.12 (0.58 - 2.17)	0.743	1.54 (0.58-4.07)	0.381	X	X	1.24 (0.72-2.14)	0.444	--
Injected with Used Syringe									
Yes	1.21 (0.58-2.56)	0.608	2.13 (0.77-5.88)	0.144	X	X	1.48 (0.81-2.69)	0.202	--
Front- or Back-Loaded									
Yes	1.67 (0.80-3.48)	0.174	2.66 (1.01-7.00)	0.048	X	X	1.98 (1.10-3.55)	0.023	--
Shared Injection Equipment									
Yes	2.71 (1.04 - 7.01)	0.04	2.12 (0.70-6.40)	0.184	X	X	2.44 (1.18-5.02)	0.016	--
Risk Behavior Score	1.18 (0.94-1.46)	0.15	1.38 (0.97-1.98)	0.074	X	X	1.23 (1.02-1.48)	0.031	--

*All models include Age, Gender, Years Since First Injection, Recent Active IDU, and History of Having Assisted IDU Initiation unless it is otherwise noted.
**For STAHR, 5 individuals identified as Transgender and were not given the option to also provide their gender indentity and were coded to be included with "Female" category
***Does not control for injection frequency
**** Describes the percentage of variability in site-specific relative risks for given factor explained by site heterogeneity as opposed to sampling error.

RR: Relative Risk, 95% CI: 95% Confidence Interval, IDU: Injection Drug Use, PWID: People Who Inject Drugs, OAT: Opioid Agonist Treatment

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6-8
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-8
		(*b*) Describe any methods used to examine subgroups and interactions	6-8
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	-
Outcome data	15*	Report numbers of outcome events or summary measures	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11

		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The Involvement of People Who Inject Drugs in Injection Initiation Events: A Cross Sectional Analysis Identifying Similarities and Differences Across Three North American Settings

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-046957.R1
Article Type:	Original research
Date Submitted by the Author:	19-Jul-2021
Complete List of Authors:	Marks, Charles; University of California San Diego, Medicine Meyers, Stephanie; University of California San Diego, Medicine Jain, Sonia; UC San Diego, Biostatistics Research Center, Herbert Wertheim School of Public Health and Human Longevity Science Sun, Xiaoying; University of California San Diego, Biostatistics Research Center, Herbert Wertheim School of Public Health and Human Longevity Science Hayashi, Kanna; Simon Fraser University, Health Sciences Gonzalez-Zuniga, Patricia; University of California San Diego, Medicine Strathdee, Steffanie; University of California San Diego, School of Medicine, Division of Infectious Disease and Global Public Health Garfein, Richard; University of California San Diego, Family Medicine and Public Health Milloy, M; British Columbia Centre on Substance Use, DeBeck, Kora; British Columbia Centre on Substance Use Cummins, Kevin; University of California San Diego, Medicine Werb, Dan; Unity Health Toronto, Centre on Drug Policy Evaluation; University of California San Diego, Division of Global Infectious Diseases and Global Public Health
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Addiction, Epidemiology, Public health
Keywords:	Substance misuse < PSYCHIATRY, PUBLIC HEALTH, EPIDEMIOLOGY, Public health < INFECTIOUS DISEASES, STATISTICS & RESEARCH METHODS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title: **The Involvement of People Who Inject Drugs in Injection Initiation Events: A Cross-Sectional Analysis Identifying Similarities and Differences Across Three North American Settings**

Charles Marks[1,2,3], Stephanie A. Meyers[1,2,3], Sonia Jain[4], Xiaoying Sun[4], Kanna Hayashi[5,6], Patricia Gonzalez-Zuniga[2], Steffanie A. Strathdee[2], Richard S. Garfein[7], M-J Milloy[6,8], Kora DeBeck[6,9], Kevin Cummins[1,2,3], Dan Werb[2,10,*]

[1] Interdisciplinary Research on Substance Use Joint Doctoral Program, San Diego State University & University of California, San Diego

[2] Department of Medicine, University of California, San Diego, USA

[3] School of Social Work, San Diego State University, USA

[4] Biostatistics Research Center, Herbert Wertheim School of Public Health and Human Longevity Science

[5] Faculty of Health Sciences, Simon Fraser University

[6] British Columbia Centre on Substance Use, Vancouver, Canada

[7] Department of Family Medicine and Public Health, University of California San Diego, La Jolla, CA, USA

[8] Department of Medicine, University of British Columbia, Vancouver, Canada

[9] School of Public Policy, Simon Fraser University, Vancouver, Canada

[10] Centre on Drug Policy Evaluation, St. Michael's Hospital, Toronto, Canada

[*] Corresponding Author: dwerb@health.ucsd.edu

Key Words: Injection drug use, injection initiation, San Diego, Tijuana, Vancouver

Tables: 2

Word Count: 4,660

Abstract

Objectives: People who inject drugs (PWID) play an integral role in facilitating the entry of others into injection drug use (IDU). We sought to assess factors influencing PWID in providing IDU initiation assistance across three distinct North American settings and to generate pooled measures of risk.

Design: We employed data from three PWID cohort studies participating in *PReventing Injecting by Modifying Existing Responses* (PRIMER), for this cross-sectional analysis.

Setting: Tijuana, Mexico; San Diego, United States; Vancouver, Canada.

Participants: A total of 2,944 participants were included in this study (Tijuana: n = 766, San Diego: n = 353, Vancouver: n = 1,825).

Measurements: The outcome was defined as recently (i.e. past 6 months) assisting in an IDU initiation event. Independent variables of interest were identified from previous PRIMER analyses. Site-specific multiple modified Poisson regressions were fit. Pooled relative risks were calculated and heterogeneity across sites was assessed via linear random effects models.

Results: Evidence across all three sites indicated that having a history of providing IDU initiation assistance (Pooled Relative Risk [pRR]: 4.83, 95% Confidence Interval [CI]: 3.49-6.66) and recently being stopped by law enforcement (pRR: 1.49, 95% CI: 1.07-2.07) were associated with a higher risk of providing assistance with IDU initiation; while recent opioid agonist treatment (OAT) enrollment (pRR: 0.64, 95% CI: 0.43-0.96) and no recent IDU (pRR: 0.21, 95% CI: 0.07-0.64) were associated with a lower risk. We identified substantial differences across site in the association of age (I^2: 52%), recent housing insecurity (I^2: 39%), and recent non-injection heroin use (I^2: 78%).

Conclusion: We identified common and site-specific factors related to PWID's risk of assisting in IDU initiation events. Individuals reporting a history of assisting IDU initiations, being recently stopped by law enforcement, and recently injecting methamphetamine/speedball were more likely to have recently assisted an IDU initiation. Whereas those who reported not recently engaging in IDU and those recently enrolled in OAT were less likely to have done so. Interventions and harm reduction strategies aimed at reducing the harms of IDU should incorporate context-specific approaches to reduce the initiation of IDU.

Word Count: 342

Strengths and Limitations of This Study

- This is the first study to assess common and differential risk factors for assisting injection drug use initiation across different geographic sites.
- By applying Zou's modified regression and extracting relative risks instead of odds ratios, the results may be readily applied to mathematical modeling studies looking at the initiation of injection drug use.
- Due to the cross-sectional nature of this study, our ability to evaluate the causal relationship between identified risk factors and assisting injection initiation is limited.
- Due to the small number of sites (three), our ability to quantiatively identify heterogeneity across sites is also limited.

Background

North America is currently facing an opioid overdose epidemic, causing the United States Department of Health and Human Services to declare a public health emergency in 2017.[1] As of January 2019, it was estimated that over 130 people died each day the previous year as a result of opioid-related overdose in the United States.[1–3] Given the increased presence of potent synthetic opioids such as fentanyl and carfentanil in illicit drug markets in North America, people who inject drugs (PWID) are exposed to a greater risk of overdose. There are an estimated 2.6M PWID in North America,[4] among whom 45% (>1M) have experienced an overdose.[5] This implies that injection drug use (IDU) is a key driver of overdose, and that **preventing IDU is key to reducing population-level overdose mortality.** PWID who practice unsafe injection drug use (IDU) are also at high risk of HIV and hepatitis B and C transmission, and are especially vulnerable to these infections within the first few years of initiating IDU.[4,6,7] Given the increase in the intensity of these risks in the months immediately after IDU initiation events, as well as the difficulty in preventing IDU-related causes of morbidity and mortality once people begin to inject, experts have suggested that efforts to prevent IDU-related harms should be focused upstream towards preventing IDU initiation.[8,9]

To that end, a large and growing evidence base has established that PWID play an integral role in the process of IDU initiation, with at least 75% of PWID across a variety of settings reporting being assisted in their IDU initiation events by another person experienced with drug injecting.[10] The *PReventing Injecting by Modifying Existing Responses* (PRIMER) study has identified a range of factors placing PWID at increased likelihood of providing IDU initiation assistance to injection-naïve individuals across differing North American contexts (Vancouver, Canada; Tijuana, Mexico; and, San Diego, United States).[8] These include age,[11] gender,[11] injection frequency, the use of particular drug types (e.g., opioids, crystal methamphetamine), non-injection drug use,[12] criminal justice system involvement,[13,14], homelessness,[15] and access to opioid agonist treatment (OAT).[16–18] While these findings reveal important similarities and differences, no effort has yet been made to pool findings across settings to assess heterogeneity in risk factors for IDU initiation assistance provision.

We therefore sought to pool findings to assess the heterogeneity of factors related to assisting IDU initiation in San Diego, Tijuana, and Vancouver in order to establish a baseline understanding of common and site-specific factors influencing the process of IDU initiation.

Methods

Setting. PRIMER is a cohort consortium study seeking to identify factors influencing the provision of IDU initiation assistance among PWID, and to investigate whether interventions to reduce HIV risk among PWID may also be effective in preventing this behavior.[19] The methods used in the PRIMER study have been previously described in full.[19] In brief, PRIMER includes quantitative data collected beginning in August 2014 from existing prospective community-recruited open cohort studies of PWID including the Proyecto El Cuete IV (ECIV) cohort (Tijuana, Mexico), the Study of Tuberculosis, AIDS, and Hepatitis C Risk (STAHR II) cohort (San Diego, US), and the linked Vancouver Drug Users Study (VDUS) and AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS). All of these cohort studies sought to investigate HIV risk behaviors among PWID living in urban settings, and ECIV and STAHR II were specifically designed as a linked binational study mechanism with highly comparable survey items.[20] ECIV inclusion criteria were that participants be 18 years or older, report IDU in the prior month, speak Spanish or English, currently be living in Tijuana with no plans to relocate, and not be participating in intervention studies.[19] STAHR II inclusion criteria were that participants be 18 years or older, report IDU in the past month, speak English or Spanish, and had no plans to move away in the next 24 months.[19] For Vancouver: VDUS is comprised of two merged cohorts, the Vancouver Injection Drug Users Study (VIDUS) and the At-Risk Youth Study (ARYS). Inclusion criteria for the VIDUS cohort were that participants be 18 years or older, report injection drug use in the prior month, and be HIV negative. Inclusion criteria for the ARYS cohort were that participants be between the ages of 14 and 26 at baseline, report illicit drug use in the past month, and either have experienced homelessness or accessed services aimed at aiding youth experiencing homelessness in the prior month. The other linked Vancouver based cohort, ACCESS, included participants 18 years or older at baseline, living with HIV, and reporting illicit drug use other than or in addition to cannabis in the prior month.[19] For the current study, only those who had reported a history of IDU were included for analysis. PRIMER

interviews collected data on the involvement of PWID in providing IDU initiation assistance as well as participants' self-reported socio-demographic information, substance use, incarceration history, OAT enrollment, and other related factors. Baseline PRIMER data collected between August 2014 and December 2016 from ECIV (n = 766), STAHR II (n = 353), and VDUS/ACCESS (n = 1,825) will be the focus for the present study. While longitudinal data was available for ECIV and VDUS/ACCESS, only cross-sectional data was available for STAHR II. As such, to maximize comparability across all three sites, we employed only baseline, cross-sectional data from each site. Since PRIMER involves linking distinct and pre-existing cohort studies, the baseline PRIMER data does not correspond necessarily to baseline cohort data.

Ethics Approval Statement. The PRIMER Study was granted ethical approval by the University of California San Diego (IRB 150866). Each study site received ethical approval from their respective institutional review boards. All participants provided consent to participate prior to enrollment in their respective cohort.

Measures. All data are self-reported and capture "recent" (defined as within the past 6 months) factors of interest. For this study, the outcome of interest was reporting having recently assisted at least one person with IDU initiation in the prior six months, coded dichotomously (yes/no). Independent variables of interest were chosen based on findings from published peer-reviewed PRIMER studies identifying site-specific factors associated with IDU initiation assistance provision. These include the following: age (in years)[11,12]; gender (male/female*)[11–13]; years since first IDU[11]; recent IDU (yes/no)[18]; having ever assisted an IDU initiation prior to the past six months (yes/no) [18]; recent housing insecurity (yes/no: defined in Vancouver as recently experiencing homelessness; in San Diego and Tijuana defined as whether or not participants reported living in at least one of the following places in the prior 6 months: on the streets, in an abandoned building, at their place of work, in a migrant worker camp, in a vehicle, at a shooting gallery, or in a homeless shelter)[16]; having recently been stopped by law enforcement (yes/no)[13]; having recently been incarcerated (yes/no)[21]; recent enrollment in OAT (yes/no)[16–18]; recent methamphetamine injection (yes/no)[16,18]; recent speedball (heroin and cocaine combined) injection (yes/no)[16,18]; any recent non-injection use of heroin, cocaine, or methamphetamine (yes/no), as well as any non-injection use of heroin, cocaine, or methamphetamine (yes/no, for each).[12] Regarding gender, across all cohorts, participants were

asked if they were "Male", "Female", or "Transgender." However, because of data sharing restrictions, we were unable to access data on all gender categories (i.e., other than "Male"/"Female") for the Vancouver cohort. Five individuals in the STAHR cohort and zero in the ECIV cohort identified as "Transgender," meaning we did not receive information about their gender identity. In-line with past research, and due to shared vulnerabilities between the two groups,[22] we opted to include those that identified as "Female" and as "Transgender" within the same group. We have opted to label this variable "Male/Female*".

Statistical Analyses. For each of the three sites, modified Poisson regression models were fit to assess the relationship between identified variables and recently assisting IDU initiation. Age (by 10 year increment), gender, years since first injection, recent IDU, and history of assisting IDU initiation were chosen as control variables across all three sites. These five variables were chosen as controls because they address: 1) demographics; 2) injection drug use behaviors; and 3) long-term history of having provided injection drug use assistance. Distinct regression models were fit to assess the relationship between each identified factor and their relationship with providing IDU initiation assistance, controlling for the five noted variables. Models assessing recent methamphetamine IDU and recent speedball IDU did not include recent IDU as a control variable to protect from the effects of confounding.

The modified Poisson regression returns log-relative risk point estimates, which we presented as relative risks.[23] Given recent publications aimed at predictive modelling of population patterns of IDU initiation,[18,24] we determined that calculating relative risks (as opposed to using logistic regression to calculate odds ratios) would provide greater utility to future modelling efforts while still applying appropriate statistical rigor. This is because the modified Poisson regression with robust variance estimation (i.e., a "sandwich" estimator) provides a statistically consistent estimate of relative risk and its estimation variance.[23] The modified Poisson regression model is preferable to the use of logistic regression where an estimate of relative risk is sought, as logistic regression does not provide an unbiased estimation of relative risk except in the special case of case-control studies.[25]

Once modified Poisson models were fit, a meta-analytic approach using participant data from across all sites was used to assess heterogeneity and to compute pooled relative risks for each predictor. This is consistent with the definitions laid out by Blettner et al.,[26] where meta-analysis is used to assess site heterogeneity and compute pooled relative risks. This approach was preferable to pooling data from all three sites into a single model because each of the parent studies was designed and implemented independent of each other with separate protocols which may have led to variations in population sampling and covariate data collection for PRIMER. Specifically, log-relative risks extracted from the modified Poisson regression models were assessed for heterogeneity using a restricted maximum-likelihood estimator and pooled by fitting linear random effects models, applying log-standard errors to establish study weight. Higgins I^2 were generated to assess site heterogeneity for each variable (excluding those included in a syringe-related risk behavior subanalysis restricted to data from participants in San Diego and Tijuana, as outlined below).[27] I^2 presents the percentage of estimated variance that can be attributed to site heterogeneity; an I^2 of 0% indicates that the differences across study are explained entirely by sampling error, while an I^2 of 100% indicates that the differences across study are explained entirely by site heterogeneity. All analyses were performed in R, with meta-analysis performed by applying the *rma* function in the *metafor* package.[28]

We present the results stratified by whether a given variable's association with providing IDU initiation assistance was homogenous or heterogenous across site. Due to low power to assess heterogeneity, and to ensure conservative thresholds of hetereogeneity, variables with an I^2 greater than 0% are presented as heterogenous. We assessed associations as homogeneous if they were in the same direction across all three sites (given the absence of tests to assess homogeneity). For all variables, we present site-specific and pooled relative risks along with their respective confidence intervals, p-values, and I^2 values.

Subanalysis: The association between IDU risk behaviors and IDU initiation assistance across sites. IDU-related risk behaviors were assessed in San Diego and Tijuana, but not Vancouver, as a result of limited data access. These behaviors were: recently providing a used syringe to another person to inject with (yes/no); recently injecting with a used syringe (yes/no); recently injecting shared drugs via frontloading or backloading (i.e. when

drugs are divvied out between PWID by using one syringe to fill another syringe; yes/no); and, recently sharing drug preparation equipment (such as cookers, water, or cotton swabs) prior to IDU (yes/no). In addition to these four categorical variables, an IDU-related risk score, ranging from 0-4, was calculated by summing together all positive responses to the four IDU-related risk behavior variables, in line with previous studies.[29] The same meta-analytic approach as described above was used to calculate site-specific and pooled relative risks, though we do not present an assessment of site heterogeneity for the subanalysis.

Results Evaluation Framework. Consistent with emerging statistical recommendations in the field calling for an end to reliance on brightline significance testing,[30–32] we opt to report study findings by applying the Post-Significance Communication Structure (POCS).[33] Instead of relying on null hypothesis significance testing to evaluate study findings, through POCS we make an evaluation of point estimates, confidence intervals, and corresponding *p*-values in relation to the underlying scientific questions to make study conclusions.[33] As such, we consider *p*-values as continuous rather than dichotomous variables and refrain from denoting significance based on a bright-line value, α.

Patient and Public Involvement. Neither patients nor the public were involved in the design, conduct, reporting, or dissemination plans of our research. The full protocol of the PRIMER study has been described elsewhere.[19]

Results

Participant Characteristics

Overall, 2,944 participants contributed data for this study from Tijuana (*n* = 766), San Diego (*n* = 353), and Vancouver (*n* = 1,825) (see **Table 1**). Of these participants, 41 (5.4%), 18 (5.1%), and 88 (4.8%) reported recently providing IDU initiation assistance, respective to each site (total *n* = 147; 4.9%). Average age of participants was 40 years old in Tijuana (Interquartile Range [IQR]: 34-47), 47 years old in San Diego (IQR: 38-55), and 42 years old in Vancouver (IQR: 31-53). Those reporting recently assisting IDU initiation in Vancouver were, on average, younger (32 years old, IQR: 23-40), which is potentially explained by the inclusion of young adults (ages 14-26) in the VDUS cohort. Recent IDU prevalence ranged by site from 86% in Tijuana to 65% in San Diego. Of those

reporting recently assisting IDU initiation, however, 93% in Tijuana, 94% in San Diego, and 97% in Vancouver reported recent IDU. While most participants reported never having assisted IDU initiation prior to the past six months, approximately half of those who provided recent assistance had a history of doing so.

<<Table 1>>

While a minority of participants reported recent housing insecurity across site, a greater proportion of those who had recently assisted IDU initiation reported housing insecurity. Similarly, a greater proportion of those who had recently assisted IDU initiation reported recently being stopped by law enforcement as compared to those who had not. A minority of participants reported recent incarceration, ranging from 9% in Vancouver to 27% in Tijuana. Only 3% of participants in Tijuana reported recent enrollment in OAT, likely reflective of lack of access to available services in the region, though OAT enrollment was higher in both San Diego (20%) and Vancouver (49%). Of those reporting recently assisting IDU initiation, only 6% in San Diego and 35% in Vancouver reported recent OAT enrollment.

Homogeneity Across Sites in Reporting Recently Providing IDU Initiation Assistance

Compared to reporting recent IDU, reporting no recent IDU was associated with at least a 36% reduced likelihood of having recently assisted IDU initiation across all three sites (Pooled Relative Risk [pRR]: 0.21, 95% Confidence Interval [CI]: 0.07-0.64, see **Table 2**). Similarly, strong evidence across all three sites indicated that having a history of assisting IDU initiation increased the likelihood of recently assisting initiation by at least 249% (pRR: 4.83, 95% CI: 3.49-6.66). Identifying as male was associated with an increased likelihood of recently assisting initiation, though the point estimate of the pooled effect and the range of the confidence interval (pRR: 1.29, 95% CI: 0.93-1.79) indicate that male gender may be associated with a 7% decrease up to a 79% increase in likelihood of recently assisting IDU initiation. Being recently stopped by law enforcement was associated with an 8% to 107% increased likelihood of having recently assisted initiation across all three sites (pRR: 1.49, 95% CI: 1.08-2.07). Evidence across sites indicated that recent methamphetamine IDU (pRR: 2.77, 95% CI: 1.92-3.98) and recent speedball IDU (pRR: 2.11, 95% CI: 1.35-3.31) were associated with a higher likelihood of having

recently assisted initiation. Recent non-injection drug use (heroin, cocaine, and/or methamphetamine) was associated with an increased likelihood of assisting IDU initiations, though the pooled effect and confidence interval (pRR: 1.30, 95% CI: 0.93-1.81) indicate that recent non-IDU may be associated with a 7% decrease up to an 81% increase in the likelihood of recently assisting IDU initiation.

<<**Table 2**>>

Heterogeneity Across Site in Reporting Recently Providing IDU Initiation Assistance

The association of age with recently assisting initiation was heterogenous across site (I^2=51.73%). Specifically, a 10-year increase in age being associated with a decreased likelihood of recently assisting in both Tijuana (RR: 0.54, 95% CI: 0.31-0.90) and Vancouver (RR: 0.66, 95% CI: 0.43-0.90), while the direction of effect could not be confidently determined for San Diego (RR: 1.02, 95% CI: 0.96-1.08). The association of years since first injection and recently assisting initiation was barely heterogenous across site (I^2=0.20%), though the direction of effect could not be confidently determined for any of the three sites. The effect of housing insecurity was also heterogeneous across site (I^2=40.11%). In Tijuana, while recent housing insecurity was associated with between a 14% decrease to a 233% increase in likelihood (RR: 1.69, 95% CI: 0.86-3.33), the existence and direction of effect could not be determined for San Diego (RR: 1.25, 95% CI: 0.46-3.38) or Vancouver (RR: 0.84, 95% CI: 0.56-1.29). Additionally, the association of recent incarceration and recently assisting initiation was heterogenous across site (I^2=56.99%), with evidence that the risk associated with recent incarceration on having recently assisted in San Diego could range from having no impact to a 478% increase in the likelihood of recently assisting IDU initiation (RR: 2.40, 95% CI: 1.00-5.78). While the direction of the effect of recent IDU on assisting IDU initiation was consistent across site, we found the magnitude of effect to be heterogenous across site (I^2=50.40%). This is likely because not recently injecting had a weaker inverse association with assisting initiation in Tijuana (RR: 0.52) compared with San Diego (RR: 0.14) and Vancouver (RR: 0.11). The association of recent non-injection heroin use with recently assisting IDU initiation was heterogenous across site (I^2=78.36%); in Tijuana, the increased likelihood of recently assisting initiation in Tijuana associated with this factor ranged from 28% to 381% (RR: 2.49, 95% CI: 1.28-4.81).

Risk Behavior Sub-Analysis of San Diego and Tijuana

The effect of recent IDU-related risk behaviors was assessed for the Tijuana and San Diego cohorts only (see **Table 1**). Across both sites, strong evidence indicated that recent piggybacking (sharing drugs via front- or back-loading) (pRR: 1.98, 95%CI: 1.10-3.55) and recently sharing IDU preparation equipment (i.e., cookers, cotton, water) (pRR: 2.44, 95%CI: 1.18-5.02) were associated with an increased likelihood of recently assisting initiation. As above, a risk score, between 0 and 4, was calculated for each participant by summing the number of risk behaviors participants indicated they had recently performed. Across both sites, an increased score was associated with a 23% to 48% increase likelihood of recently assisting initiation (pRR: 1.23, 95%CI: 1.02-1.48).

Discussion

This is the first study to pool findings across distinct cohort studies to assess factors associated with IDU initiation events. The findings presented indicate that, like other dynamic population-level health phenomena such as infectious disease epidemics, the dissemination of IDU initiation assistance across vulnerable populations is driven by both shared and setting-specific factors. For example, we found that a history of assisting IDU initiation, recently being stopped by law enforcement, and recent methamphetamine and speedball injection were associated with an increased likelihood of recently assisting IDU initiation across all three sites. These findings are consistent with prior literature. Evidence suggests that a minority of PWID are responsible for assisting the IDU initiation of a majority of injection-naïve individuals[10] and having a history of assisting IDU initiation may be an effective proxy measurement for capturing individuals who assist many IDU initiations. In Tijuana, law enforcement has been found to focus on neighborhoods with established and visible drug markets[34] and, as such, it is possible that PWID who are most visible to law enforcement (such as those living in Vancouver's Downtown Eastside or by the Tijuana River Canal) may also be most visible to injection-naïve individuals seeking initiation assistance. And, finally, while most of the research connecting stimulant use with increased likelihood of providing IDU initiation assistance used data from the same cohorts,[11,16,21] it appears that the use of crystal meth may play an important role for street youth who use drugs, including assisting them in staving off hunger, heightening sexual pleasure, and making it easier to behave in a "socially acceptable" manner, compared to other available drugs.[35,36]

Given that crystal meth use is associated with increased risk of initiating IDU,[37] the utility of crystal meth use among street-involved youth makes this population particularly vulnerable to IDU initiation. Further, we found that reporting not engaging in recent IDU and recent OAT enrollment were associated with a decreased likelihood of assisting IDU initiation across all three sites. These results have implications for efforts to prevent or delay transitions to IDU and other injection-related harms, in a range of sociocultural and geographic settings.

The current study highlights the considerable heterogeneity in the influence of factors on recently assisting IDU initiation—including recent non-injection heroin and cocaine use, recent incarceration, and recent housing insecurity—which we found were influential in only specific settings. For example, recent non-injection heroin use was positively associated with recently assisting IDU initiation in Tijuana but, within the study sample in San Diego (a contiguous metropolitan setting), was negatively associated with recently assisting. This may be explained by a historically high geographic concentration of non-injection drug use and IDU in the Tijuana River canal, where up to 1,000 people were recently believed to have resided,[38] whereas San Diego does not have a location with a similarly dense concentration of PWID and people who use drugs (PWUD) through other routes of administration cohabitating. Thus, we may consider one source of site-specific heterogeneity as the presence of geographically concentrated public injecting such as that found both in the Tijuana River canal and Vancouver's Downtown Eastside neighborhood, which has a disproportionately dense and stable population of PWID.[38,39] Locations with higher concentrations of public IDU may facilitate interactions between PWID and injection-naïve PWUD and thereby increase the likelihood of IDU initiation assistance occurring.[40,41] However, future research is required to further examine the factors that may explain site-specific outcomes. In the case of public IDU, we hypothesize that the more visible IDU is to injection-naïve individuals, the more likely it is that observed PWID will be in positions to provide IDU initiation assistance.

This study implies directions for future research and interventions aimed at disrupting IDU transition events and related harms. Break the Cycle (BTC) and the adapted Change the Cycle, for example, are behavioral interventions aimed at reducing the likelihood that PWID assist IDU initiation in the future.[42,43] The interventions use motivational interviewing, role playing, and resource education to empower PWID to not assist IDU

initiation.[42,43] Recent preliminary evidence from New York City, USA and Tallinn, Estonia[43] as well as Toronto, Canada[42] indicate potential efficacy of this program. Our findings indicate that, across settings, engaging current PWID who inject methamphetamine and/or speedball, are not enrolled in OAT, and/or with a history of assisting IDU initiation may lead to improved efficacy of BTC. Further, they indicate that factors such as incarceration and housing insecurity should be incorporated into sampling strategies on a context-specific basis.

With respect to other interventional approaches, we found that recent OAT enrollment is associated with a decreased likelihood of assisting IDU initiation, even though we had insufficient power to assess the direction and magnitude of this relationship in Tijuana (as only 3% of our Tijuana sample reported recent OAT enrollment). This is likely explained in large part by the lack of available OAT treatment in Tijuana, the prohibitive cost of OAT,[44] stigma related to OAT,[38] as well as restrictions on OAT provision,[45] and suggests a critical limitation of the use of OAT in under-resourced settings as a mode to reduce IDU initiation assistance among PWID. This is in juxtaposition to US and Canadian settings, where policies promoting a highly regulated expansion of OAT services in response to the current opioid crisis continue to expand.[46] It is noteworthy, though, that OAT regulatory environments in the US (which are stricter and controlled by federal policy) and Canada (which are more relaxed and subject to provincial policy),[46] create unique contexts which may influence the efficacy and collateral health effects of OAT on the incidence of IDU initiation assistance provision. It is clear that future research that seeks to assess the potential use of OAT as an IDU initiation prevention intervention in other contexts must account for setting-specific policies surrounding the provision of substance use treatment.[47]

Limitations

This study has limitations inherent to exploratory analysis of observational data from multiple distinct cohort studies. For instance, our ability to assess heterogeneity between sites was limited by two factors: limited statistical power to analyze site-specific data (particularly for Tijuana and San Diego); and the limited number of sites (n = 3) from which we pooled data. These findings must therefore be interpreted in light of this uncertainty. In particular, because of the low power that we have to detect heterogeneity we can be confident in the presence of heterogeneity among those variables identified as such given the magnitude of heterogeneity required to

generate signal. We also caution that an I^2 of 0% for a given factor does not mean that that factor is homogenous across sites, but, more likely, that we were not powered to detect heterogeneity.

In addition, this study has limitations that are typical of observational cross-sectional research. For example, non-probability sampling was employed, and thus the participants sampled may not be representative of the broader PWID population in each study setting. In particular, we likely were able to recruit the most visible PWID and PWID most connected with health and social services. As such, it is possible that our sample under-represented two vulnerable groups of PWID: 1) those who inject alone and 2) those without access to medical and social services. The population under study is also highly mobile and the high degree of human traffic between San Diego and Tijuana opens up the possibility that some of the IDU initiation assistance events reported by San Diego participants may have occurred in Tijuana, and vice versa. Furthermore, providing IDU initiation assistance is highly stigmatized and sensitive in nature.[48] As a result, relying on self-report within the current study likely led to underreporting of this behavior. If patterns of underreporting are not explained by the factors explored in this study, this bias would likely skew results towards the null. We highlight that our findings are consistent with research that a minority of PWID are responsible for providing assistance to the IDU initiation of a majority of PWID,[10] and, as such, we note that future research and interventions may want to focus specifically on this sub-population. Further research is needed to determine if underreporting is explained by any of these factors. Finally, data for this study was collected at the onset of the emergence of fentanyl in the illicit drug market.[49] It is likely that concerns over drug contamination have resulted in modifications in IDU practices and, therefore, will be important for future studies to investigate how the emergence of fentanyl has impacted the provision of IDU initiation assistance. It is possible that the presence of fentanyl will increase the perceived importance of receiving IDU initiation assistance from experienced PWID, as injection-naïve individuals may rely upon these experienced individuals as a safety precaution.

Conclusion

The current study is the first to pool cross-national data to assess commonality and heterogeneity in factors influencing IDU initiation assistance provision across distinct settings. These findings can inform interventions

and policies seeking to prevent IDU initiation across distinct sociocultural contexts. Furthermore, our results imply that interventions targeting transitions into IDU and injection-related harms will need to move past a "one size fits all" approach and be adapted to address unique factors specific to each geographic and sociocultural context.

Funding Statement

PRIMER and Dan Werb are supported by a US National Institute on Drug Abuse Avenir Award (DP2-DA040256-01), the Canadian Institutes of Health Research via a New Investigator Award, the Ontario Ministry of Research, Innovation and Science via an Early Researcher Award, and by a project grant from the Canadian Institutes of Health Research. El Cuete IV was supported through NIDA grant R37 DA019829. STAHR II was supported through NIDA grant R01DA031074. VDUS is supported by NIDA grant U01DA038886, and the ACCESS Study is supported by NIDA grant U01DA021525.

Competing Interests

We have no competing interests to disclose.

Author Contributions

CM contributed to project conceptualization, analytic design, data analysis, and original manuscript writing. SM contributed to project conceptualization, analytic design, and manuscript editing. SJ contributed to analytic design and manuscript editing. XS contributed to analytic design and manuscript editing. KH contributed to data collection and manuscript editing. PGZ contributed to data collection and manuscript editing. SAS contributed to data collection and manuscript editing. RSG contributed to data collection and manuscript editing. MJM contributed to data collection and manuscript editing. KD contributed to data collection and manuscript editing. KC contributed to analytic design and manuscript editing. DW contributed to project conceptualization, project supervision, funding acquisition, data collection, and manuscript editing.

Data Availability Statement

The data for this study cannot be made public due to human subjects protections.

References

1. United States Department of Health and Human Services. What is the U.S. Overdose Crisis? https://www.hhs.gov/opioids/about-the-epidemic/index.html. Published 2019.
2. National Institute on Drug Abuse. Opioid Overdose Crisis. https://www.drugabuse.gov/drugs-abuse/opioids/opioid-overdose-crisis. Published 2019. Accessed March 12, 2019.
3. Haskins J. Suicide, opioids tied to ongoing fall in US life expectancy: Third year of drop. *Nation's Heal*. 2019;49(1):1 LP - 10. http://thenationshealth.aphapublications.org/content/49/1/1.2.abstract.
4. Degenhardt L, Peacock A, Colledge S, et al. Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. *Lancet Glob Heal*. 2017;5(12):e1192-e1207. doi:10.1016/S2214-109X(17)30375-3
5. Colledge S, Peacock A, Leung J, et al. The prevalence of non-fatal overdose among people who inject drugs: A multi-stage systematic review and meta-analysis. *Int J Drug Policy*. 2019;73:172-184.

doi:10.1016/j.drugpo.2019.07.030

6. 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):258-267. doi:10.1007/s10900-010-9231-z

7. Garfein RS, Doherty MC, Monterroso ER, Thomas DL, Nelson KE, Vlahov D. Prevalence and Incidence of Hepatitis C Virus Infection Among Young Adult Injection Drug Users. *JAIDS J Acquir Immune Defic Syndr*. 1998;18.

8. Werb D, Buxton J, Shoveller J, Richardson C, Rowell G, Wood E. Interventions to prevent the initiation of injection drug use: A systematic review. *Drug Alcohol Depend*. 2013;133(2):669-676. doi:10.1016/j.drugalcdep.2013.08.017

9. Vlahov D, Fuller CM, Ompad DC, Galea S, Jarlais DC Des. Updating the Infection Risk Reduction Hierarchy : Preventing Transition into Injection. *J Urban Health*. 2004;81(1):14-19.

10. Gicquelais RE, Werb D, Marks C, et al. Prevalence and Correlates of Providing and Receiving Assistance With the Transition to Injection Drug Use. *Epidemiol Rev*. 2020;42(1):4-18. doi:10.1093/epirev/mxaa008

11. Meyers SA, Scheim A, Jain S, et al. Gender differences in the provision of injection initiation assistance: a comparison of three North American settings. *Harm Reduct J*. 2018;15(1):59. doi:10.1186/s12954-018-0270-6

12. Ben Hamida A, Rafful C, Jain S, et al. Non-injection Drug Use and Injection Initiation Assistance among People Who Inject Drugs in Tijuana, Mexico. *J Urban Heal*. 2018;95(1):83-90. doi:10.1007/s11524-017-0188-4

13. Melo JS, Garfein RS, Hayashi K, et al. Do law enforcement interactions reduce the initiation of injection drug use? An investigation in three North American settings. *Drug Alcohol Depend*. 2018;182(24):67-73. doi:10.1016/j.drugalcdep.2017.10.009

14. Bouck Z, Jain S, Sun X, Milloy M-J, Werb D, Hayashi K. Recent incarceration and risk of first-time injection initiation assistance: A prospective cohort study of persons who inject drugs. *Drug Alcohol Depend*. 2020;212:107983. doi:10.1016/j.drugalcdep.2020.107983

15. Marks C, Bouck Z, Jain S, et al. The impact of recent homelessness on the provision of injection drug use initiation assistance among persons who inject drugs in Tijuana, Mexico and Vancouver, Canada. *Drug Alcohol Depend*. 2021;225:108829. doi:10.1016/j.drugalcdep.2021.108829

16. Mittal ML, Jain S, Sun S, et al. Opioid agonist treatment and the process of injection drug use initiation. *Drug Alcohol Depend*. 2019;197(January):354-360. doi:10.1016/j.drugalcdep.2018.12.018

17. Mittal ML, Vashishtha D, Sun S, et al. History of medication-assisted treatment and its association with initiating others into injection drug use in San Diego, CA. *Subst Abuse Treat Prev Policy*. 2017;12(42). doi:10.1186/s13011-017-0126-1

18. Marks C, Borquez A, Jain S, et al. Opioid agonist treatment scale-up and the initiation of injection drug use: A dynamic modeling analysis. Tsai AC, ed. *PLOS Med*. 2019;16(11):e1002973. doi:10.1371/journal.pmed.1002973

19. Werb D, Garfein R, Kerr T, et al. A socio-structural approach to preventing injection drug use initiation: rationale for the PRIMER study. *Harm Reduct J*. 2016;13(25). doi:10.1186/s12954-016-0114-1

20. Robertson AM, Garfein RS, Wagner KD, et al. Evaluating the impact of Mexico's drug policy reforms on people who inject drugs in Tijuana, B.C., Mexico, and San Diego, CA, United States: a binational

mixed methods research agenda. *Harm Reduct J*. 2014;11(4). doi:10.1186/1477-7517-11-4

21. Rafful C, Melo J, Medina-Mora ME, et al. Cross-Border Migration and Initiation of Others into Drug Injecting in Tijuana, Mexico. *Drug Alcohol Rev*. 2018;37(3):S277-S284. doi:10.1111/dar.12630

22. Shannon K, Kerr T, Strathdee SA, Shoveller J, Montaner JS, Tyndall MW. Prevalence and structural correlates of gender based violence among a prospective cohort of female sex workers. *BMJ*. 2009;339:b2939-b2939. doi:10.1136/bmj.b2939

23. Zou G. A Modified Poisson Regression Approach to Prospective Studies with Binary Data. *Am J Epidemiol*. 2004;159(7):702-706. doi:10.1093/aje/kwh090

24. Tan J, Altice FL, Madden LM, Zelenev A. Effect of expanding opioid agonist therapies on the HIV epidemic and mortality in Ukraine: a modelling study. *Lancet HIV*. December 2019. doi:10.1016/S2352-3018(19)30373-X

25. Knol MJ, Le Cessie S, Algra A, Vandenbroucke JP, Groenwold RHH. Overestimation of risk ratios by odds ratios in trials and cohort studies: alternatives to logistic regression. *Can Med Assoc J*. 2012;184(8):895-899. doi:10.1503/cmaj.101715

26. Blettner M, Sauerbrei W, Schlehofer B, Scheuchenpflug T, Friedenreich C. Traditional reviews, meta-analyses and pooled analyses in epidemiology. *Int J Epidemiol*. 1999;28(1):1-9. doi:10.1093/ije/28.1.1

27. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558. doi:10.1002/sim.1186

28. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. *J Stat Softw*. 2010;36(3). doi:10.18637/jss.v036.i03

29. Rafful C, Jain S, Sun X, et al. Identification of a Syndemic of Blood-Borne Disease Transmission and Injection Drug Use Initiation at the US–Mexico Border. *JAIDS J Acquir Immune Defic Syndr*. 2018;79(5):559-565. doi:10.1097/QAI.0000000000001858

30. Wasserstein RL, Schirm AL, Lazar NA. Moving to a World Beyond " p < 0.05." *Am Stat*. 2019;73(sup1):1-19. doi:10.1080/00031305.2019.1583913

31. Hurlbert SH, Levine RA, Utts J. Coup de Grâce for a Tough Old Bull: "Statistically Significant" Expires. *Am Stat*. 2019;73(sup1):352-357. doi:10.1080/00031305.2018.1543616

32. Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. *Nature*. 2019;567(7748):305-307. doi:10.1038/d41586-019-00857-9

33. Cummins KM, Marks C. Farewell to Bright-Line: A Guide to Reporting Quantitative Results Without the S-Word. *Front Psychol*. 2020;11. doi:10.3389/fpsyg.2020.00815

34. Gaines T, Werb D, Arredondo J, Alaniz VM, Beletsky L. The spatial–temporal relationship of policing in areas with high drug activity. *Drug Alcohol Depend*. 2015;156:e77. doi:10.1016/j.drugalcdep.2015.07.1126

35. Werb D, Kerr T, Zhang R, Montaner JS, Wood E. Methamphetamine use and malnutrition among street-involved youth. *Harm Reduct J*. 2010;7(1):5. doi:10.1186/1477-7517-7-5

36. Fast D, Kerr T, Wood E, Small W. The multiple truths about crystal meth among young people entrenched in an urban drug scene: A longitudinal ethnographic investigation. *Soc Sci Med*. 2014;110:41-48. doi:10.1016/j.socscimed.2014.03.029

37. Werb D, Kerr T, Buxton J, et al. Crystal methamphetamine and initiation of injection drug use among street-involved youth in a Canadian setting. *Can Med Assoc J*. 2013;185(18):1569-1575.

doi:10.1503/cmaj.130295

38. Rafful C, Medina-Mora ME, González-Zúñiga P, et al. "Somebody Is Gonna Be Hurt": Involuntary Drug Treatment in Mexico. *Med Anthropol*. May 2019:1-14. doi:10.1080/01459740.2019.1609470

39. 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 Alcohol Depend*. 2013;132(3):486-490. doi:10.1016/j.drugalcdep.2013.03.011

40. Tobin KE, Davey-Rothwell M, Latkin CA. Social-Level Correlates of Shooting Gallery Attendance: A Focus on Networks and Norms. *AIDS Behav*. 2010;14(5):1142-1148. doi:10.1007/s10461-010-9670-7

41. Mazhnaya A, Tobin KE, Owczarzak J. Association between injection in public places and HIV/HCV risk behavior among people who use drugs in Ukraine. *Drug Alcohol Depend*. 2018;189:125-130. doi:10.1016/j.drugalcdep.2018.04.036

42. Strike C, Rotondi M, Kolla G, et al. Interrupting the social processes linked with initiation of injection drug use: Results from a pilot study. *Drug Alcohol Depend*. 2014;137:48-54. doi:10.1016/j.drugalcdep.2014.01.004

43. Des Jarlais D, Uuskula A, Talu A, et al. Implementing an Updated "Break the Cycle" Intervention to Reduce Initiating Persons into Injecting Drug Use in an Eastern European and a US "opioid epidemic" Setting. *AIDS Behav*. 2019;23(9):2304-2314. doi:10.1007/s10461-019-02467-y

44. Burgos JL, Cepeda JA, Kahn JG, et al. Cost of provision of opioid substitution therapy provision in Tijuana, Mexico. *Harm Reduct J*. 2018;15(1):28. doi:10.1186/s12954-018-0234-x

45. Goodman-Meza D, Medina-Mora ME, Magis-Rodríguez C, Landovitz RJ, Shoptaw S, Werb D. Where Is the Opioid Use Epidemic in Mexico? A Cautionary Tale for Policymakers South of the US–Mexico Border. *Am J Public Health*. 2019;109(1):73-82. doi:10.2105/AJPH.2018.304767

46. Priest KC, Gorfinkel L, Klimas J, Jones AA, Fairbairn N, McCarty D. Comparing Canadian and United States opioid agonist therapy policies. *Int J Drug Policy*. 2019;74:257-265. doi:10.1016/j.drugpo.2019.01.020

47. Vashishtha D, Mittal ML, Werb D. The North American opioid epidemic: current challenges and a call for treatment as prevention. *Harm Reduct J*. 2017;14(7). doi:10.1186/s12954-017-0135-4

48. Guise A, Horyniak D, Melo J, McNeil R, Werb D. The experience of initiating injection drug use and its social context: a qualitative systematic review and thematic synthesis. *Addiction*. 2017;112(12):2098-2111. doi:10.1111/add.13957

49. Ciccarone D. The triple wave epidemic: Supply and demand drivers of the US opioid overdose crisis. *Int J Drug Policy*. 2019;71:183-188. doi:10.1016/j.drugpo.2019.01.010

Table 1. Recent Injection Initiation Assistance Provision and Related Factors Among People Who Inject Drugs in San Diego, USA; Tijuana, Mexico; and Vancouver, Canada, 2014-2018 (n = 2,944)

Variable	Tijuana		San Diego		Vancouver	
	Did not recently assist injection initiation (n=725)	Recently assisted injection initiation (n=41)	Did not recently assist injection initiation (n=335)	Recently assisted injection initiation (n=18)	Did not recently assist injection initiation (n=1737)	Recently assisted injection initiation (n=88)
Age (mean (SD))	40.72 (9.13)	38.25 (8.10)	46.87 (11.19)	46.61 (12.70)	42.86 (12.64)	32.44 (10.65)
Gender						
Female	289 (39.9)	12 (29.3)	94 (28.1)	4 (22.2)	657 (37.9)	31 (35.6)
Male	436 (60.1)	29 (70.7)	234 (70.3)	14 (77.8)	1078 (62.1)	56 (64.4)
Transgender	0 (0.0)	0 (0.0)	5 (1.5)	0 (0.0)	--	--
Years Since First Injection (mean (SD))	19.68 (9.97)	19.23 (8.85)	23.98 (13.19)	23.06 (12.53)	21.05 (13.50)	12.06 (10.60)
Recent Active IDU						
Yes	625 (86.2)	38 (92.7)	231 (69.0)	17 (94.4)	1133 (65.2)	85 (96.6)
No	100 (13.8)	3 (7.3)	104 (31.0)	1 (5.6)	604 (34.8)	3 (3.4)
History of Having Assisted IDU Initiation						
No	645 (89.0)	22 (53.7)	222 (66.3)	8 (44.4)	1399 (80.5)	35 (39.8)
Yes	80 (11.0)	19 (46.3)	113 (33.7)	10 (55.6)	338 (19.5)	53 (60.2)
Recent Housing Insecurity						
No	605 (83.4)	31 (75.6)	250 (74.6)	12 (66.7)	1287 (74.1)	51 (58.0)
Yes	120 (16.6)	10 (24.4)	85 (25.4)	6 (33.3)	449 (25.9)	37 (42.0)
Recently Stopped by Law Enforcement						
No	397 (54.8)	15 (36.6)	182 (54.3)	7 (38.9)	1097 (63.2)	31 (35.2)
Yes	328 (45.2)	26 (63.4)	153 (45.7)	11 (61.1)	640 (36.8)	57 (64.8)
Recently Incarcerated						
No	532 (73.4)	32 (78.0)	267 (79.7)	11 (61.1)	1584 (91.6)	76 (86.4)
Yes	193 (26.6)	9 (22.0)	68 (20.3)	7 (38.9)	146 (8.4)	12 (13.6)
Recent OAT Enrollment						
No	704 (97.1)	40 (97.6)	267 (79.7)	17 (94.4)	873 (50.3)	57 (64.8)
Yes	21 (2.9)	1 (2.4)	68 (20.3)	1 (5.6)	864 (49.7)	31 (35.2)
Recent Methamphetamine Injection						
No	617 (85.1)	27 (65.9)	183 (54.6)	6 (33.3)	1147 (66.0)	20 (22.7)
Yes	108 (14.9)	14 (34.1)	152 (45.4)	12 (66.7)	590 (34.0)	68 (77.3)
Recent Speedball Injection						
No	703 (97.0)	38 (92.7)	314 (93.7)	16 (88.9)	1626 (93.6)	74 (84.1)
Yes	22 (3.0)	3 (7.3)	21 (6.3)	2 (11.1)	111 (6.4)	14 (15.9)
Recent Non-Injection Use of Heroin, Cocaine, or Methamphetamine						
No	419 (57.8)	17 (41.5)	108 (32.2)	3 (16.7)	758 (43.6)	28 (31.8)
Yes	306 (42.2)	24 (58.5)	227 (67.8)	15 (83.3)	979 (56.4)	60 (68.2)
Recent Non-Injection Use of Heroin						
No	665 (91.7)	33 (80.5)	258 (77.0)	16 (88.9)	1494 (86.0)	64 (72.7)
Yes	60 (8.3)	8 (19.5)	77 (23.0)	2 (11.1)	243 (14.0)	24 (27.3)
Recent Non-Injection Use of Methamphetamine						
No	441 (60.8)	18 (43.9)	127 (37.9)	5 (27.8)	1256 (72.3)	45 (51.1)

Yes	284 (39.2)	23 (56.1)	208 (62.1)	13 (72.2)	481 (27.7)	43 (48.9)
Recent Non-Injection Use of Cocaine						
No	693 (95.6)	35 (85.4)	286 (85.4)	15 (83.3)	1013 (58.3)	44 (50.0)
Yes	32 (4.4)	6 (14.6)	49 (14.6)	3 (16.7)	724 (41.7)	44 (50.0)
Risk Behaviors Sub-Analysis						
Recent Risk Behaviors: Gave Used Syringe To Other PWID						
No	288 (40.7)	12 (29.3)	237 (71.0)	9 (50.0)	--	--
Yes	419 (59.3)	29 (70.7)	97 (29.0)	9 (50.0)	--	--
Injected with Used Syringe						
No	293 (41.4)	12 (29.3)	213 (67.6)	7 (38.9)	--	--
Yes	414 (58.6)	29 (70.7)	102 (32.4)	11 (61.1)	--	--
Front- or Back-Loaded						
No	288 (40.7)	11 (26.8)	231 (69.0)	6 (33.3)	--	--
Yes	419 (59.3)	30 (73.2)	104 (31.0)	12 (66.7)	--	--
Shared Injection Equipment						
No	251 (35.5)	6 (14.6)	199 (59.4)	5 (27.8)	--	--
Yes	456 (64.5)	35 (85.4)	136 (40.6)	13 (72.2)	--	--
Recent Risk Behavior Score* (mean (SD))	2.36 (1.73)	3.00 (1.38)	1.31 (1.52)	2.50 (1.65)	--	--

*Recent Risk Behavior Score is the sum of how many of the four individual risk behaviors participants responded recently having performed, resulting in a score between 0 and 4.
SD: Standard Deviation, IDU: Injection Drug Use, PWID: People Who Inject Drugs, OAT: Opioid Agonist Treatment

Table 2. Multiple Modified Poisson Regressions and Pooled Relative Risks Assessing the Association Between Related Factors and Assisting IDU Initiation Across San Diego, USA, Tijuana, Mexico, and Vancouver, Canada, 2014-2018 (n = 2,944).

	Tijuana		San Diego		Vancouver		Pooled		I²****
	RR (95%CI)*	p	RR (95%CI)	p	RR (95%CI)	p	RR (95%CI)	p	
Age (10 Year Increment)	0.54 (0.31 - 0.90)	0.028	1.22 (0.66 – 2.16)	0.597	0.66 (0.43 - 0.90)	0.023	0.74 (0.48 - 1.10)	0.116	51.73%
Gender**									
Male	1.47 (0.77-2.82)	0.243	1.41 (0.48 - 4.19)	0.532	1.21 (0.80 - 1.82)	0.368	1.29 (0.93 - 1.79)	0.131	0.00%
Years Since First Injection	1.03 (0.97-1.08)	0.309	0.98 (0.94-1.03)	0.460	0.99 (0.95-1.03)	0.588	1.00 (0.97-1.02)	0.795	0.20%
Recent Active IDU									
No	0.52 (0.17-1.57)	0.246	0.14 (0.02 - 1.02)	0.052	0.11 (0.04-0.34)	<0.001	0.21 (0.07-0.64)	0.006	50.40%
History of Having Assisted IDU Initiation									
Yes	5.4 (2.95-9.90)	<0.001	2.48 (1.00-6.19)	0.052	5.26 (3.46-8.00)	<0.001	4.83 (3.49-6.66)	<0.001	0.00%
Recent Housing Insecurity									
Yes	1.69 (0.86-3.33)	0.127	1.25 (0.46-3.38)	0.657	0.84 (0.56-1.29)	0.432	1.13 (0.70-1.83)	0.621	40.11%
Recently Stopped by Law Enforcement									
Yes	1.66 (0.91-3.03)	0.096	1.52 (0.62-3.76)	0.362	1.40 (0.91-2.16)	0.125	1.49 (1.08-2.07)	0.017	0.00%
Recently Incarcerated									
Yes	0.85 (0.41-1.77)	0.67	2.40 (1.00-5.78)	0.051	0.81 (0.44-1.47)	0.483	1.11 (0.59-2.10)	0.740	56.99%
Recently Enrolled in OAT									
Yes	1.03 (0.14 - 7.71)	0.974	0.28 (0.04 - 1.99)	0.201	0.65 (0.43 - 1.00)	0.048	0.64 (0.43-0.96)	0.032	0.00%
Recent Methamphetamine Injection***									
Yes	2.27 (1.22-4.22)	0.009	2.15 (0.81-5.72)	0.124	3.38 (2.04-5.62)	<0.001	2.77 (1.92-3.98)	<0.001	0.00%
Recent Speedball Injection***									
Yes	2.16 (0.81-5.76)	0.122	2.36 (0.47-11.96)	0.300	2.07 (1.22-3.53)	0.007	2.11 (1.35-3.31)	0.001	0.00%
Recent Non-Injection Use of Heroin, Cocaine, or Meth									
Yes	1.68 (0.90 - 3.13)	0.105	1.27 (0.32-4.96)	0.734	1.16 (0.77-1.76)	0.479	1.30 (0.93-1.81)	0.127	0.00%
Recent Non-Injection Use of Heroin									
Yes	2.49 (1.28-4.81)	0.007	0.32 (0.07-1.53)	0.152	1.16 (0.73-1.82)	0.530	1.19 (0.46-3.07)	0.726	78.36%
Recent Non-Injection Use of Methamphetamine									
Yes	1.76 (0.96-3.23)	0.067	0.93 (0.31-2.75)	0.895	1.17 (0.79-1.73)	0.435	1.28 (0.94-1.76)	0.123	0.00%
Recent Non-Injection Use Of Cocaine									
Yes	2.43 (1.08-5.44)	0.031	0.91 (0.23-3.67)	0.899	1.30 (0.88-1.91)	0.183	1.46 (0.96-2.21)	0.078	15.07%
Recent Risk Behaviors: Gave Used Syringe to Other PWID									
Yes	1.12 (0.58 - 2.17)	0.743	1.54 (0.58-4.07)	0.381	X	X	1.24 (0.72-2.14)	0.444	--
Injected with Used Syringe									
Yes	1.21 (0.58-2.56)	0.608	2.13 (0.77-5.88)	0.144	X	X	1.48 (0.81-2.69)	0.202	--
Front- or Back-Loaded									
Yes	1.67 (0.80-3.48)	0.174	2.66 (1.01-7.00)	0.048	X	X	1.98 (1.10-3.55)	0.023	--
Shared Injection Equipment									
Yes	2.71 (1.04 - 7.01)	0.04	2.12 (0.70-6.40)	0.184	X	X	2.44 (1.18-5.02)	0.016	--
Risk Behavior Score	1.18 (0.94-1.46)	0.15	1.38 (0.97-1.98)	0.074	X	X	1.23 (1.02-1.48)	0.031	--

*All models include Age, Gender, Years Since First Injection, Recent Active IDU, and History of Having Assisted IDU Initiation unless it is otherwise noted.
**For STAHR, 5 individuals identified as Transgender and were not given the option to also provide their gender indentity and were coded to be included with "Female" category
***Does not control for injection frequency
**** Describes the percentage of variability in site-specific relative risks for given factor explained by site heterogeneity as opposed to sampling error.

RR: Relative Risk, 95% CI: 95% Confidence Interval, IDU: Injection Drug Use, PWID: People Who Inject Drugs, OAT: Opioid Agonist Treatment

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6-8
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-8
		(*b*) Describe any methods used to examine subgroups and interactions	6-8
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	-
Outcome data	15*	Report numbers of outcome events or summary measures	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11

		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.