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Polydrug use and risk of HIV and overdose among people who inject drugs in San Diego, California, and Tijuana, Baja California, Mexico

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Polydrug use and risk of HIV and overdose among people who inject drugs in San Diego, California, and Tijuana, Baja California, Mexico

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy

in

Public Health (Global Health)

by

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Professor Mark Reed

2015

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2015

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Chapter 2, “Prevalence and correlates of heroin-methamphetamine co-injection in two parallel cohorts of persons who inject drugs in San Diego, CA, and Tijuana, BC, Mexico,” in full, is currently being prepared for resubmission to the *Journal of Studies on Alcohol and Drugs*. Steffanie Strathdee, Gudelia Rangel, Richard Armenta, Tommi Gaines, and Richard Garfein are co-authors.

Chapter 3, “Latent Classes of Polydrug Use and Associations with HIV Risk Behaviors and Overdose among PWID in Tijuana, BC, Mexico,” is currently being prepared for submission to *Drug and Alcohol Dependence*. Scott Roesch, Steffanie Strathdee, and Tommi Gaines are co-authors.

Chapter 4, “Latent Transitions in Polydrug and Polyroute Use among PWID in Tijuana, BC, Mexico,” is currently being prepared for publication. Steffanie Strathdee, Tommi Gaines, and Scott Roesch are co-authors.

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### PUBLICATIONS

#### Published

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2. Collins, K.M.; Abromovitz, D.A.; **Meacham, M.C.**; Gonzalez-Zuniga, P.E.; Patrick, K.; Garfein, R.S. (2015) Cell phone use among persons who inject drugs in Tijuana, BC, Mexico. *Journal of Mobile Technology in Medicine*.
3. **Meacham, M.C.**, A.E. Rudolph, S.A. Strathdee, M.L. Rusch, K.C. Brouwer, T.L. Patterson, A. Vera, G. Rangel, S.C. Roesch. (2015) Polydrug use and HIV risk among people who inject heroin in Tijuana, México: A latent class analysis. *Substance Use & Misuse*.
4. Kosterman, R., Hill, K. G., Lee, J. O., **Meacham, M. C.**, Abbott, R. D., Catalano, R. F., & Hawkins, J. D. (2014). Young adult social development as a mediator of alcohol use disorder symptoms from age 21 to 30. *Psychology of Addictive Behaviors*. Vol. 28. Issue 2, Page 348-358.
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dependence, alcohol use disorder, and co-occurring problems. *Drug and Alcohol Dependence*. Vol. 118, Issues 2-3, Pages 444-451.

7. **Meacham, M.C.**; Starks, H.; Edwards, K.; Burke, W. (2010) Researcher Perspectives on Disclosure of Incidental Findings in Genetic Research. *Journal of Empirical Research on Human Research Ethics*. Vol. 5, Issue 3, Pages 31-41.
8. Griffiths, P; **Meacham, M**; McKettin, R. (2008) Global Illicit Drug Trends. *International Encyclopedia of Public Health*. Elsevier. Pages 515-523.

#### Submitted and Under Review

1. **Meacham, M.C.**, Strathdee, S.A., Rangel, G., Armenta, R.F., Gaines, T., Garfein, R.S. Prevalence and correlates of co-injection of heroin and methamphetamine in two parallel cohorts of persons who inject drugs in San Diego, CA, and Tijuana, BC, Mexico. *Journal of Studies on Alcohol and Drugs*. (accepted with minor revisions)

## **ABSTRACT OF THE DISSERTATION**

Polydrug use and risk of HIV and overdose among people who inject drugs in San Diego, California, and Tijuana, Baja California, Mexico

by

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Doctor of Philosophy in Public Health (Global Health)

University of California, San Diego, 2015

San Diego State University, 2015

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**Background:** Patterns of polydrug use among people who inject drugs (PWID) may be differentially associated with overdose as well as with unique risk factors for HIV transmission. This dissertation examines patterns of polydrug use

among PWID in Tijuana, Baja California, Mexico, and San Diego, California and the relationship of these patterns to HIV risk behaviors and overdose.

**Methods:** These analyses use data from two prospective cohort studies of PWID in San Diego (N=576) (Chapter 2) and Tijuana (N=735) (Chapters 2-4). Chapter 2 assesses prevalence and correlates of methamphetamine and heroin co-injection in a binational sample of PWID from both San Diego and Tijuana using logistic regression. Chapter 3 applies latent class analysis to identify classes of polydrug use and multinomial logistic regression to determine associations with HIV risk behaviors and overdose among PWID in Tijuana. Chapter 4 applies latent transition analysis to describe dynamic statuses of polydrug use at baseline and 6 month follow up, determine probabilities of transitioning between statuses, and examine whether these probabilities are modified by self-report needed for help for drug use.

**Results:** Chapter 2 findings show that prevalence of heroin and methamphetamine co-injection in the past 6 months was 39.9% overall, was higher in Tijuana (55.8%) than in San Diego (19.8%), and was significantly associated with HIV injection risk behavior in both locations and associated with overdose only in San Diego. Chapter 3 findings show that PWID in Tijuana exhibited 5 distinct patterns of substance use behaviors. Compared to primarily heroin injectors, polydrug and polyroute class membership was associated with HIV injection and sexual risk behaviors. Chapter 4 findings showed that over a third (39.1%) of PWID in Tijuana transitioned to a different subgroup of heroin and methamphetamine polydrug use over 6 months. Those who reported greater need for help for drug use were more

likely to transition to subgroups characterized by greater polydrug and polyroute use 6 months later.

**Conclusions:** Findings highlight the heterogeneity in substance use patterns among PWID in Tijuana and San Diego and demonstrate that polydrug and polyroute users are a high-risk subgroup who may require more tailored prevention and treatment interventions.

## CHAPTER 1: INTRODUCTION

### OVERVIEW

Although many people who inject drugs (PWID) typically inject heroin, they also use methamphetamine, cocaine, and other substances through injection and non-injection routes of administration. While it is well known that injecting drug use is a major risk factor for HIV and mixing substances is a risk factor for overdose, less is known about how specific polydrug use patterns contribute to these negative health outcomes among marginalized drug users in resource poor settings. The overall goal of this dissertation project is to conduct a longitudinal study examining patterns of polydrug use among PWID in Tijuana, Baja California, Mexico, and San Diego, California, and the relationship of these patterns to HIV risk behavior and overdose. The specific aims of this dissertation are (1) to identify and compare factors associated with co-injection of heroin and methamphetamine in a combined international sample of PWID from Tijuana and San Diego, (2) to identify discrete subgroups defined by polydrug use patterns in the cohort of PWID from Tijuana and the relationship of these patterns to HIV risk behavior and overdose, and (3) to describe and predict changes in membership over 6 months between subgroups defined by polydrug use patterns in the cohort of PWID from Tijuana.

To meet these aims, I assess the prevalence and correlates of heroin and methamphetamine co-injection at baseline in a binational sample of PWID (Aim 1), apply latent class analysis and latent transition analysis techniques to longitudinal data on substance use behaviors to define cross sectional and temporal patterns in polydrug use (Aims 2 & 3) and assess the association of polydrug use patterns with HIV risk behavior and overdose health outcomes (Aims 1 & 2). This will

contribute to better understanding of the complexity of drug use behaviors and negative health outcomes in high risk substance using populations in this dynamic U.S.-Mexico border region. Results will have implications for studying polydrug use in other settings and for developing targeted prevention and treatment interventions.

## **BACKGROUND**

### **Illicit Drug Use and the Global Burden of Disease**

According to the 2010 Global Burden of Diseases, Injuries, and Risk Factors (GBD) Study, illicit drug use disorders accounted for 20 million disability adjusted life years (DALYs), or .8% of all cause DALYs.<sup>1</sup> Opioid dependence contributed to nearly half of this burden (9.2 million DALYs), followed by amphetamine dependence (2.6 million DALYs).<sup>1</sup> Injecting drug use is a major risk factor for HIV and accounted for 2.1 million DALYs and drug dependence is noted as a major risk factor for suicide and overdose.<sup>1</sup> UNAIDS estimates that about 30% of new HIV infections outside of Sub-Saharan Africa are attributable to injection drug use.<sup>2</sup> Compared to estimates from 1990, drug use has moved up in rank as a major risk factor contributing to the global burden of disease, from 25<sup>th</sup> in 1990 to 19<sup>th</sup> in 2010. Within the Americas, its rank is even higher: 10<sup>th</sup> in high income North America and 16<sup>th</sup> in Central Latin America.<sup>3</sup> In the United States, there has also been a significant increase in overdose mortality.<sup>4</sup>

While the United Nations Office on Drugs and Crime (UNODC) World Drug Report<sup>5</sup> and GBD Study take a substance-specific approach to their valuable global statistics on drug use and dependence prevalence and related disease burden, there is growing recognition that drug use behavior at the individual and population level involves use of multiple drugs and that descriptions of these patterns of use and their

relationship to health harms warrant further study.<sup>6-8</sup> In a 2012 Lancet article, Degenhardt and Hall<sup>7</sup> argue that “Intelligent policy responses to drug problems need better data for the prevalence of different types of illicit drug use and the harms that their use causes globally.” This dissertation research aims to contribute to knowledge of prevalence of different types of illicit drug use—as characterized by polydrug and polyroute use—and related harms in a dynamic binational setting, at the nexus of intense global movements of people and material.

### **Polydrug Use**

Polydrug use is described most broadly as the use of more than one substance, but different studies use varying time frames and specifications of polydrug use, making comparisons and deeper understanding of this complex but common phenomenon more difficult.<sup>6,9-11</sup> Most illicit drugs come in at least two forms (e.g. powder vs. tar heroin, powder cocaine vs. crack) and are used through multiple routes (i.e. injecting, snorting, smoking, or swallowing) that affect absorption rates into the bloodstream and thus the intensity and duration of a ‘high.’<sup>12</sup> Two or more drugs may be co-administered to create novel effects or counteract negative effects of one or both drugs.<sup>12</sup> For example, opiates and stimulants may be administered together (e.g., in the same syringe) to achieve a stronger high or to counteract the drowsiness and torpor produced by opiate use. Although descriptive statistics have been used to profile polydrug use in many general population and high risk samples, the use of specific substances and routes of administration may differ by population, location, and historical contexts.<sup>13</sup>

Use of different substances and different routes of administration are associated with specific negative health outcomes. Compared to single drug users, polydrug users tend to be more marginalized than other drug users, have higher

levels of drug dependence, be in poorer health, and have more unstable housing.<sup>14,15,16</sup> While heroin users are at high risk for overdose because of the drug's depressant effect on breathing,<sup>14,17</sup> use of opiates such as heroin mixed with stimulants like cocaine or methamphetamine also contribute to high risk for overdose through increased toxicity, decreased cognitive function, and physiological stress. Injecting drug use and sharing of needles and syringes is a significant method of transmission for HIV and hepatitis B and C virus infections.<sup>15</sup> Non-injection routes of administration, especially for stimulants and alcohol, are also associated with increased risk of infectious disease transmission through unsafe sexual behaviors.<sup>13</sup> A more complete assessment of polydrug use patterns will inform the relationship between specific combinations of substance type, timing, route of administration, and frequency of use with negative health outcomes, such as HIV and overdose.

### **Latent Class and Transition Modeling of Polydrug Use Patterns**

Latent variable approaches and mixture modeling are useful in disentangling which of the numerous possible combinations of substance use behaviors are most probable in a population with heterogeneous behaviors. Latent class analysis (LCA) is a person centered nonparametric approach that assigns individuals to classes on a probabilistic basis based on responses to a set of discrete indicator variables, allowing comparison of covariates across classes.<sup>18</sup> It approaches and groups observations based on similarity, with the goal of dividing a heterogeneous population into more homogenous subgroups.<sup>19,20</sup> This method has been used in general population samples<sup>21-26</sup> to model patterns of substance use as well as in high risk populations<sup>27-29</sup> and drug using populations<sup>30,31</sup> in the United States and Canada – specifically inner city heroin and cocaine users in Baltimore,<sup>13,32</sup> illegal opioid users in Canadian cities,<sup>33,34</sup> cocaine users in Montreal,<sup>35</sup> and club drug users in Ohio.<sup>36,37</sup>

These analyses found considerable heterogeneity in drug use patterns in terms of both substances used and route of administration. Significant class membership differences were detected for age, gender, homelessness, HIV and hepatitis C infection, and needle and syringe sharing. Latent transition analysis (LTA) models stability within and change between discrete latent classes over time by estimating the probability of transition between latent classes conditional on class membership at the previous time point.<sup>38,39</sup> LTA has also been applied to modeling transitions in drug use patterns, but to a lesser extent than latent class analysis.<sup>40,41</sup> Latent class analysis with covariates will be applied Aim 2 and latent transition analysis with covariates will be applied in Aim 3.

### **Study Setting**

This dissertation research was conducted in the Tijuana-San Diego border region. These two cities are located adjacent to each other on the southwest corner of the U.S.-Mexico border and are connected by the busiest land border crossing in the Western Hemisphere. The San Ysidro Port of Entry reports 56 million border crossings per year, which includes 62,000 Tijuana residents who cross daily for work.<sup>42</sup> Additionally, about 1 in 5 deportations from the United States happen at the San Ysidro Border Crossing into Tijuana.<sup>43</sup> The region has a combined population of nearly 5 million residents; with 1.4 million residents the city of San Diego is 8<sup>th</sup> largest city in the United States, while with 1.7 million residents Tijuana is the 6<sup>th</sup> largest city in Mexico. Both cities are relatively new (San Diego incorporated in 1850, Tijuana founded in 1889) with rapid urban development in the mid to late 20<sup>th</sup> century. They also have high proportions of internal migrants from elsewhere in the United States and Mexico, drawn to the military, tourism, and business opportunities in San Diego

and to the post-NAFTA manufacturing job opportunities and proximity to the United States in Tijuana.<sup>44</sup>

In addition to bidirectional traffic of people and goods, a major illegal drug trafficking route runs from south to north through this region. In Tijuana, trafficking of heroin, methamphetamine, and cocaine through this border region contributes to a high prevalence of drug use and a large injecting drug user population at high risk for HIV and overdose.<sup>45-47</sup> There are an estimated 10,000 injecting drug users in Tijuana. HIV prevalence is estimated to be 4% in male PWID and 10% in female PWID,<sup>48,49</sup> and HIV incidence is estimated at ~2 per 100 person years. Although San Diego has much higher income and resources than Tijuana, HIV prevalence is estimated to be about 4% in PWID.<sup>67</sup> Given the substantial bidirectional traffic of people and goods there are significant implications for the diffusion of drug use behaviors and related infectious diseases like HIV into the United States and vice versa.

Another notable factor potentially influencing drug use and related harms in this region is recent drug decriminalization legislation in Mexico and California. In California medical marijuana has been legal since 1996, and since 2011 possession of small amounts of marijuana has been treated as an infraction rather than a misdemeanor or felony. In 2009, Mexico partially decriminalized possession of specific small amounts of illicit drugs and shifted responsibility for legal prosecution to the state level, with an additional provision for diverting drug users into treatment rather than jail.<sup>50</sup> The parent studies from which dissertation data were drawn were designed to evaluate the impact of this 'Narcomenudeo' reform on substance using and HIV risk behaviors of PWID in Tijuana and San Diego.

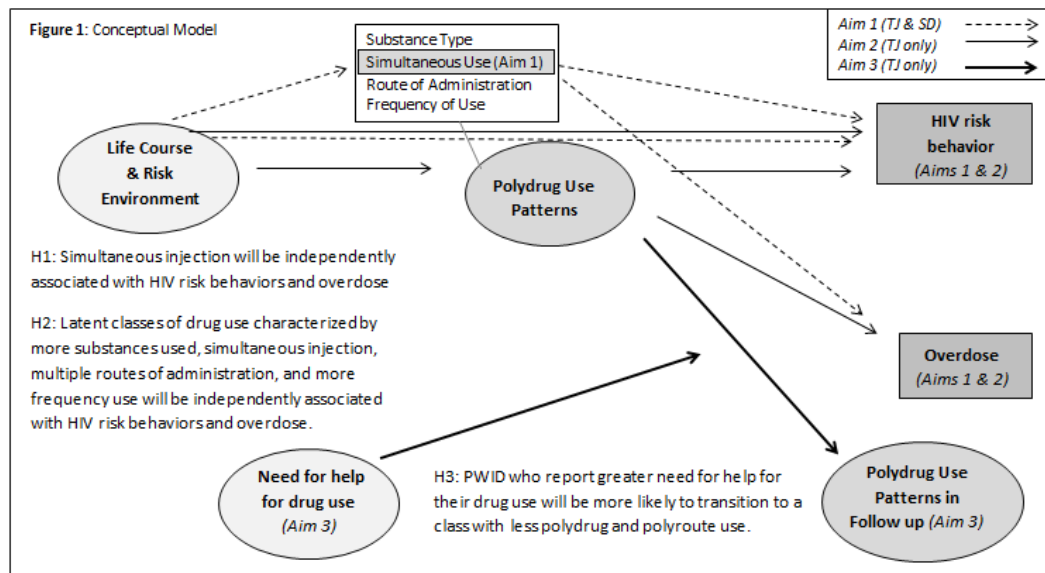
## CONCEPTUAL FRAMEWORK

The theoretical framework for this dissertation research draws on the HIV Risk Environment for drug related harms<sup>51</sup> and the Life Course Perspective on drug use trajectories.<sup>52</sup> The Risk Environment framework aims to better understand and reduce drug related harm, in particular HIV infection associated with injection drug use, by focusing on social situations and physical places where harm is produced and may be reduced. The space of the risk environment comprises two dimensions of factors that interact with each other to produce or reduce harm: (1) physical, social, economic, and policy environments at (2) micro and macro levels.

The Life Course framework for understanding drug use trajectories provides a multidisciplinary and comprehensive conceptual approach for understanding intra-individual drug use patterns over time and the interplay of these patterns with drug treatment systems. This framework highlights the concepts of transitions, turning points, and social capital in understanding processes of stability and change. It also recognizes the chronic nature of substance use disorders; heterogeneity of drug use patterns across the life span; the need to consider historical context, social environments, and individual differences; and the frequent contacts of drug users with multiple service systems.

Hypothesized relationships between life course and risk environment factors, polydrug use patterns, and HIV risks behaviors and overdose are depicted in Figure 1.1. For Aims 1 and 2, individual differences in life course and interplay with the risk environment will be associated with polydrug use patterns, which in turn are hypothesized to be associated with HIV risk behaviors and overdose, even after controlling for these individual differences and the risk environment. In Aim 1, polydrug use is operationalized as simultaneous or co-injection of heroin and

methamphetamine in both the Tijuana and San Diego PWID cohorts. In Aim 2, polydrug use is operationalized as having four dimensions (substance type, simultaneous or co-injection, route of administration, frequency of use), which are used to inform indicator selection for latent classes. For Aim 3, intra-individual heterogeneity in polydrug use is assessed over time, with self-reported need for help for drug use hypothesized to drive transitions in polydrug use patterns.



**Figure 1.1:** Conceptual model of dissertation aims and hypotheses

## AIMS AND HYPOTHESES

Based on the conceptual framework described above and a review of the relevant literature on polydrug use and associations with negative health outcomes, this dissertation has the following aims and corresponding hypotheses:

**Aim 1:** To identify and compare socio-demographic and behavioral factors associated with simultaneous injection of heroin and methamphetamine in two parallel cohorts of PWID in Tijuana, Baja California, Mexico, and San Diego, California, USA. *Hypothesis 1.1:* PWID who simultaneously inject heroin and methamphetamine will be more likely to have engaged in HIV risk behaviors like

sharing syringes, having unprotected sex, and using drugs before or during sex.

Hypothesis 1.2: There will be a significant difference in odds of sharing syringes by those who co-inject compared those who do not co-inject between the two study locations. Hypothesis 1.3: There will be a significant difference in odds of recent overdose by those who co-inject compared those who do not co-inject between the two study locations.

Aim 2: To identify discrete classes of polydrug use in a cohort of PWID in Tijuana and the association of class membership with prevalence of HIV risk behaviors and overdose. Hypothesis 2: Discrete patterns of polydrug use will be characterized by preference for opiate use vs. stimulant use, by use via non-injection routes of administration, by co-injection behavior, and by frequency of use.

Hypothesis 2.1: PWID in classes with more injection use (vs. non-injection use) and more frequent injecting will be more likely to engage in HIV injection risk behaviors like syringe sharing. Hypothesis 2.2: PWID in classes with more stimulant use will be more likely to engage in HIV sexual risk behaviors like drug use before sex.

Hypothesis 2.3: PWID in classes with multiple routes of administration will have a higher prevalence of recent overdose.

Aim 3: To describe heroin and methamphetamine polydrug use classes and transitions between classes among PWID over 6 months and determine whether class transitions are moderated by self-reported need for help for drug use.

Hypothesis 3.1: A substantial proportion of PWID will transition to a class characterized by a different profile of polydrug use at 6 month follow-up. Hypothesis 3.2: Reporting greater need for help for drug use will be associated with transitions to classes with fewer substances.

## **GLOBAL HEALTH IMPLICATIONS**

Findings from this research on polydrug use will contribute to better understanding of the complex nature of drug use and related harms and inform the development and timing of HIV and overdose preventive interventions and treatment options for polydrug users in resource-limited settings. If different classes of PWID are identified based on preference for certain substance types or routes of administration, such analyses can be used to identify subgroups of PWID who require targeted services, which is helpful for resource allocation in resource-limited settings. These analyses will also demonstrate the feasibility and utility of this latent variable mixture modeling approach to analysis of longitudinal epidemiological survey data. Findings may also contribute to understanding of general and substance-specific patterns of substance use and etiology of substance use disorders.<sup>53</sup> Finally, results may inform security and health policy responses to shifts in drug production and distribution due to economic, political, and environmental changes in other parts of the world.

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## CHAPTER 2: PREVALENCE AND CORRELATES OF HEROIN- METHAMPHETAMINE CO-INJECTION IN TWO PARALLEL COHORTS OF PEOPLE WHO INJECT DRUGS IN SAN DIEGO, CA, AND TIJUANA, BC, MEXICO

### ABSTRACT

**Background:** Although people who inject drugs (PWID) in the western U.S.-Mexico border region are known to inject both heroin and methamphetamine, less is known about the prevalence and risks associated with co-injection of this depressant-stimulant combination (also known as “goofball” and “Mexican speedball”).

**Methods:** Baseline data from parallel cohort studies of PWID conducted concurrently in San Diego and Tijuana were used to measure the prevalence and identify correlates of heroin-methamphetamine co-injection. PWID age  $\geq 18$  years who reported injecting illicit drugs in the past month were recruited using street outreach and targeted advertising in San Diego (n=576) and Tijuana (n=735). Participants completed interviewer-administered questionnaires that included socio-demographics and past 6 month drug use, overdose history, and engagement in HIV-associated injection and sexual risk behaviors. Bivariate and multivariable logistic regression analyses were used to identify correlates of heroin-methamphetamine co-injection.

**Results:** The prevalence of co-injection in the past 6 months was 39.9% overall, and was higher in Tijuana (55.8%) than in San Diego (19.8%). In multivariable analyses adjusting for study site, distributive syringe sharing [AOR = 1.87], purchasing a prefilled syringe [AOR = 1.66], finding it hard to get new syringes [AOR = 1.54], reporting great or urgent need for treatment [AOR = 1.46], and younger age [AOR = 0.93 per 5 year increase] were independently associated with co-injection. A significant interaction between overdose and study site showed that overdose in the

past 6 months was associated with a higher odds of co-injection in San Diego [AOR = 3.08, 95% CI: 1.53-6.08] than in Tijuana [AOR = 1.27, 95% CI: 0.76-2.13].

**Conclusions:** These findings indicate that heroin-methamphetamine co-injection is more common in Tijuana than in San Diego, yet this practice had a stronger association with overdose in San Diego than in Tijuana. Heroin-methamphetamine co-injection was also independently associated with HIV injection risk behaviors. Overdose prevention interventions should address co-injection of depressants and stimulants.

## INTRODUCTION

Although heroin is the main illicit drug injected worldwide,<sup>1</sup> methamphetamine has emerged as a major drug of abuse by injection and smoking routes of administration, especially in western U.S. states and northwestern Mexico. Methamphetamine production has increased in Mexico<sup>1-3</sup> following U.S. state and federal government crackdowns on labs and regulation of precursor chemicals in the 1990s and Mexico has replaced Columbia as the major regional producer of heroin.<sup>4</sup> Tijuana, Baja California, Mexico, and San Diego, California, USA, are adjacent cities on the westernmost edge of the U.S.-Mexico border, connected by the busiest land border crossing in the Western Hemisphere and situated on a major drug trafficking route.<sup>2</sup> Production and trafficking of heroin and methamphetamine in Mexico and trafficking to other countries, mainly the United States, has had a 'spillover' effect into local consumption markets. This spillover effect is seen particularly along the U.S.-Mexico border, where higher consumption of methamphetamine in northwestern Mexico mirrors the east-west cocaine-methamphetamine gradient of use observed north of the border.<sup>2,3,5</sup>

Polydrug use, or use of multiple substances, has been associated with greater dependence, younger age, and male gender.<sup>6,7</sup> Use of multiple substances also places great strain on the respiratory and cardiac functions of the body, placing users at greater risk for overdose.<sup>8</sup> While use of heroin, a central nervous system depressant,<sup>9</sup> increases risk for overdose because of lowered respiratory rate, methamphetamine is a central nervous system stimulant that increases the heart rate and, correspondingly, oxygen demands.<sup>10</sup> Thus, co-injection of these two substances may increase the risk for overdose both through cessation of respiration and cardiac arrest. Furthermore, stimulants allow users to inject larger doses of opioids and

respiratory related overdose may occur when the shorter lasting stimulant effect wears off.

Methamphetamine use has been linked to high risk sexual behaviors, including greater number of casual partners and inconsistent condom use,<sup>11-15</sup> which could increase the likelihood of HIV seroconversion.<sup>14,16</sup> It is not clear from the existing research if this increased sexual risk for HIV among methamphetamine users is also increased for heroin-methamphetamine co-injectors. In addition to increased sexual libido, motivations for methamphetamine use include increased sociability and energy and loss of inhibitions,<sup>12,13,15</sup> this is in contrast to the analgesic, depressant, and dissociative effects of heroin. Although the majority of people who inject drugs (PWID) inject heroin and other opioids, PWID who co-inject heroin and methamphetamine may engage in more unsafe injecting practices due to the added socializing and dis-inhibitory effects of methamphetamine.

Stimulant-heroin combinations were reported as common among PWID in qualitative interviews in Tijuana in 2004. Participants reported that the combination of drugs was cheaper than buying heroin alone,<sup>5</sup> and that the combination is also used to intensify the effect of low purity heroin. Specific “street names” for this combination in Mexico include “speedball” or “*espibulazo*,” (which may also refer to cocaine and heroin combinations), “Mexican speedball,” as well as “*coctel de muerte*” (cocktail of death).<sup>5,17</sup> Field staff in Tijuana have reported that this combination is also referred as “*speedys*.” In the United States this combination may be referred to as “goofball”<sup>18,19</sup> or “Mexican speedball.”

The U.S.-Mexico border region is characterized by dramatic income disparities between the two countries and high levels of migration.<sup>17</sup> Injection drug use, a large red light district (*zona roja*) attracting sex tourism, and high levels of social and

economic disparities have contributed to a localized HIV epidemic in Tijuana. Given the substantial bidirectional traffic of people and goods in this region, there are significant implications for cross-border spread of unsafe injecting practices that heighten the risk of blood borne infections including HIV and hepatitis C. Although PWID are known to inject both heroin and methamphetamine,<sup>11,20-23</sup> less is known about the prevalence of and risks associated with mixed or co-injection of this depressant-stimulant combination.

The present analysis sought to examine the prevalence and correlates of heroin-methamphetamine co-injection among PWID in San Diego, California, and Tijuana, Baja California. Given the production of methamphetamine in Mexico and more limited access to resources, we hypothesized that past 6 month prevalence of heroin-methamphetamine co-injection would be higher among PWID in Tijuana. We also hypothesized that PWID who co-injected heroin and methamphetamine would be more likely to engage in HIV-associated injection and sexual risk behaviors and to have experienced a recent overdose. Examining prevalence and correlates of co-injection of these two substances may indicate that this is high risk behavior associated with HIV and overdose among PWID in these two adjacent border cities facing methamphetamine use epidemics.

## **METHODS**

### **Study Participants and Procedures**

Data for these analyses comes from the baseline assessments of two parallel prospective cohort studies of people who inject drugs (PWID) in Tijuana (*Proyecto El Cuete Phase IV*) and in San Diego (*STAIR II*). The studies were designed to be comparable in their methods, aims, and survey content.<sup>24</sup> From March 2011 to May 2012, Proyecto El Cuete IV enrolled 735 participants who completed quantitative

surveys and HIV testing every 6 months for three years. From June 2012 to January 2014, STAHR II enrolled 576 participants who completed quantitative surveys and HIV testing every 6 months for two years.

Potential participants were recruited through convenience sampling using targeted street and venue based outreach by local staff and peer referrals. These individuals were referred to storefront offices where they were screened for eligibility and underwent informed consent procedures. Eligibility criteria included: (1) injecting illicit drugs within the past month, confirmed by track marks; (2) age 18 or older; (3) speaking Spanish or English; (4) current residence in Tijuana (El Cuete) or San Diego (STAHR) with no plans to move for 2 years.

Trained interviewers administered quantitative questionnaires in English or Spanish using computer assisted personal interview (CAPI) technology on a laptop in a private room. The baseline assessment included questions about socio-demographics and lifetime and past 6 month history of drug use and related health behaviors. Participants were reimbursed for completing the baseline assessment and disease testing (\$25 USD for STAHR II and \$20 USD for El Cuete IV). Pre- and post-test counseling for HIV was performed according to CDC guidelines and HIV-positive individuals were given referrals for free or reduced-cost healthcare. Additional details regarding HIV testing and parallel study procedures may be found in a previously published paper.<sup>24</sup> The University of California San Diego Human Research Protection Program approved both study protocols. The Institutional Review Board for el Colegio de la Frontera Norte (COLEF) also approved the study protocol for El Cuete IV.

## Measures

*Dependent variable:* Participants were asked about their lifetime and frequency of past 6 month heroin-methamphetamine co-injection. Frequency of *heroin-methamphetamine co-injection* was dichotomized into yes or no for past 6 month use of this combination.

*Socio-demographic characteristics* assessed at baseline included age, gender, education level, race and ethnicity, income, housing status, birthplace, and years living in Tijuana or San Diego. For this comparative analysis, education level was dichotomized to completion of high school in San Diego (yes/no) and to completion of *preparatoria* in Tijuana (yes/no) (i.e., 12 years of education). For housing status, participants were asked where they had lived or slept in the past 6 months. From an identical list of options for both studies, responses of sleeping most often in a vehicle, abandoned building, shelter, in the streets, or in a shooting gallery were classified as sleeping in places consistent with being homeless (yes/no). Participants also reported their age of first injection; the difference between age and age of first injection was calculated to provide an estimate of duration of injection behavior.

*HIV-associated injection behaviors* included past 6 month engagement in receptive syringe sharing; distributive syringe sharing; sharing of cookers, cotton, or rinse water; sharing unbleached syringes; dividing drugs using a syringe; and purchasing a prefilled syringe.

*HIV-associated sexual behaviors* included past 6 month engagement in unprotected sex with a casual partner; having two or more casual partners; exchanging sex for food, money, drugs, or shelter; and using drugs during or within two hours before having sex.

*HIV and overdose.* A dichotomous variable was used for whether participants tested positive for *HIV* through serologic testing. Participants self-reported lifetime and past 6 month history of *overdose*, which was also described by the interviewer as a time the participant passed out due to drug use, could not wake, or lips turned blue.

*Need for harm reduction services* was assessed by two questions regarding need for help for drug use and difficulty of accessing sterile syringes. Participants were asked to state to what degree they *need help for their drug use* with response options of no need, some need, great need, and urgent need, which were dichotomized into no or some need versus great or urgent need. Participants were also asked *how hard it was to obtain sterile syringes*, with responses dichotomized into easy or very easy versus hard or very hard.

### **Statistical Analysis**

Univariate descriptive statistics were assessed overall and by study location (Tijuana vs. San Diego). Chi-squared tests and Wilcoxon rank sum tests were used to determine bivariate associations between co-injection and socio-demographic characteristics, HIV associated risk behaviors, HIV status, recent overdose, harm reduction service need, and study location. Covariates with a significance level of  $p < 0.10$  were considered for inclusion in multivariable logistic regression analysis to determine independent associations. These covariates were then added by conceptual blocks hierarchically into a logistic regression model in a manual step-wise fashion starting with injection behaviors and followed by sexual behaviors, health outcomes, harm reduction service need, and socio-demographic characteristics. Covariates with regression coefficients significant at  $p < 0.05$  were retained in the final model.

Interaction terms with study location and covariates significant in the main effects model were tested to determine if associations with co-injecting behavior were different in the two locations. In order to determine if they were potential confounders, variables significant at the bivariate level, but not in the final model, were added to assess changes in coefficients of more than 10% for variables in the final multivariable model. We also checked for linearity on the logit scale for the continuous covariate variables.

## RESULTS

### Sample Characteristics and Prevalence of Co-injection

Among the 1,311 participants from both cohorts (San Diego:  $n=576$ ; Tijuana;  $n=735$ ), 32.7% were female and the median age was 39 (range: 18-70). Less than one-quarter (22.4%) had completed high school or *preparatoria* and 42.0% slept in places consistent with being homeless in the past 6 months. About one-third of participants (35.7%) were born in the city where they were enrolled. Participants had resided in San Diego or Tijuana for a median of 23.9 years and had been injecting for a median of 17.9 years, with a median age at first injection at 20 years. There were quite a few significant differences between the two cohorts for several socio-demographic characteristics. A greater percentage of participants from Tijuana were female (38.0 vs. 26.3%,  $p<0.001$ ). Tijuana participants were also less likely than San Diego participants to have completed *preparatoria*, were less likely to be homeless, had a younger median age, and had lived fewer years in their city of residence (Table 2.1).

Overall prevalence of past 6 month heroin-methamphetamine co-injection was 39.9%, and was significantly higher in Tijuana than in San Diego (55.8% vs. 19.8%;  $p<0.001$ ). HIV prevalence overall was 6.1%, and was higher in the San Diego

cohort than in the Tijuana cohort. Past 6 month prevalence of overdose was 9.1%. Nearly all HIV-associated injection behaviors, except for purchasing a prefilled syringe, were reported by a majority of participants (55.6%-69.2%). Three-quarters of participants reported using drugs before or during sex. About one third reported having 2 or more casual sexual partners in the past 6 months and having unprotected sex with a casual sex partner. One-fifth reported exchanging sex in the past 6 months, with a greater percentage reporting this in Tijuana than in San Diego. (See Table 2.1)

### **Correlates of Heroin-Methamphetamine Co-Injection**

In bivariate analyses (Table 2.2), those who co-injected heroin and methamphetamine were more likely to be younger, to have spent less time in the region, to have injected for less time, and to have started injecting at a younger age. Consistent with our hypothesis, those who co-injected were more likely to have engaged in HIV-associated injection risk behaviors. They were also more likely to have exchanged sex for something they needed, used drugs before or during sex, and overdosed in the past 6 months. Furthermore, PWID who co-injected heroin and methamphetamine were more likely to report great or urgent need for help for their drug use and to report that it was hard or very hard to obtain sterile syringes.

### **Independent Associations with Co-Injection**

In multivariable logistic regression analyses adjusting for study site (Table 2.3), heroin-methamphetamine co-injection was independently and positively associated with distributive syringe sharing (AOR: 1.87, 95% CI: 1.41-2.47), purchasing a prefilled syringe (AOR: 1.66, 95% CI: 1.09-2.49), finding it hard to obtain sterile syringes (AOR: 1.54, 95% CI: 1.11-2.13), reporting great or urgent need for help for drug use (AOR: 1.46, 95% CI: 1.12-1.86), and younger age (AOR: 0.93 per 5

years, 95% CI: 0.88-0.99). A significant interaction ( $p=0.046$ ) between overdose and study location showed that the odds of co-injection was higher for those with a recent overdose compared to those without a recent overdose in San Diego (AOR: 3.05, 95% CI: 1.53-6.08) and Tijuana (AOR: 1.27, 95% CI: 0.76-2.13), although the 95% confidence interval for the adjusted odds ratio overlapped with 1 in Tijuana.

## **DISCUSSION**

Findings indicate that heroin-methamphetamine co-injection among PWID is more common in Tijuana than in San Diego, yet this practice had a positive independent association with overdose in San Diego and a lower and positive though not significant independent association in Tijuana. Heroin-methamphetamine co-injection was also independently associated with injection risk behaviors but not independently associated with sexual risk behaviors. PWID who co-injected these two drugs were younger and reported more difficulty finding sterile syringes and being in greater need of help for their drug use.

Prevalence of past 6 month heroin-methamphetamine co-injection in Tijuana and San Diego was similar or higher than previous reports. From 2006-2007 the prevalence of heroin-methamphetamine co-injection among PWID in Tijuana was 53.3%,<sup>21</sup> and from 2009-2010 the prevalence of past 6 month co-injection of heroin with methamphetamine or cocaine among San Diego PWID aged 18-40 was 7.2%.<sup>20</sup> This increase in prevalence may indicate a potential increase in this behavior in San Diego.

Few other epidemiologic studies have reported on heroin-methamphetamine co-injection. Other reports of heroin-methamphetamine co-injection in the United States include 11.0% of Seattle syringe exchange program participants reporting past year use in 2009<sup>18</sup> and 23.0% of young PWID in San Francisco reporting past 3

month use in 2000-2001.<sup>19</sup> These studies also found that this behavior was associated with past year non-fatal overdose.

Another simulant-depressant combination – heroin and cocaine co-injection – known as “speedball,” has been reported as more common in the U.S. east coast,<sup>25</sup> where cocaine is more commonly used than methamphetamine. PWID on the west coast may be co-injecting heroin and methamphetamine for similar reasons as those injecting speedballs on the east coast, but using the more locally available methamphetamine instead of cocaine.

While all of these independent associations with HIV injection behaviors, service need, and age were of similar magnitude in both cities, the finding that odds of co-injection among those with a recent overdose was significantly higher only in San Diego is concerning. Given the lower prevalence of this behavior in San Diego, this finding may reflect that it is engaged in by mainly higher risk taking PWID in San Diego, whereas it may be more common and normalized among PWID in Tijuana. Nevertheless, overdose prevention efforts in both cities should address co-injection of heroin and methamphetamine.

Although it was hypothesized that sexual risk behavior would be greater among PWID who co-injected heroin and methamphetamine, this was not supported in multivariable analyses, perhaps because the independent association with HIV drug injection behaviors overshadowed the smaller bivariate association with sex exchange and using drugs before sex. Independent associations with distributive syringe sharing and prefilled syringe purchase may be indicative of the social circumstances surrounding co-injection, such as reciprocal sharing of drugs and minimizing other risks. This finding is consistent with the higher energy and greater sociability reported by methamphetamine users, yet also suggests that this co-

injection behavior may increase the chances of transmitting HIV through sharing of injection equipment.

The positive association between co-injection and the need for harm reduction services (e.g. drug treatment and sterile syringe access) in both cities emphasizes and reinforces the need for improved access to non-coercive treatment and syringe exchange programs. Treatment programs focusing on opiate substitution therapy may have limited effectiveness for PWID who are also co-injecting methamphetamine. The association of need for help for drug use and co-injection also aligns with previous research that polydrug users may be more drug dependent.<sup>7</sup>

There are several limitations to this analysis that must be considered. Self-report of drug using behavior and possible recall bias may raise questions about underreporting of substance use, but many papers have demonstrated the general validity of PWID self-reports<sup>26</sup> and participants had already disclosed their injection behavior as an eligibility criteria for enrolling in these studies. Although the two studies were conducted concurrently and were designed to be comparable, these two populations of PWID and the environment in which they live are quite different. Given that this analysis was conducted with cross-sectional data, we are unable to determine temporal sequence between heroin-methamphetamine co-injection and overdose occurrence. Future studies should obtain greater specificity regarding the proximity of these events. Generalizability of these findings may also be limited to regions where heroin and methamphetamine use is common, though global drug use statistics indicate that co-occurrence of heroin use, methamphetamine use, and injection behaviors may be growing several regions.<sup>1</sup>

As drug production regions and trans-shipment routes shift in response to environmental, economic, and policy changes, there is a need to pay attention to

spillover effects into local drug consumption markets, particularly in lesser developed regions with growing numbers of urban migrants.<sup>27</sup> This is one of the first studies to specifically examine the association between heroin-methamphetamine co-injection with health risk behaviors in a large of sample of PWID in a dynamic binational border setting. Findings indicate the need to consider use of multiple substances as a correlate of HIV-associated risk behaviors and overdose occurrence, as well as a potential indicator in global drug use surveillance efforts.<sup>28</sup> Future research on specific drug combinations and routes of administration, as well as event level motivations and contextual drug market factors, will further contribute to effective and appropriate responses and interventions to prevent HIV transmission and overdose.

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**Table 2.1:** Comparison of socio-demographics, heroin-methamphetamine co-injection, HIV risk behaviors, overdose, HIV status, and service need between PWID in San Diego and Tijuana (N = 1,311)

Background	San Diego (N = 576) N (%)	Tijuana (N = 735) N (%)	p- value
Male	418 (72.8)	456 (61.9)	<0.001
Female	149 (26.3)	279 (38.0)	<0.001
Transgender	6 (1.1)	0	<0.001
Completed High School or <i>Preparatoria</i>	207 (36.1)	87 (11.8)	<0.001
Slept mostly in places consistent with homelessness	300 (52.1)	199 (27.1)	<0.001
Born in city of residence	201 (35.0)	266 (36.2)	0.660
Income over \$10,000/year	182 (31.7)		
Income over 3500 pesos/month		202 (27.6)	
Age (median, SD)	45.0 (11.7)	37.0 (8.9)	<0.001
Years in San Diego or Tijuana (median, SD)	25.1 (17.4)	21.0 (14.2)	<0.001
Age of first injection (median, SD)	20.0 (8.2)	19.0 (6.8)	0.001
Years injecting (median, SD)	20.0 (13.4)	16.0 (9.6)	<0.001
Heroin-methamphetamine co-injection			
Ever co-injected	236 (41.2)	513 (69.6)	<0.001
Past 6 months co-injected	111 (19.8)	411 (55.8)	<0.001
Past 6 months co-injected weekly	35 (6.1)	347 (47.2)	<0.001
Past 6 months co-injected daily	15 (2.6)	283 (38.5)	<0.001
Injection risk behavior (past 6 months)			
Receptive syringe sharing	289 (54.3)	525 (71.4)	<0.001
Distributive syringe sharing	291 (56.6)	531 (72.2)	<0.001
Cooker, cotton, rinse water sharing	365 (67.0)	490 (66.9)	0.963
Shared unbleached syringe	198 (37.2)	483 (65.8)	<0.001
Divided drugs with syringe	283 (55.6)	444 (60.6)	0.080
Purchased prefilled syringe	26 (4.5)	109 (14.9)	<0.001
Sex risk behavior (past 6 months)			
2+ casual partners	163 (28.4)	261 (35.9)	0.004
Unprotected sex with casual partner	180 (31.3)	241 (33.1)	0.490
Exchanged sex	40 (7.8)	226 (31.1)	<0.001
Drug use before or during sex	405 (71.4)	567 (77.4)	0.017
HIV & Overdose			
Ever overdosed	238 (41.5)	401 (54.6)	<0.001
Past 6 months overdose	45 (7.9)	74 (10.1)	0.167
Tested HIV positive	52 (9.4)	26 (3.5)	<0.001
Need for Harm Reduction Services			
Hard to find sterile syringes	93 (16.2)	136 (18.5)	0.278
Great or urgent need for help for drug use	218 (38.4)	376 (51.2)	<0.001

**Table 2.2:** Bivariate analysis of factors associated with heroin-methamphetamine co-injection in the past 6 months among PWID in San Diego and Tijuana (N = 1,311)

	Overall (N = 1311)		Co-injected (N = 522)		Did not co- inject (N = 773)		p-value
	N	%	N	%	N	%	
<b>Background</b>							
Female	428	32.7%	179	34.3%	244	31.6%	0.232
Completed High School or <i>Preparatoria</i>	294	22.5%	91	17.4%	198	25.5%	<0.001
Homeless/Unstable housing	499	38.1%	193	37.0%	296	38.3%	0.631
Born in city of residence	467	35.7%	181	34.7%	282	36.5%	0.544
Age (median, SD)	39.0	10.6	38.0	9.6	42.0	11.1	<0.001
Years in region (median, SD)	23.9	15.8	21.0	14.8	25.6	16.3	<0.001
Age first injection (median, SD)	20.0	7.5	19.0	6.6	20.0	8.0	0.002
Years since 1st injected (median, SD)	17.0	11.7	16.0	10.5	18.0	12.3	<0.001
Site (ref: San Diego)	735	56.1%	411	78.7%	324	41.9%	<0.001
<b>Injection risk behavior (past 6 months)</b>							
Receptive syringe sharing	814	64.3%	393	76.3%	412	55.8%	<0.001
Distributive syringe sharing	822	65.8%	394	77.0%	418	54.2%	<0.001
Cooker, cotton, water sharing	855	53.8%	391	75.5%	454	60.9%	<0.001
Shared unbleached syringe	681	58.5%	347	67.4%	325	44.0%	<0.001
Divided drugs with syringe	727	58.5%	347	68.5%	371	51.2%	<0.001
Purchased prefilled syringe	135	10.3%	87	16.3%	50	6.5%	<0.001
<b>Sex risk behavior (past 6 months)</b>							
2+ casual partners	424	32.5%	183	35.0%	239	31.1%	0.111
Unprotected sex with casual partner	421	32.3%	182	35.1%	236	30.7%	0.095
Exchanged sex	266	21.4%	146	29.1%	119	16.3%	<0.001
Drug use before or during sex	972	74.8%	406	78.4%	556	72.4%	0.015
<b>HIV &amp; Overdose</b>							
Ever overdose	639	48.9%	312	59.8%	320	41.5%	<0.001
Past 6 month overdose	119	9.1%	66	12.6%	49	6.4%	<0.001
Tested HIV positive	78	6.1%	19	3.7%	58	7.7%	0.003
<b>Need for Harm Reduction Services</b>							
Hard to obtain sterile syringes	229	17.5%	115	22.1%	110	14.3%	<0.001
Great or urgent need for help for drug use	594	45.6%	274	52.8%	311	40.4%	<0.001

**Table 2.3:** Multivariable analysis of factors associated with heroin-methamphetamine co-injection in the past 6 month among PWID in San Diego and Tijuana (N=1,224)

	Unadjusted Bivariate		Model 1 (Main Effects)		Model 2 (Interaction)	
	OR	95% CI	AOR	95% CI	AOR	95% CI
Age (per 5 year increase)	0.85	0.80-0.89	0.93	0.88-0.99	0.93	0.88-0.99
Distributive syringe sharing	2.44	1.89-3.14	1.88	1.42-2.49	1.87	1.41-2.47
Purchase prefilled syringe	2.08	1.94-4.05	1.64	1.09-2.12	1.66	1.09-2.49
Past 6 month overdose	2.14	1.45-3.15	1.74	1.13-2.83	--	--
Hard to obtain sterile syringes	1.71	1.28-2.78	1.53	1.11-2.14	1.54	1.11-2.13
Great or urgent need for help for drug use	1.65	1.32-2.06	1.44	1.12-1.84	1.46	1.12-1.86
Tijuana cohort vs. San Diego cohort	5.13	3.98-6.61	4.27	3.23-5.65	--	--
Overdose*Site						
Tijuana					1.27	0.76-2.13
San Diego					3.05	1.53-6.08

OR = Unadjusted Odds Ratio, AOR = Adjusted Odds Ratio, CI = Confidence Intervals

*p*-value for overdose\*site term = .046

Reference group is "did not co- inject heroin and methamphetamine in the past 6 months"

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### CHAPTER 3: LATENT CLASSES OF POLYDRUG USE AND ASSOCIATIONS WITH HIV RISK BEHAVIORS AND OVERDOSE AMONG PEOPLE WHO INJECT DRUGS IN TIJUANA, BAJA CALIFORNIA, MEXICO

#### ABSTRACT

**Aims:** Patterns of polydrug use among people who inject drugs (PWID) may be differentially associated with overdose as well as with unique risk factors for HIV transmission. Subgroups of PWID in Tijuana, Mexico, were probabilistically identified based on substances used, route of administration, frequency of use, and co-injection indicators.

**Methods:** Participants were PWID residing in Tijuana age  $\geq 18$  who reported injecting an illicit substance in the past month (N = 735). Latent class analysis was conducted to determine discrete classes of polydrug use as characterized by 11 indicators of past 6 month substance use. Multinomial logistic regression examined class membership association with HIV injection and sexual risk behaviors, overdose, and other covariates using an automated 3 step procedure in Mplus to account for classification error.

**Results:** PWID in Tijuana were classified into five distinct subgroups. Two polydrug and polyroute classes were defined by use of multiple substances through several routes of administration and were primarily distinguished from each other by cocaine use (Class 1: 5% vs. Class 2: 29%). The other three classes consisted primarily of injectors, distinguished by the substances injected: cocaine, methamphetamine, and heroin injection and co-injection (Class 3: 4%); methamphetamine and heroin injection and co-injection (Class 4: 10%); and heroin injection (Class 5: 52%). Regression analyses showed that, compared to the heroin injection class, memberships in the two polydrug and polyroute use classes were significantly

associated with HIV risk behaviors and overdose, as well as with pre-disposing and risk environment factors.

**Conclusions:** Findings highlight the heterogeneity in substance use patterns among PWID in Tijuana and demonstrate that polydrug and polyroute users are a high-risk subgroup who may require more tailored prevention and treatment interventions.

Polyroute users may also represent an HIV transmission “bridge population” to social networks of non-injection drug users.

## INTRODUCTION

Injection of illicit substances is a significant global public health problem associated with multiple negative health outcomes, including transmission of HIV, hepatitis B and C, as well as higher risk for overdose related morbidity and mortality.<sup>1</sup> Although most people who inject drugs (PWID) primarily inject heroin, some PWID also inject methamphetamine and cocaine and report use of these and other substances through smoking, snorting, or ingestion routes of administration. Polydrug use is described most broadly as the use of more than one substance, but different studies use varying time frames and specifications of polydrug use, making comparisons and deeper understanding of this complex but common phenomenon more difficult.<sup>2-5</sup> While the United Nations Office on Drugs and Crime (UNODC) World Drug Report and Global Burden of Disease Study<sup>6</sup> take a substance-specific approach to summarizing global statistics on drug use and related disease burden, there is growing recognition that substance use behaviors often involve use of multiple drugs and that descriptions of these patterns of use and their relationship to drug related harms warrant further study.<sup>6-8</sup>

Use of different substances and different routes of administration are associated with specific negative health outcomes. While heroin users are at high risk for overdose because of the drug's depressant effect on breathing,<sup>9,10</sup> mixing of opiates like heroin with stimulants like cocaine or methamphetamine can contribute to high risk for overdose through increased toxicity, decreased cognitive function, and cardiac stress.<sup>11</sup> The sharing of needles and syringes among PWID can transmit HIV and hepatitis B and C. Non-injection drug use, especially for stimulants and alcohol, is also associated with increased risk of HIV acquisition and/or transmission. Stimulants and alcohol lower inhibitions, and when used in the context of

transactional sex and immediately before sex, may decrease power to negotiate condom use.<sup>12</sup> Use of different substances and routes of administration may also differ with respect to gender, age, place of origin, socioeconomic status, and initial drug use and injection experiences. Earlier initiation of drug use is typically associated with worse outcomes<sup>13</sup> and initial drug use experiences may be related to pharmacological preference and networks of peers who use similar substances.

The environment where one lives, acquires, and uses drugs, also has important implications for drug related harms. Tijuana, Baja California, Mexico, exhibits many of the characteristics of the risk environment for drug related harms, a framework that conceptualizes macro and micro level physical, social, economic, and policy dimensions<sup>14,15</sup> that are important to consider in relation to health behaviors and health outcomes. At the macro-level, Tijuana is physically situated on a major drug trafficking route, which contributes to elevated rates of illicit drug use in Tijuana, especially among socially marginalized migrant, deportee, and unstably housed populations. Limited resources for health services, and high levels of social and economic inequality have contributed to a localized HIV epidemic in this city on the western Mexico-U.S. border.<sup>16,17</sup> At the micro-level, PWID in Tijuana encounter abusive and extra-legal interactions with law enforcement<sup>18</sup> and targeted in crackdowns that disrupt social networks, especially in the Zona Norte area and in the Tijuana river canal that runs along the U.S.-Mexico border (known as 'El Bordo'). Most PWID also face severe economic deprivation and have limited access to harm reduction services (i.e. NGO run needle and syringe exchanges and privately run methadone maintenance programs).

Latent class analysis (LCA) has been increasingly applied in recent years to examine patterns of substance use among both general and high risk populations.

Several of these LCA studies have examined how distinct polydrug use classes are associated with HIV risk and overdose, finding that use of more substances was associated with greater risk for these negative health outcomes.<sup>19-22</sup> Despite findings of considerable heterogeneity of drug use patterns and associations with HIV risk behaviors and overdose, most of these studies were conducted in high income countries and therefore may not be generalizable to populations in different contextual environments in lower and middle income countries (LMIC), such as Mexico.

Previous work investigating polydrug use and HIV and overdose risk among PWID in the U.S.-Mexico border setting has found that PWID differ with respect to which substances they inject or smoke and that these differences were associated with demographics, health status, and risk behaviors.<sup>23,24</sup> Applying latent class analysis, we previously identified three classes of polydrug use (as characterized by methamphetamine and cocaine injection and non-injection) among an earlier cohort of heroin injectors sampled from 2006-2007 in Tijuana.<sup>25</sup> The present analysis expands on this earlier work by examining a more contemporary cohort (assessed 2011-2012) of PWID in Tijuana and a broader range of substance use indicators that also include frequency of use (daily vs. less than daily), co-injection of heroin with methamphetamine and heroin with cocaine, and use of marijuana and tranquilizers.

The objectives of the present analysis are (1) to identify discrete classes of polydrug use in a cohort of PWID using 4 dimensions of indicators (substance, route of administration, co-injection, and frequency) and (2) to determine the association of class membership with HIV associated risk behaviors and recent overdose, above background or pre-disposing demographic and risk environment covariates. It was hypothesized that classes characterized by more substances, routes of

administration, and co-injection would be more likely to experience overdose than classes characterized by use of fewer substances and routes of administration; that classes with more stimulant use would be more likely to engage in HIV sexual risk behaviors than classes without stimulant use; and that classes with more frequent injection use would be more likely to engage in HIV injection risk behaviors than classes with less frequent injection use.

## **METHODS**

### **Study Participants and Procedures**

The present study sample consisted of 735 male and female participants from the baseline assessment of *Proyecto El Cuete Phase IV*, a prospective cohort study of people who inject drugs in Tijuana, Baja California, Mexico <sup>26</sup>. Participants were recruited through convenience sampling using targeted street outreach from March 2011 to May 2012. Eligibility criteria included (1) injecting illicit drugs within the past month, confirmed by track marks; (2) age 18 or older; (3) speaking Spanish or English; (4) current residence in Tijuana with no plans to move for 3 years. Trained interviewers administered quantitative interviews in English or Spanish using computer assisted personal interview (CAPI) technology on a laptop in a private room. All participants provided written informed consent and were reimbursed \$20 USD for completing the baseline assessment. HIV testing was conducted with rapid Determine® HIV tests followed by a second, different rapid test for HIV-positive results. Confirmatory HIV testing was performed with Western Blot assay at the San Diego County Health and Human Services Agency laboratory. HIV-positive individuals were given referrals for free or reduced-cost healthcare. The University of California San Diego Human Research Protection Program and the Institutional

Review Board for the Colegio de la Frontera Norte (COLEF) approved the study protocol.

## **Measures**

*Drug use indicators for latent class analysis.* Participants were asked about their lifetime use and frequency of past 6 month use by route of administration of numerous illicit drugs. These drugs included marijuana, heroin (both black tar and “china white”), methamphetamine, cocaine, OxyContin and other non-prescription opioids, hallucinogens, ketamine, ecstasy/MDMA, PCP, inhalants, tranquilizers, and barbiturates. Co-injection of heroin, methamphetamine, and cocaine was also assessed.

Drug use was dichotomized into past 6 month use (yes vs. no). Drugs used by at least 5% of the sample were selected as drug use indicators. Due to a low prevalence of smoking or snorting routes of heroin and cocaine use, these non-injection routes of administration were combined into single indicators (i.e. heroin snorting/smoking and cocaine snorting/smoking). Three indicators (methamphetamine smoking, methamphetamine injection, and methamphetamine and heroin co-injection) with over 10% daily use were selected as frequency indicators and were converted into an ordinal three level variable of daily use, less than daily use, or no use in the past 6 months. The resulting 11 indicators were: heroin smoking/snorting, heroin injection, cocaine smoking/snorting, cocaine injection, heroin and cocaine co-injection (speedball), frequency of methamphetamine smoking, methamphetamine snorting, frequency of methamphetamine injection, frequency of methamphetamine and heroin co-injection, marijuana smoking, and tranquillizer ingestion. (Table 3.2)

*Covariates.* *HIV-associated injection behaviors* included past 6 month engagement in receptive syringe sharing; distributive syringe sharing; and sharing of cookers, cotton, or rinse water. *HIV-associated sexual behaviors* included past 6 month engagement in unprotected sex with a casual partner; having two or more casual partners; exchanging sex for food, money, drugs, or shelter; and using drugs during or within two hours before having sex. A dichotomous variable was used for whether participants tested positive for *HIV* through serologic testing. Participants self-reported lifetime and past 6 month history of *overdose*, which was described by the interviewer as a time the participant passed out due to drug use, could not wake, or lips turned blue.

*Background demographics* assessed at baseline included age, gender, education level, deportation history, and whether participants had spent their whole life in Tijuana. Participants also reported their age of first injection and first illegal drug use, as well as the type of drug injected or used for the first time. Responses for first drug injected were dichotomized into heroin vs. other and responses for first drug used were dichotomized into marijuana vs. other. Lifetime history of ever being forced to have sex was also assessed.

To assess interactions with the *risk environment*, participants reported information about past 6 month socioeconomic status that included typical number of hours spent on the street and monthly income (dichotomized into greater or less than \$2,500 Mexican pesos/month, or about \$200 USD in 2011). Participants also reported if they had been being stopped or arrested by the police or gone to jail in the past 6 months and in which neighborhood they inject most often (dichotomized into Zona Norte/'El Bordo' vs. other). To determine need for harm reduction services, participants were asked to state to what degree they need help for their drug use

(dichotomized into no need vs. some, great, or urgent need) as well as how hard it was to obtain sterile syringes (dichotomized into easy or very easy vs. hard or very hard). Participants also reported whether they were currently on or had ever received methadone maintenance.

### **Statistical Analysis**

Latent class analysis (LCA) is an exploratory person-centered nonparametric approach used to probabilistically determine and classify a heterogeneous population into more homogenous latent or unobserved subgroups, based on a set of observed indicator variables.<sup>27,28</sup> A three-step LCA with covariates was used to examine patterns of polydrug use. Compared to traditional approaches of assigning individuals to classes or estimating associations as part of the model fitting process, the three-step procedure improves efficiency and corrects for measurement and classification bias in determining associations between latent class membership and covariates. Assigning individuals to classes may result in classification error that may underestimate associations with covariates. In contrast, a three step approach fixes, or constrains, the measurement relationship between assigned most likely class membership and latent class to account for this error.<sup>29</sup>

*LCA Measurement Model (Step 1):* First, a latent class analysis was conducted in Mplus version 7.0<sup>30</sup> to determine latent classes of polydrug use, using 11 indicators of past 6 month polydrug use (8 dichotomous indicators and 3 ordinal indicators). Models were fit with increasing number of classes until model fit decreased. Each model was run with 500 iterations and 50 random starts. Models of differing class numbers were compared using statistical fit indices of Akaike's information criteria (AIC), Bayesian information criteria (BIC), sample size adjusted Bayesian information criteria (sBIC), and Lo-Mendell-Rubin adjusted Likelihood Ratio

Test (LMRT), and descriptive fit index of entropy. The best fitting model was selected based on smallest AIC, BIC, and sBIC; significant LMRT ( $p < 0.05$ ); highest entropy; classification quality; and substantive interpretability. Resulting conditional response probabilities (probability of endorsing an indicator given class membership) were used to characterize classes.

*LCA with covariates.* Logits of classification probabilities were extracted (*Step 2*) to incorporate measurement error for most likely class membership into an auxiliary model (*Step 3*) with most likely class and fixed measurement error using the automated 3 step approach in Mplus.<sup>29,31,32</sup> Resulting logit parameter estimates from univariate multinomial logistic regression analyses were converted into odds ratios to determine bivariate associations between most likely class membership and covariates, with the largest class as the reference group.

*Multivariate model building:* Covariates significantly associated with class membership in the univariate multinomial logistic regression analyses at  $p < 0.1$  were selected for inclusion into multivariate models. Separate multivariate analyses were run with three blocks of covariates, run separately and then with covariates significantly different at  $p < 0.1$  added to a larger model sequentially, starting with (1) HIV risk behaviors and overdose, followed by (2) background factors, and then (3) risk environment factors. Covariates were retained in the final model if  $p < .1$ .

## **RESULTS**

### **Sample characteristics**

Among this sample of PWID in Tijuana (N=735), 38.0% were female and the median age was 37.0. Slightly over a third (36.2%) had spent their whole lives in Tijuana while one fifth (22.7%) came to Tijuana after being deported. Additional descriptive statistics are found in Table 3.1.

Nearly all participants in this sample reported injecting heroin (95.2%) with nearly all (90.0%) reporting daily injection of heroin in the past 6 months. Over half reported co-injecting heroin and methamphetamine together (55.9%), with over one-third injecting this combination daily (38.5%). More than a quarter (28.4%) reported injecting methamphetamine, with 13.1% reporting injecting daily. Two-fifths (41.4%) reported methamphetamine smoking, with 16.1% reporting smoking daily. Nearly a third of participants reported smoking marijuana (31.6%), and although use of prescription opiates and hallucinogens was quite low (<5%), one in five (19.5%) reported ingesting tranquilizers.

A majority of participants (up to 71.4%) reported engaging in HIV injection risk behaviors in the past 6 months. About a third reported engaging in HIV sexual risk behaviors (up to 35.9%). A majority (77.4%) also reported using drugs before or during sex. The HIV prevalence was 3.5% and over half the participants reported ever having overdosed (54.6%), with one in ten (10.1%) reporting an overdose in the past 6 months.

Participants spent the majority of their time on the streets, were of low socioeconomic status and had frequent interactions with the criminal justice system. Reported need for harm reduction services was high. Nearly all participants (87.2%) reported some, great, or urgent need for help for their drug use. Two-fifths of participants (18.5%) reported that it was hard or very hard to find sterile syringes. While a quarter reported ever being on methadone (27.8%), only one in 20 (4.8%) were currently on methadone.

### **Determining number of latent classes**

After comparing the fit indices across models fit to increasing numbers of classes, the 5 class solution was selected given a significant LMRT, highest entropy,

low AIC and sBIC, classification quality, class size, and spread of conditional response probabilities relative to the 4, 6, and 7 class solutions. (Table 3.1)

### **Class descriptions**

Class 1 (*polydrug and polyroute + cocaine; 5% of sample*). Participants in this class had the highest probabilities of non-injection use of heroin, methamphetamine, marijuana, tranquilizer, and cocaine use as well as high probabilities of injection and co-injection drug use. (Table 3.2, Figure 3.1)

Class 2 (*polydrug and polyroute; 29% of sample*). In addition to high probabilities of injection use of methamphetamine and heroin, participants in this class had moderate to high probabilities of non-injection use of other substances, but in contrast to class 1, had much lower probabilities of any cocaine use. Classes 1 and 2 also had relatively high probabilities of less than daily use for methamphetamine injection and smoking and for heroin and methamphetamine co-injection. These two classes used multiple substances and routes of administration and had higher probabilities of less than daily use.

Class 3 (*daily stimulant and heroin injection; 4% of sample*) had high probabilities of injection, especially for heroin injection, heroin and cocaine co-injection, and daily heroin and methamphetamine co-injection. This and the other two classes were characterized mainly by injection drug use, but were different from each other in substances injected.

Class 4 (*daily methamphetamine and heroin injection, 10% of sample*) also had high probabilities of daily injection, but were different from class 3 mainly in that they did not use cocaine.

Class 5 (*predominantly heroin injection; 52% of sample*) comprised the largest class and was characterized primarily by a high probability of injecting heroin, the majority of which was daily injection.

### **Latent class analysis with covariates**

Compared to the predominantly heroin injection class, (Table 3.3) membership in the polydrug and polyroute using classes (i.e., classes 1 and 2) was significantly associated with both injection and sexual risk behaviors, with higher odds ratios for the polydrug and polyroute + cocaine class (class 1). Membership in class 1 was also significantly associated with having an overdose in the past 6 months. Those in these polydrug and polyroute use classes were also more likely to be younger, female, slightly more educated, and to have not spent their whole life in Tijuana. Those in these classes were also much more likely to have experienced forced sex in their lifetimes and were more likely to have had police encounters and been in jail in the past 6 months. Curiously, these people were also more likely to have ever been on methadone.

Compared to the predominantly heroin injection class, the other two injection classes (i.e., classes 3 and 4) had fewer differences. Still, of note, the small stimulant and heroin injection class was more likely to have had a lifetime overdose yet was much less likely to test HIV positive (though this may be due to the small class size and low HIV prevalence). They also reported more difficulty finding sterile syringes. This class and the polydrug and polyroute use classes were also much less likely to have injected heroin the first time they injected.

In the final multivariate model (Table 3.4), compared to heroin injecting (class 5), membership in the polydrug and polyroute classes (i.e., classes 1 and 2) was

independently associated with sharing cookers, cotton, or rinse water and using drugs before or during sex, as well as ever experiencing forced sex. Higher income was also independently associated with being in the polydrug and polyroute class (class 2). Again, injecting a drug other than heroin at first injection was independently associated with membership in the stimulant and heroin injection class (class 3). Finally, reporting any current need for help for drug use was marginally associated with methamphetamine and heroin injector class membership (class 4).

## **DISCUSSION**

This latent class analysis of drug use among PWID in Tijuana identified 5 classes of polydrug use that captured 4 dimensions of polydrug use: type of substance, route of administration, co-injection, and frequency of use. The five classes were: polydrug and polyroute + cocaine use, polydrug and polyroute use, stimulant and heroin injection, methamphetamine and heroin injection, and heroin injection. The two polydrug and polyroute classes (1 and 2) characterized by use of multiple substances and route of administration were more likely to report HIV risk behaviors, and those in the polydrug and polyroute + cocaine use class were more likely to have overdosed compared to those in the heroin injecting class. These polydrug and polyroute classes were both independently associated with HIV risk behaviors of sharing cookers, cotton, or rinse water and using drugs before or during sex. In general, those in these polydrug and polyroute classes were also younger, more likely to be female, and less likely to be from Tijuana, and reported more criminal justice interactions, lifetime history of methadone use, and history of forced sex. Only the bivariate findings are consistent with the initial hypothesis that polydrug and polyroute users are at higher risk for overdose, compared to heroin injectors (class 5). Findings are also only partially consistent with hypotheses that the daily

cocaine and methamphetamine injection classes (class 3) would have higher HIV injection risk, compared to heroin injectors (class 5) and that cocaine using classes (1 and 3) would have higher HIV sexual risk.

Findings are however largely consistent with existing literature from other settings, which demonstrated that polydrug using classes were more likely to have higher HIV and overdose risk relative to mainly heroin or opiate using classes. Kuramoto et al., for example, found that, among inner city drug users in Baltimore, a heroin and cocaine injecting class was more likely to report HIV injection risk behavior than a heroin injecting class.<sup>19</sup> Similarly, Harrell et al. found that members of a polysubstance using class were more likely to share needles and have casual sex and members of a crack and nasal heroin using class were more likely to have sold drugs for sex than those in a heroin injecting class.<sup>20</sup> Among illicit opioid users in Canada, Monga et al. found that a class of benzodiazepine users were more likely to have overdosed than those in an injecting class,<sup>21</sup> and Patra et al. found that a polydrug use class was associated with higher levels of sharing needles or injection equipment compared to classes characterized by single substance use.<sup>22</sup> Two other studies of opioid users in treatment found that polydrug users<sup>33</sup> and illicit opioid users<sup>34</sup> were at higher risk for HIV than non-polydrug users. Among PWID in San Diego, Roth et al. found that heroin users were more likely to have overdosed than methamphetamine multi-route users, though this latter group was more likely to be HIV positive.<sup>24</sup>

Latent classes of polydrug use have also been associated with the HIV sexual risk behaviors examined in this study. For example, in Montreal, Canada, cocaine smokers were more likely than cocaine injectors to report inconsistent condom use.<sup>35</sup> Likewise, in Pretoria, South Africa, crack users reported more transactional sex and

marijuana users reported more drug use before sex compared to low substance users.<sup>36</sup> Similarly, studies of drug use among men who have sex with men in the United States and Malaysia<sup>37-40</sup> and among vulnerable women in South Africa<sup>41</sup> also found that polydrug using classes were more likely to report unprotected sex, sex exchange, and drug use before sex than low or single substance use classes.

Findings from this study add to the preceding literature in showing how simultaneously considering dimensions of polydrug use that include five substance types, four routes of administration, co-injection, and frequency of use characterize multiple classes of polydrug use variation in this population of PWID in Tijuana. Polyroute users in particular may be a type of HIV transmission “bridge population” to social networks of non-injection drug users. In our study, polydrug and polyroute users (class 1 & 2) were more likely to report riskier injection behaviors than heroin injectors. The sharing of injection equipment among the polydrug and polyroute users may be part of a “moral economy of sharing,”<sup>42</sup> in which PWID share any available resources of drugs or injection equipment (in addition to food or shelter) to establish and maintain social and economic ties. The strong association between history of forced sex and polydrug and polyroute use in this study may be indicative of drug use as a trauma coping mechanism. These results also indicate the need for policy and practice endeavors to target the micro-risk environment, particularly interactions with the criminal justice system as well as non-coercive and accessible treatment options for both opiate and stimulant use.

These findings add to the literature additional evidence of variability among drug using populations, even within this population defined by route of administration (i.e. injection), and that in this low resource setting polydrug and polyroute users are at greater risk for HIV and overdose. For future latent class analyses, these findings

demonstrate the feasibility of using indicators with less than 15% prevalence, ordinal indicators, and a large number of indicators<sup>43</sup>; the integration of the 3 step procedure into determining associations between class membership and covariates; and the ability to detect differences between small classes (i.e. with 4-5% prevalence).

### **Study Limitations**

There are several limitations to these findings. All substance use was self-reported by participants, though several studies have demonstrated the general validity of self-report<sup>44</sup> and participants were already admitted illicit drug users to be eligible for the study. These classes may not be generalizable to other substance using populations in other places and times and given the cross-sectional nature of the data, associations are not causal. Small class sizes may have limited power to detect some associations and individuals missing data on several covariates were left out of the multivariate analysis, however only 1-4 individuals were dropped per covariate. Quantity of substances used and concurrent alcohol use may also inform polydrug use profiles, however these factors were not assessed in this study at baseline, nor was presence of mental health comorbidities. Finally, caution should be taken in interpreting findings given that these are probabilistic and not deterministic.

### **Conclusions and Future Research**

Findings from this analysis highlight the heterogeneity in substance use patterns among PWID in Tijuana and demonstrate that polydrug and polyroute users are a high-risk subgroup. To reduce HIV and overdose risk in resource limited settings, resources may need to be targeted towards polydrug and polyroute users. Future research should explore longitudinal changes in these patterns over time, as

well as users' motivations and rationales for using different substances and routes of administration.

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Chapter 3, in full, is in preparation for submission to Drug and Alcohol Dependence: Meacham, M.C., Roesch, S.C., Strathdee, S.A., Gaines, T. "Latent Classes of Polydrug Use and Associations with HIV Risk Behaviors and Overdose among People Who Inject Drugs in Tijuana, Baja California, Mexico." Meredith Meacham, the dissertation author, is the primary author of this material.

**Table 3.1:** Fit statistics for latent class models fit to 2-7 classes (N = 735 PWID in Tijuana)

Classes	AIC	BIC	sBIC	LMRT	Entropy
2	7970.809	8104.205	8012.12	<.0001	0.732
3	7818.46	8020.855	7881.14	<.0001	0.792
4	7715.792	<b>7987.184</b>	7799.839	0.0074	0.786
<b>5</b>	7656.911	7997.302	7762.327	<b>0.0089</b>	<b>0.851</b>
6	7613.863	8023.251	<b>7740.646</b>	0.3231	0.833
7	<b>7603.749</b>	8082.135	7751.9	0.9622	0.825

AIC = Akaike Information Criteria, BIC = Bayesian Information Criteria, sBIC = sample size adjusted Bayesian Information Criteria, LMRT = Lo-Mendell-Rubin adjusted Likelihood Ratio Test p-value

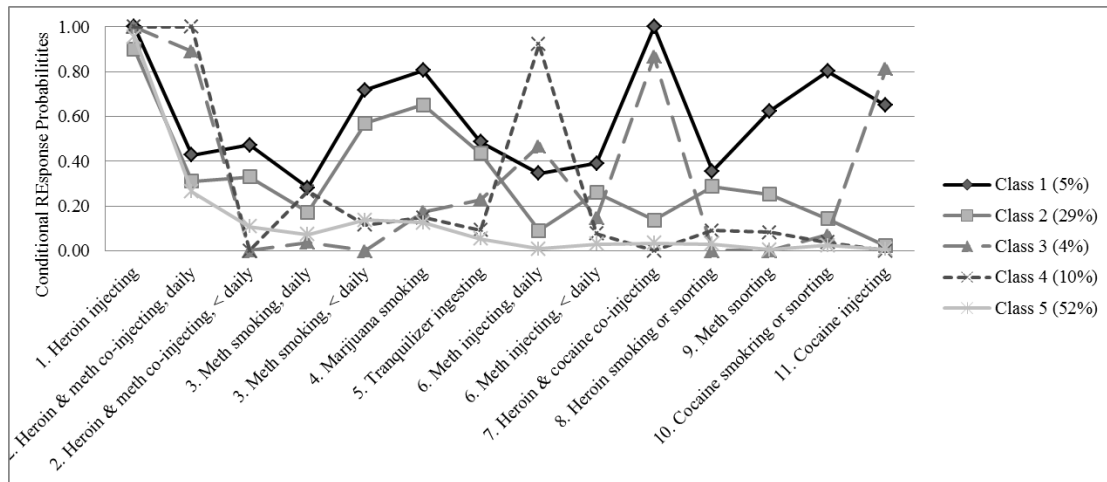
**Bold** = Ideal number of classes given fit statistic

5-class model selected for further analyses

**Table 3.2:** Substance use indicator prevalence and conditional response probabilities of 11 substance use indicators given class membership for 5 latent class model (N = 735 PWID in Tijuana)

Classes	Overall	Class 1: Polydrug and polyroute + cocaine	Class 2: Polydrug and polyroute	Class 3: Stimulant and heroin injecting	Class 4: Meth and heroin injecting	Class 5: Heroin injecting
<i>Probability of Class Membership</i>						
<i>Indicators</i>		0.05	0.29	0.04	0.10	0.52
1. Heroin injecting	0.95	<b>1.00</b>	<b>0.90</b>	<b>1.00</b>	<b>1.00</b>	<b>0.96</b>
2. Heroin & meth co-injecting, daily	0.39	<b>0.43</b>	0.31	<b>0.89</b>	<b>1.00</b>	0.26
2. Heroin & meth co-injecting, < daily	0.17	<b>0.47</b>	0.33	0.00	0.00	0.11
3. Methamphetamine smoking, daily	0.13	0.28	0.17	0.04	0.27	0.07
3. Methamphetamine smoking, < daily	0.28	<b>0.72</b>	<b>0.57</b>	0.00	0.12	0.14
4. Marijuana smoking	0.31	<b>0.81</b>	<b>0.65</b>	0.17	0.15	0.13
5. Tranquilizer ingesting	0.20	0.49	0.44	0.23	0.09	0.05
6. Methamphetamine injecting, daily	0.16	<b>0.35</b>	0.09	<b>0.47</b>	<b>0.92</b>	0.01
6. Methamphetamine injecting, < daily	0.12	<b>0.39</b>	0.26	0.15	0.08	0.03
7. Heroin & cocaine co-injecting	0.14	<b>1.00</b>	0.14	<b>0.87</b>	0.00	0.03
8. Heroin smoking or snorting	0.12	0.36	0.29	0.00	0.09	0.03
9. Methamphetamine snorting	0.11	<b>0.63</b>	0.25	0.00	0.08	0.00
10. Cocaine smoking or snorting	0.10	<b>0.80</b>	0.14	0.07	0.04	0.02
11. Cocaine injecting	0.08	<b>0.65</b>	0.02	<b>0.81</b>	0.00	0.01

**Bold** = conditional response probabilities over .5 or over .33 for three-level frequency indicators (2, 3, 6)



Class 1: High polydrug and polyroute, Class 2: Low polydrug and polyroute, Class 3: Stimulant and heroin injecting, Class 4: Methamphetamine and heroin injecting, Class 5: Heroin injecting

**Figure 3.1:** Conditional response probabilities of 11 substance use indicators (N = 735 PWID in Tijuana)

**Table 3.3:** Bivariate associations between class membership and HIV risk behaviors, overdose, background, risk environment among PWID in Tijuana (N = 735)

	N (%)	Class 1: Polydrug and polyroute + cocaine (5%)		Class 2: Polydrug and polyroute (29%)		Class 3: Stimulant and heroin injecting (4%)		Class 4: Meth and heroin injecting (10%)	
		OR	p-value	OR	p-value	OR	p-value	OR	p-value
HIV injection risk behavior (past 6 months)									
Receptive syringe sharing	525 (71.4)	<b>3.66</b>	0.016	<b>3.20</b>	<.001	1.07	0.87	1.26	0.43
Distributive syringe sharing	531 (72.2)	<b>5.34</b>	0.006	<b>3.43</b>	<.001	1.40	0.45	1.49	1.81
Cooker, cotton, rinse water sharing	490 (66.9)	<b>5.39</b>	0.002	<b>4.48</b>	<.001	1.89	0.15	1.46	0.19
HIV sex risk behavior (past 6 months)									
2+ casual partners	261 (35.9)	<b>2.38</b>	0.026	<b>1.55</b>	0.05	0.91	0.83	1.23	0.48
Unprotected sex with casual partner	241 (33.1)	<b>3.08</b>	0.004	<b>2.31</b>	<.001	1.01	0.99	1.24	0.48
Exchanged sex	226 (31.1)	<b>4.01</b>	<.001	<b>2.55</b>	<.001	0.61	0.38	1.42	0.25
Drug use before or during sex	567 (77.4)	<b>5.16</b>	0.016	<b>3.82</b>	<.001	1.20	0.69	1.69	0.12
HIV & Overdose									
Ever overdose	401 (54.6)	1.63	0.20	1.04	0.87	<b>2.71</b>	0.04	1.27	0.39
Past 6 months overdose	74 (10.1)	<b>3.35</b>	0.01	1.68	0.15	1.89	0.30	1.15	0.77
HIV positive	26 (3.5)	2.04	0.291	0.63	0.47	<b>&lt;.001</b>	<.001	0.25	0.30
Background									
Age (mean, SD)	37.0 (8.9)	<b>0.95</b>	0.04	0.98	0.18	1.00	0.83	0.99	0.56
Female	279 (38.0)	<i>1.88</i>	0.09	<b>1.95</b>	0.00	0.60	0.30	1.37	0.27
Years Education (mean, SD)	7.9 (3.01)	<b>1.18</b>	0.04	<b>1.16</b>	<.001	<b>1.13</b>	0.03	1.07	0.15
Deported to Tijuana	176 (22.7)	0.94	0.91	1.36	0.57	1.46	0.55	1.15	0.79
Whole life in Tijuana	266 (36.2)	<b>0.41</b>	0.04	<b>0.45</b>	0.00	1.38	0.43	1.28	0.37
Ever experienced forced sex	117 (15.9)	<b>3.23</b>	0.01	<b>3.35</b>	<.001	1.81	0.29	1.07	0.89
Age of first injection (mean, SD)	21.2 (6.8)	0.94	0.13	<b>1.04</b>	0.02	0.97	0.53	0.97	0.25
Heroin first drug injected	578 (78.6)	0.53	0.14	<b>0.53</b>	0.02	<b>0.23</b>	0.00	0.64	0.18
Age of first drug use (mean, SD)	14.7 (4.4)	0.82	0.19	0.97	0.20	<b>0.91</b>	0.04	0.99	0.66
Marijuana first drug used	464 (63.1)	0.89	0.81	1.21	0.66	1.25	0.63	1.18	0.69
Risk Environment (past 6 months)									
Hours on Street (mean, SD)	13.2 (6.9)	1.04	0.20	<b>0.97</b>	0.05	<b>1.08</b>	0.01	1.02	0.34
Income over 2500 pesos/month	362 (49.5)	1.92	0.08	<b>3.95</b>	<.001	1.63	0.23	1.49	0.15
Stopped or Arrested	373 (50.8)	1.26	0.52	<b>1.73</b>	0.01	1.54	0.29	1.02	0.95
Inject most often in Zona Norte or 'El Bordo'	301 (41.8)	0.89	0.77	<b>1.60</b>	0.03	0.66	0.36	1.31	0.34
In jail past 6 months	270 (36.7)	<b>2.52</b>	0.01	<b>2.11</b>	0.00	0.93	0.88	0.88	0.67
Hard to find sterile syringes	136 (18.5)	1.73	0.21	1.46	0.18	<b>2.89</b>	0.02	1.31	0.45
Ever on methadone	204 (27.8)	<b>2.58</b>	0.01	<b>1.91</b>	0.01	0.84	0.73	1.44	0.24
Currently on methadone	35 (4.8)	<i>2.94</i>	0.09	1.58	0.352	0.80	0.85	0.56	0.54
Any need for help for drug use	640 (87.2)	1.49	0.51	1.33	0.40	0.85	0.77	2.86	0.08

Reference class: Class 5 Heroin injecting

Bivariate associations from univariate multinomial logistic regression with fixed measurement relationship between most likely latent class membership and latent class

**Bold =  $p < .05$ , Italics =  $p < .10$**

**Table 3.4:** Independent associations between class membership and covariates among PWID in Tijuana (N = 707)

	Class 1: Polydrug and polyroute + cocaine (5%)		Class 2: Polydrug and polyroute (29%)		Class 3: Stimulant and heroin injectors (4%)		Class 4: Meth and heroin injectors (10%)	
	AOR	p-value	AOR	p-value	AOR	p-value	AOR	p-value
Cooker, cotton, rinse water sharing	<b>7.22</b>	0.005	<b>4.35</b>	<.001	1.54	0.349	1.30	0.399
Drug use before or during sex	<b>7.31</b>	0.022	<b>3.55</b>	0.002	1.15	0.767	1.64	0.152
Years Education	<i>1.18</i>	0.053	1.09	0.048	<i>1.12</i>	0.086	1.06	0.306
Age of first injection	0.96	0.426	<b>1.05</b>	0.013	0.99	0.792	0.98	0.433
Heroin first drug injected	0.61	0.289	0.59	0.110	<b>0.26</b>	0.004	0.73	0.397
Ever experienced forced sex	<b>3.70</b>	0.008	<b>3.10</b>	0.003	1.68	0.380	0.90	0.845
Hours on Street	<i>1.06</i>	0.057	0.98	0.243	<b>1.09</b>	0.009	1.03	0.239
Income over 2500 pesos/month	1.34	0.496	<b>3.35</b>	<.001	1.64	0.258	1.45	0.210
Any current need for help for drug use	2.37	0.232	1.49	0.322	1.02	0.972	3.19	0.081

Reference class: Class 5 Heroin injecting

Adjusted associations from multivariate multinomial logistic regression with fixed measurement relationship between most likely latent class membership and latent class

**Bold =  $p < .05$ , Italics =  $p < .10$**

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## CHAPTER 4: LATENT TRANSITIONS IN POLYDRUG AND POLYROUTE USE AMONG PEOPLE WHO INJECT DRUGS IN TIJUANA, BAJA CALIFORNIA, MEXICO

### ABSTRACT

**Aims:** Little is known about the stability of polydrug use patterns among actively injecting populations. Within a cohort of people who inject drugs (PWID) in Tijuana, Baja California, Mexico, we sought (1) to characterize polydrug use profiles from baseline to 6 month follow up, (2) to identify factors associated with baseline status membership in polydrug/polyroute classes, and (3) to determine transition probabilities between statuses and whether self-reported need for help for drug use modified these transition probabilities.

**Methods:** Latent transition analysis (LTA) with covariates was used to examine changes in heroin and methamphetamine polydrug use profiles from baseline to 6 month follow up in a prospective cohort of PWID in Tijuana, Baja California, Mexico (N=735). The main eligibility criterion for enrollment into this cohort was injecting an illicit substance in the past month.

**Results:** LTA identified 4 classes/statuses of polydrug use profiles: heroin injectors (38% at both baseline and 6 month follow up); heroin and methamphetamine co-injectors (3% at baseline, 15% at follow up); heroin and methamphetamine injectors (37% at baseline, 32% at follow up); and polydrug and polyroute users (22% at baseline, 14% at follow up). PWID classified into the polydrug and polyroute use status at baseline reported greater prevalence of sharing syringes, engaging in unprotected sex, having a recent overdose, and history of drug treatment. Polydrug and polyroute users had the lowest probability of remaining in the same class at

follow up (.47), followed by co-injectors (.48), heroin and methamphetamine injectors (.60), and then heroin injectors (.71). Over half of the sample (51.2%) reported great or urgent need for help at baseline; these participants were more likely to transition to a status with more substances or routes used at follow up.

**Conclusions:** More than one third (39.1%) of PWID in Tijuana transitioned to a different latent status of drug use within 6 months: 13.2% transitioned to a greater polydrug use status and 25.9% to a lesser polydrug use status. Greater need for help was associated with transitioning to a status with more polydrug use, emphasizing the need for non-coercive, evidence based, and accessible treatment options to prevent drug use related morbidity and mortality.

## INTRODUCTION

Among drugs of potential misuse, heroin and methamphetamine use are widely recognized as contributing to great physical, dependence, and social harms.<sup>1</sup> Previous studies have demonstrated that use of multiple substances (polydrug use) through multiple routes of administration (polyroute use) is associated with greater drug dependence,<sup>2,3</sup> worse mental health outcomes,<sup>4</sup> and overdose occurrence<sup>5</sup> as well as greater risk for HIV through higher likelihood of sharing of injection equipment and unprotected sex.<sup>6</sup> While there is recognition that individual substance use profiles change over time as people try new substances or attempt to cease use, many of these studies focus on intra-individual changes in adolescent and young adult substance use in general population or school based samples in the United States.<sup>7-12</sup> Typically, these studies focus on changes in use of tobacco, alcohol, and marijuana. Less is known about the stability and transitions in substance use profiles among very actively using populations of heroin and methamphetamine, and has not been explored in depth among people who inject drugs (PWID). Research that identifies how stable or dynamic substance use profiles are and factors associated with transitions in substance use profiles among PWID can inform interventions to reduce the harms associated with substance use.

The life course framework for understanding drug use trajectories provides a multidisciplinary and comprehensive conceptual approach for understanding intra-individual drug use patterns over time and the interplay of these patterns with drug treatment systems.<sup>13</sup> This framework highlights the concepts of transitions, turning points, and social capital in understanding processes of stability and change. It also recognizes the chronic nature of substance use disorders; heterogeneity of drug use patterns across the life span; the need to consider historical context, social

environments, and individual differences; and the frequent contacts of drug users with multiple service systems. In addition to examining age specific pathways and major events in the life course, this framework also draws on the “situated choice” notion from developmental criminality (in which the life course is a dynamic combination of personal choice and institutional options), and draws on health services literature in identifying the beginning stages of chronic illness management as an individual recognizing their health problem and utilizing care. Recognition of problematic drug use and intending to seek care may influence changes in substance use over time.

While many studies have explored sequencing and trajectories of substance use over time using generalized linear models for correlated data and growth curve modeling,<sup>14</sup> these techniques often model only continuous or dichotomous outcomes that may not reflect the greater heterogeneity of substance use behaviors. Latent transition analysis (LTA) is a longitudinal extension of latent class analysis (LCA), an exploratory non-parametric approach used to probabilistically detect more homogenous subpopulations within a more heterogeneous population based on responses to a set of observed behaviors.<sup>15</sup> LCA assumes that the patterns of these observed responses can be represented by an underlying latent class grouping variable and that conditional on this latent class variable, members of the same class will have similar patterns of observed behaviors.

LTA is used to model changes in latent class, or latent status, membership over time by estimating the probabilities of transitioning to latent status at a follow up time point given latent status membership at a previous time point. This technique allows for a more parsimonious summarization of complex patterns of use of multiple substances over time.<sup>8,16</sup> LTA has been used to model transitions in patterns of alcohol use,<sup>17</sup> syringe exchange use,<sup>18</sup> adolescent substance use,<sup>7</sup> adult substance

use,<sup>8,19</sup> and trauma symptoms.<sup>20</sup> However, LTA has not yet been used to model transitions in patterns of heroin and methamphetamine use among PWID, nor how these transitions may be affected by need for drug treatment services in low resource settings outside the United States and Europe.

This study examines prospective changes over 6 months in drug use profiles among PWID in Tijuana, Baja California, Mexico. Tijuana is the northwestern corner of Mexico and shares a heavily crossed border with the United States. Trafficking of heroin and methamphetamine through this border region contributes to a high prevalence of use of these substances and a large population of PWID.<sup>21,22</sup> Heroin in this region is usually in the form of black tar, which is typically injected.<sup>22</sup> Methamphetamine is increasingly being manufactured in Mexico, and although it is typically smoked, it is also injected alone or in combination with heroin.<sup>21</sup> Methamphetamine is the most commonly reported substance for which treatment is sought in Baja California according to treatment center intake records.<sup>23</sup>

The objectives of this analysis were to (1) characterize polydrug use profiles from baseline to 6 month follow up within a cohort of actively injecting PWID in Tijuana; (2) identify life course and negative health risk factors associated with baseline status membership; and (3) determine transition probabilities between statuses and whether self-reported need for help at baseline modified these transition probabilities.

## **METHODS**

### **Study Participants and Procedures**

The present study sample consisted of 735 participants from *Proyecto El Cuete Phase IV*, a cohort study of PWID in Tijuana, Baja California, Mexico.<sup>24</sup> Participants were recruited through convenience sampling using targeted street

based outreach from March 2011 to May 2012. Eligibility criteria included (1) injecting illicit drugs within the past month, confirmed by track marks; (2) age 18 or older; (3) speaking Spanish or English; (4) current residence in Tijuana with no plans to move for 3 years. Trained interviewers administered quantitative interviews in English or Spanish using computer assisted personal interview (CAPI) technology on a laptop in a private room. Local outreach workers returned to recruitment venues and contacted participants via phone, if available, to remind participants of follow up visits. All participants provided written informed consent and were reimbursed \$20 USD at each visit. The University of California San Diego Human Research Protection Program and Institutional Review Board of the Colegio de la Frontera Norte (COLEF) approved the study protocol.

### **Measures**

To assess heroin and methamphetamine use at baseline and 6 month follow up, participants were asked about their frequency of past 6 month use of heroin injection, methamphetamine injection, methamphetamine smoking, and heroin and methamphetamine co-injection. Drug use was dichotomized into past 6 month (yes vs. no) to create four binary indicators for latent class and transition analyses.

Life course factors assessed included age, gender, whether participants had spent their whole life in Tijuana, current monthly income (greater or less than 2500 pesos/month, or about \$200 USD in 2011), and the age and substance used at first injection experience (heroin vs. other).

Self-reported need for help was assessed with the question, "To what extent would you say that you currently need help for your drug use?" with response options of no need, some need, great need, urgent need (dichotomized into no or some need vs. great or urgent need). Participants also reported lifetime utilization of professional

help for use of drugs or alcohol, in general, and specifically at inpatient rehabilitation center, methadone program, or 12 step program treatment modalities.

Negative health consequences assessed included HIV risk behaviors and overdose. HIV associated risk behaviors included past 6 month engagement in receptive syringe sharing; sharing of cookers, cotton, or rinse water; engagement in unprotected sex with a casual partner; exchanging sex for food, money, drugs, or shelter; and using drugs during or within two hours before having sex. Participants self-reported past 6 month history of overdose, which was described by the interviewer as a time the participant passed out due to drug use, could not wake, or lips turned blue.

### **Statistical Analysis**

LCA was conducted at baseline and follow up with the data fit to increasing numbers of classes to get an idea of the number of classes, or statuses, to expect. LTA with latent statuses at follow up regressed onto latent statuses at baseline were then run with increasing number of statuses specified. LCA and LTA were conducted in Mplus Version 7.<sup>16,25</sup> Model fit was compared using AIC, BIC, sample sized adjusted BIC, and Entropy, prioritizing lower AIC, BIC, and sBIC, and higher Entropy. Characteristics of each status based on conditional response probabilities (CRPs) were also used to determine model selection. To ease interpretation of transitions, CRPs were constrained to be equal over time. This constrained model was compared to an unconstrained model using a likelihood ratio test. Mplus uses full information maximum likelihood (FIML), so individuals who did not return at 6 month follow up were not dropped from the analyses, but rather their status was probabilistically determined based on their baseline responses and the overall model structure.

To further understand differences between statuses, individuals were assigned to their most likely status membership at baseline, and life course demographics and HIV risk behaviors and overdose were compared across statuses. Chi-square tests and ANOVAs were used to determine overall statistical differences between status membership and these covariates. These bivariate analyses were conducted in SAS 9.4.

In addition to transition probabilities reported by Mplus, need for help was included as a moderator of these transition probabilities (using the KNOWNCLASS option), and two sets of transition probabilities stratified by more or less need for help were reported by Mplus.<sup>25,26</sup> These transition probabilities were then converted into odds of transitioning to a different status relative to remaining in the same status. The ratio of these odds of transitioning for those who reported more need for help versus odds of transitioning for those who reported less need for help were calculated to provide an odds ratio. This odds ratio represents the odds of transition to a different status for those who reported more need for help compared to those who reported less need.

## **RESULTS**

### **Sample Characteristics**

Among this sample of PWID in Tijuana (N=735), 38.0% were female and the median age was 37 years. Slightly over a third (36.2%) had spent their whole lives in Tijuana. At 6 month follow up, 572 participants (77.8%) returned for an interview. In attrition analyses, methamphetamine injectors, males, and those who had spent their whole lives in Tijuana were significantly less likely to return for a follow up interview at 6 months (chi-square  $p$ -value <0.05) but there were no significant differences in

attrition for other substances used, age, income, having a recent overdose, or need for help ( $p > 0.05$ ).

At both baseline and follow up, the primary substance used was heroin injection (95.0% baseline, 82.3% follow up), followed by heroin and methamphetamine co-injection (55.9%, 51.2%), methamphetamine smoking (41.1%, 38.1%), and then methamphetamine injection (28.2%, 31.2%).

### **Determining Number of Latent Statuses**

LCA indicated that 3 or 4 class models fit the data best at both baseline and follow up. In LTA, the 3 status model had the highest entropy but the 4 status model had the lowest sample size adjusted BIC and only slightly lower entropy. (Table 4.1) In the 4 status model, a distinct status with methamphetamine smokers emerged from a status of methamphetamine injectors and smokers in the 3 status model. This 4 status model was selected for subsequent analyses. We then tested for measurement invariance by constraining conditional response probabilities to be equal across time, which did not significantly improve model fit (likelihood ratio test  $p > 0.05$ ). Nevertheless, this constraint was specified in subsequent models to improve ease of interpretation of transition probabilities and because of similarities between conditional response probabilities for the four statuses at baseline and follow up.

### **Latent Status Descriptions**

Latent transition analyses identified 4 polydrug use profiles (listed here from low to high polydrug/polyroute use): *Heroin Injectors* (38% at both baseline and 6 month follow up), characterized by high probability of injection heroin but zero or low probabilities of any other drug use. *Heroin and methamphetamine co-injectors* (3% baseline, 15% follow up) were characterized by moderately high probability of co-injection of heroin and methamphetamine but zero probability of injecting heroin.

*Heroin and methamphetamine injectors* (37% baseline, 32% follow up) were characterized by high probabilities of injecting heroin and co-injecting heroin and methamphetamine and moderate probability of injecting methamphetamine. *Polydrug and polyroute users* (22% baseline, 14% follow up) were characterized by high probabilities of injecting heroin, co-injecting heroin and methamphetamine, and smoking methamphetamine. (Table 4.2, Figure 4.1)

PWID classified into the polydrug and polyroute status at baseline reported greater prevalence of sharing syringes, engaging in unprotected sex, and having a recent overdose. They were also more likely to be female, younger, and to have been injecting for less time. And they were more likely to have ever been in a rehabilitation center, in a methadone program, or in a 12 step program. (Table 4.3)

### **Transitions between statuses**

Transition probabilities showed that while the majority of participants remained in the same status, 39.1% transitioned to a different status. Polydrug and polyroute users were the least stable status (.47 probability of being in the same status at follow up), followed closely by co-injectors (.48) and then heroin and methamphetamine injectors (.60) and heroin injectors (.71). (Table 4.4a) After remaining in the same class, polydrug and polyroute users were most likely to transition “down” to the heroin injection class (.23) (i.e. to stop injecting methamphetamine), then to the heroin and methamphetamine injection class (.18) (i.e. to stop smoking methamphetamine), and then to the heroin and methamphetamine co-injection status (.13) (i.e. to stop injecting heroin). After remaining in the same status, heroin and methamphetamine injectors were more likely to transition to the heroin and methamphetamine co-injection status (.21) (i.e. to stop injecting heroin) or “down” to the heroin injecting class (.18) (i.e. to stop injecting methamphetamine). After remaining in the same

status, heroin injectors were most likely to transition “up” to the heroin and methamphetamine injection status (.13) (i.e. add methamphetamine injection).

### **Transitions Modified by Need for Help**

Over half of the sample (51.2%) reported great or urgent need for help at baseline, and those who did so and were in the heroin injection or co-injection statuses at baseline were more likely to transition to the other statuses reflecting greater polydrug use or poly-route use (ORs=2.11, 2.49, 1.31). (Table 4d) Those in the heroin and methamphetamine injection status were less likely to transition to statuses with less substance use if they reported more need for help at baseline (ORs=.31, .68). Results were less consistent for members of the polydrug and polyroute users, who were similarly less likely to transition to the heroin and methamphetamine injection status if they reported more need for help (OR=.41), but more likely to transition to heroin and co-injection statuses if reported more need for help (ORs=1.60, 1.63).

### **DISCUSSION**

This latent transition analysis of heroin and methamphetamine use among PWID in Tijuana identified 4 latent statuses of polydrug use: heroin injectors, co-injectors, heroin and methamphetamine injectors, and polydrug and polyroute users. LTA findings demonstrate that while 60.8% of PWID remained in the same polydrug use profile status, 39.2% transitioned to a different status—13.2% transitioned to a greater polydrug use status and 25.9% to a lesser polydrug use status. While the proportion of the sample in the heroin injection status remained consistent over time (38%), the proportion of the sample in a given status increased for the co-injector status (3% to 15%), and decreased for the heroin and methamphetamine injection status (37% to 32%) and the polydrug and polyroute use status (22% to 14%).

In the context of the life course approach <sup>13</sup>, these findings highlight the continued heterogeneity of substance using patterns, even among older and regular drug users over a short period of time, and that older and more established users tend to use fewer substances. For PWID who transition to a status characterized by use of fewer substances, this may indicate that subtypes of PWID are actively cutting back on their substance use and may be more willing to engage in targeted interventions, particularly if they are in a life course “turning point.” However, transitioning from heroin injection to co-injection of methamphetamine and heroin, or to methamphetamine injection or smoking, may limit the effectiveness of treatment programs designed for heroin injection (e.g. opiate replacement therapy).

The high proportion of those reporting great or urgent need for help, and the increased odds of transitioning to a status with more polydrug use for those who reported more need for help indicates a broader need for evidence based and humane treatment options for this population. Currently, treatment options for substance use disorders are limited in Tijuana. Many programs are ‘*ayuda mutua*’ or mutual-aid/self-help/peer support groups based on the 12-step Narcotics Anonymous model. While methadone maintenance is available for opiate users, it is currently run out of private clinics that charge far beyond what most people can pay (60-80 pesos/day or \$5-7 USD/day). While many in-patient rehabilitation centers also exist, most have none or limited certification and attendees report poor conditions.<sup>23</sup> In general, PWID have limited access to health care services due to their limited ability to pay for or travel to services and their highly stigmatized behaviors and appearances.

Those who report great or urgent need for help for their drug use may be in a period of recognizing (1) that their drug use is negatively impacting their life (not

merely a separate or coping behavior) and (2) that they may have attempted to cut back their use but have been unsuccessful. Drawing from the stages of change theory,<sup>27</sup> they may be in a contemplative or preparation stage of change and inclined to cut back on their drug use, but with limited treatment options or social mobility within their environmental and historical context, they are unable to do so and instead transition to different substances or routes of use. These PWID who transition to statuses with a broader range of substances and routes may not be as adept at managing risks associated with overdose and HIV as they are with more stable drug using behaviors.

Although this appears to be the first latent transition analysis applied to substance use behaviors reported by PWID, findings are similar to other LTAs of substance use behaviors that found that while there were high probabilities of remaining in the same status over time, there were noteworthy transitions to profiles of single or multiple drug use.<sup>7,8,17,19</sup> Unlike other LTAs, however, our analyses did not identify a substantial group of non-users, though this may be due to the nature of this very actively using population and the limited follow up time.

Similar to a previous latent class analyses using a broader range of indicators with this same cohort [Chapter 3/Paper 2], we again found that at baseline the largest class or status was made up of primarily heroin injectors (38% vs. 52%), that the majority of the cohort were primarily injectors (78% vs. 66%), and that there was a substantial subgroup that used multiple drugs through multiple routes (22% vs. 34%). Also consistent with findings from this previous analysis and other papers, those in the polydrug and polyroute status at baseline were more likely to engage in HIV risk behaviors and to have had a recent overdose.

### **Study Limitations**

There are a number of limitations to this analysis. Self-report of drug using behavior and possible recall bias may raise questions about underreporting of substance use, but participants were already admitted illicit drug users to be in the study and the 6 month recall time is short enough to minimize this recall bias. These findings may not be generalizable to other populations of drug users or PWID in other times and places with different illicit drug markets and different availability of health and social services. Similarly, these exploratory analyses of probabilities should be interpreted with caution and not as definitive categories. Attrition of a fifth of the sample at 6 month follow up meant that latent status membership at follow up was determined on less information, though by using FIML procedures these individuals were not dropped from the analysis. Another limitation is the lack of statistical tests or variance estimates for the transition probabilities or odds ratios, as these are not yet available as output from Mplus. Finally, there are other life course factors that may be related to transitions that were either not measured (e.g. stages of change, psychiatric comorbidities, drug availability), or were of too low prevalence in this sample over a short time frame (recent jail or treatment attendance) to be evaluated as moderators of status membership change in this analysis.

### **Conclusions and Future Research**

Nevertheless, findings from this analysis highlight the variation over time in heroin and methamphetamine use patterns among PWID in Tijuana and demonstrate the feasibility of using latent transition analyses to model this heterogeneity. Findings also emphasize the need for non-coercive, evidence based, and accessible treatment options in order to prevent drug use related morbidity and mortality. Future research should continue to explore changes in substance use over longer periods of time,

user reported motivations for changes in substance use, and individual and contextual level barriers to health and social services.

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Chapter 4, “Latent Transitions in Polydrug and Polyroute Use among PWID in Tijuana, BC, Mexico,” is currently being prepared for publication. Steffanie Strathdee, Tommi Gaines, and Scott Roesch are co-authors. Meredith Meacham, the dissertation author, is the primary author of this material.

**Table 4.1:** Fit statistics for latent transition models fit to 2-6 statuses (N = 735 PWID in Tijuana)

Statuses	AIC	BIC	sBIC	Entropy
2	5492.054	<b>5579.452</b>	5519.12	0.736
<b>3</b>	5435.087	5582.283	5480.672	<b>0.809</b>
<b>4</b>	5411.749	5627.943	<b>5478.702</b>	0.786
5	5398.242	5692.633	5489.412	0.798
6	<b>5394.046</b>	5775.835	5512.282	0.795

AIC = Akaike Information Criteria, BIC = Bayesian Information Criteria, sBIC = sample size adjusted Bayesian Information Criteria

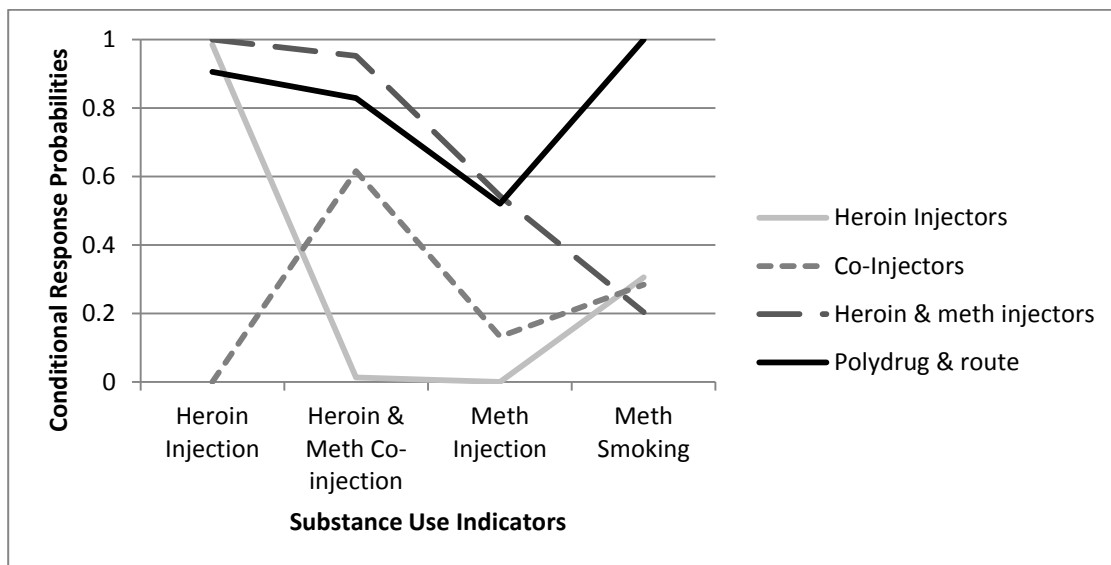
**Bold** = Ideal number of classes given fit statistic

4-class model selected for further analyses

**Table 4.2:** Substance use indicator prevalence and conditional response probabilities of 4 substance use indicators for 4 latent status model (N = 735)

	Baseline Prevalence (N=735)	Follow Up Prevalence (N=572)	Conditional Response Probabilities			
			Heroin Injectors	Co-Injectors	Heroin & meth injectors	Polydrug & route
Heroin Injection	95.0%	82.3%	<b>0.99</b>	0.00	<b>1.00</b>	<b>0.91</b>
Co-injection	55.9%	51.2%	0.01	<b>0.62</b>	<b>0.95</b>	<b>0.83</b>
Methamphetamine Injection	28.2%	31.2%	0.00	0.13	<b>0.54</b>	<b>0.52</b>
Methamphetamine Smoking	41.1%	38.1%	0.31	0.28	0.20	<b>1.00</b>

**Bold** = conditional response probabilities over .5



**Figure 4.1:** Conditional response probabilities of 4 substance use indicators for 4 status model at baseline and 6 month follow up (N = 735)

**Table 4.3:** Bivariate associations between assigned baseline status membership and life course, health risks, and treatment need and use factors (N=735)

	Overall N=735	Heroin Injectors N=282		Heroin & Meth Co-injectors N=18		Heroin & meth injectors N=244		Polydrug & polyroute N=191		Chi- square or ANOVA p-value
		N or mean	% or SD	N or mean	% or SD	N or mean	% or SD	N or mean	% or SD	
<b>Life Course</b>										
Female	279 (38.0)	110	0.39	6	0.33	67	0.27	96	0.50	<0.001
Age (mean)	37.0 (8.9)	38.2	9.67	38.7	9.04	37.7	7.58	35.7	9.15	0.015
Income (over 3500 pesos/month)	202 (27.6)	70	0.25	6	0.33	59	0.24	67	0.35	0.037
Whole life in Tijuana	199 (27.1)	125	0.44	5	0.28	88	0.36	60	0.31	0.023
Heroin at first injection	578 (79.0)	255	0.90	11	0.61	176	0.72	136	0.71	<0.001
Age first injection (mean)	21.2 (6.75)	21.5	6.93	21.2	6.47	20.8	6.47	21.3	6.90	0.771
Years since first injection (mean)	16.0 (9.6)	16.8	10.10	17.6	8.12	16.9	8.79	14.4	9.63	0.022
<b>Past 6 Month HIV Risk and Overdose</b>										
Receptive Syringe Sharing	525 (71.4)	174	0.62	11	0.61	177	0.73	163	0.85	<0.001
Cooker, Cotton, Water Sharing	490 (66.9)	156	0.55	12	0.67	165	0.68	157	0.82	<0.001
Unprotected Sex	241 (33.1)	73	0.26	8	0.44	78	0.32	82	0.43	0.001
Sex exchange	226 (31.1)	70	0.25	9	0.50	59	0.24	88	0.46	<0.001
Drug use before sex	567 (77.4)	208	0.74	17	0.94	179	0.73	163	0.85	0.001
Overdose	74 (10.1)	22	0.08	2	0.11	22	0.09	28	0.15	0.095
<b>Treatment Need and History</b>										
Need for help	376 (51.2)	126	0.45	6	0.33	144	0.59	100	0.52	0.005
Ever received treatment	417 (56.7)	146	0.52	9	0.50	143	0.59	119	0.62	0.115
Ever in rehabilitation center	375 (51.0)	123	0.44	8	0.44	135	0.55	109	0.57	0.011
Ever in methadone program	204 (27.8)	70	0.25	4	0.22	60	0.25	70	0.37	0.017
Ever in NA/12 step program	131 (17.8)	36	0.13	3	0.17	37	0.15	55	0.29	<0.001

**Table 4.4:** Transition probabilities for the four status model overall and by self-reported need for help (N=735)

(a) Overall Transition Probabilities				
	Heroin Injection (38%)	Co-Injection (15%)	Heroin & Meth Injection (32%)	Polydrug & Polyroute (14%)
Heroin Injection(38%)	<b>0.71</b>	0.09	0.13	0.07
Co-Injection (3%)	0.00	<b>0.48</b>	0.35	0.18
Heroin & Meth Injection(37%)	0.18	0.21	<b>0.60</b>	0.02
Polydrug & Polyroute (22%)	0.23	0.13	0.18	<b>0.47</b>

(b) Probabilities of transitioning between statuses if reported great or urgent need for help				
	Heroin Injection (38%)	Co-Injection (15%)	Heroin & Meth Injection (32%)	Polydrug & Polyroute (14%)
Heroin Injection(38%)	<b>0.66</b>	0.13	0.08	0.13
Co-Injection (3%)	0.00	<b>0.53</b>	0.00	0.47
Heroin & Meth Injection(37%)	0.21	0.08	<b>0.53</b>	0.18
Polydrug & Polyroute (22%)	0.18	0.24	0.01	<b>0.58</b>

(c) Probabilities of transitioning between statuses if reported none or some need for help				
	Heroin Injection (38%)	Co-Injection (15%)	Heroin & Meth Injection (32%)	Polydrug & Polyroute (14%)
Heroin Injection(38%)	<b>0.77</b>	0.07	0.04	0.12
Co-Injection (3%)	0.00	<b>0.46</b>	0.31	0.24
Heroin & Meth Injection(37%)	0.24	0.19	<b>0.40</b>	0.18
Polydrug & Polyroute (22%)	0.13	0.17	0.03	<b>0.67</b>

(d) Odds ratios of transitioning for those reporting great or urgent need for help vs. none or some need for help				
	Heroin Injection (38%)	Co-Injection (15%)	Heroin & Meth Injection (32%)	Polydrug & Polyroute (14%)
Heroin Injection(38%)	<b>1.00</b>	2.11	2.49	1.31
Co-Injection (3%)	(--)	<b>1.00</b>	0.00	1.67
Heroin & Meth Injection(37%)	0.68	0.31	<b>1.00</b>	0.72
Polydrug & Polyroute (22%)	1.60	1.63	0.41	<b>1.00</b>

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## CHAPTER 5: DISCUSSION

### OVERVIEW

This dissertation research was conducted to better understand patterns of polydrug use and their association with HIV risk behaviors and overdose among people who inject drugs (PWID) in San Diego, California, USA, and Tijuana, Baja California, Mexico. The following aims were addressed by this research: (1) identify and compare factors associated with co-injection of heroin and methamphetamine in a combined binational sample of PWID from Tijuana and San Diego, (2) identify discrete subgroups defined by polydrug use patterns in the cohort of PWID from Tijuana and the relationship of these patterns to HIV risk behavior and overdose, and (3) describe and predict changes in membership over 6 months between subgroups defined by polydrug use patterns in the cohort of PWID from Tijuana. This research fills a gap in existing knowledge regarding the variety and prevalence of use of multiple substances through multiple routes among PWID, as well as the associations of specific patterns of use with drug related harms.

Broadly, results indicate two main findings. First, beyond conventional conceptions that PWID are primarily heroin injectors, a substantial proportion of PWID in this U.S.-Mexico border region report a complex variety of substance using behaviors that change over time. Second, findings show that the greater the quantity and complexity of substance using behaviors, the greater the risks for negative health outcomes, specifically for HIV and overdose. In resource limited settings, these findings suggest that resources and interventions should be targeted towards these polydrug and polyroute users.

Specifically, in chapter 2 (Aim 1) findings showed that among a binational sample of PWID, the prevalence of heroin and methamphetamine co-injection in the past 6 months was 39.9% overall, and was higher in Tijuana (55.8%) than in San Diego (19.8%). Across both locations, past 6 month HIV injection risk behaviors, need for harm reduction services, and younger age were independently associated with co-injection of these two drugs, while experiencing an overdose in the past 6 months was only independently associated with co-injection of these drugs in San Diego.

In chapter 3 (Aim 2), findings showed that PWID in Tijuana exhibited 5 distinct patterns of substance use behaviors, as characterized by substance type, route of administration, co-injection, and frequency of use. Compared to primarily heroin injectors, a small subgroup characterized by the greatest polydrug and polyroute use was more likely to report an overdose in the past 6 months, and the two subgroups characterized by both polydrug and polyroute use were independently associated with HIV injection and sexual risk behaviors. Other potentially modifiable factors independently associated with greater polydrug use included life course factors of substance used at first injection and lifetime experience of forced sex as well as hours spent on the street and income level, which relate to PWID exposure to the risk environment.

In chapter 4 (Aim 3), findings showed that over a third (39.1%) of PWID in Tijuana transitioned to a different subgroup of heroin and methamphetamine polydrug use over a 6 months. Of the four dynamic subgroups identified in analyses, subgroups characterized by polydrug and polyroute use were again more likely at baseline to engage in HIV risk behaviors, to report greater need for help for drug use, and to have ever attended treatment services. Membership in these subgroups was less stable compared to a primarily heroin injector subgroup, with lower probability of

remaining in the same group 6 months later. Finally, those who reported greater need for help for drug use were more likely to transition to subgroups characterized by greater polydrug and polyroute use 6 months later.

In the context of the conceptual frameworks of the Risk Environment and the Life Course Perspective, findings support the application of these frameworks in the following ways. The Risk Environment macro-level physical environment of Tijuana and San Diego on heroin and methamphetamine trafficking routes contribute to these two substances being the primary drugs used by PWID in these cities. At the micro-level economic and policy environments, PWID in Tijuana who were in polydrug and polyroute classes were more likely to report criminal justice system interactions and involvement in sex exchange, as well as more need for help despite previous drug treatment experiences. With respect to the Life Course Perspective, findings showed that initial drug of injection was independently associated with current drug use preferences and that polydrug users were more likely to have experienced forced sex in their lifetimes. By looking at substance using patterns over time, findings also demonstrate that these patterns are not static (even for older regular users) and better services are needed to support PWID willing to cut back on their drug use.

## **IMPLICATIONS**

These findings have a number of implications and associated recommendations. A primary implication is the need for improved harm reduction services in San Diego and Tijuana for users of both heroin and methamphetamine. Although there is a strong evidence base for the role of needle and syringe exchange programs (NSP)<sup>1</sup> in reducing the incidence of HIV and connecting PWID with health and social services, available services in this border region are quite limited. NSPs in

San Diego County are only open a total of 6 hours a week across two locations, a challenge in a large region with limited public transportation options. Existing support for NSPs in Tijuana through the Global Fund for AIDS, TB, and Malaria ended in 2013 following the re-categorization of Mexico to an upper middle income country which renders the country no longer eligible for such funds. Currently, two non-governmental organizations in Tijuana continue to exchange syringes, but their supplies are limited and services are inconsistent. With respect to polydrug use, regional and global efforts at reducing sharing of needles, syringes, and other injection equipment should be targeted not just at heroin users but also towards methamphetamine and other stimulant users. Additionally, polyroute users who do not exclusively inject may represent an HIV transmission “bridge population” to social networks of non-injection drug users, who may become injectors themselves or acquire HIV through sexual contact within their network. Efforts to prevent initiation or re-initiation of injection, promote condom use, and early testing and treatment for HIV could be targeted towards these non-injecting social contacts.

In addition to the need for non-coercive, evidence based, and accessible treatment options to prevent drug use related morbidity and mortality, opiate substitution therapies (OST) have also been shown to reduce drug related harm. Providing opiate users with a daily dose of methadone or buprenorphine helps users cut back or stop use by addressing withdrawal symptoms and assisting users in creating stability and improved functionality in their lives.<sup>1</sup> Nevertheless, such services are limited and prohibitively expensive for many PWID, especially in Tijuana, where existing programs at only 3 private clinics charge up to \$7 USD per day and are located too far from where many PWID live to be regularly accessible.

With respect to polydrug use, existing interventions that aim to prevent opioid related overdose (like access to OST and to the overdose reversing drug naloxone) may need to be expanded to address co-injection and co-use of depressants and stimulants. While naloxone is available over the counter in the United States and is increasingly being carried by first responders and distributed to users, it is not yet available in Mexico.

Globally, needle and syringe exchange program (NSP) and OST coverage is quite varied, but remains low in many areas of the world. As a broad region, Latin America and the Caribbean have some of the lowest coverage rates at .3 needle-syringes per 100 PWID per year and <1 OST recipient per 100 PWID per year.<sup>2</sup> Even within the United States, NSP coverage is quite varied despite increasing prevalence of opioid misuse and injection. A 2015 outbreak of HIV in rural Indiana was linked injection of oxycodone<sup>3</sup> and NSP services were only permitted temporarily by the state in response to this outbreak.<sup>4</sup> Federal funding of NSPs in the United States is currently prohibited by federal laws.

The disparity between those reporting need for treatment and those receiving treatment is referred to by the World Health Organization (WHO) as the mental health treatment gap, and has been estimated at 81.4% in Mexico (76.6% for alcohol abuse/dependence, unavailable for drug abuse/dependence), compared to 58.9%, 59.6%, and 55.3%, respectively, for the United States.<sup>5</sup> The total healthcare expenditure per person in Mexico was reported as \$664 in 2014, but with only \$1.96 per capita spent on mental health services. WHO also reports only 9.5 mental health workers per 100,000 people in Mexico, compared with 125.2 per 100,000 people in the United States.<sup>6</sup> Though the United States mental health system could certainly be improved, investment in mental health service strengthening and workforce

development in Mexico would also contribute to reducing the harms from substance use.

Another harm reduction service that may reduce drug related harms from polydrug use, especially overdose deaths, is programs and partnerships that share information on drug formulations with users. For example, the Royal Canadian Mounted Police sends out notices to British Columbian harm reduction organizations when police street buys detect dangerous decreases in purity or increases in adulterants. And there are several harm reduction organizations, such as DanceSafe, and companies, such as BunkPolice, that provide “test kits” for users to determine the safety of the drugs they are using. However, these services tend to be oriented towards electronic dance music (EDM) communities and there is little objective data on their accuracy.<sup>7</sup> Test kit services and sharing of local trends in drug composition between public safety and public health sectors are quite limited in general, but should be developed further, especially given the increasing number and spread of synthetic drugs globally. Such expanded services would benefit both drug using populations at risk for HIV and overdose and could serve as a possible means of surveillance to detect drug use patterns.

Findings from this dissertation research also indicate the need to consider use of multiple substances as a potential indicator in global drug use surveillance efforts, as well as a correlate of HIV-associated risk behaviors and overdose occurrence in other international settings located on drug trafficking routes. Populations on drug trans-shipment routes tend to be located in lower and middle income countries (LMIC), which have limited resources to counter the consequences of unintended local consumers.<sup>8</sup> In addition to the higher prevalence of methamphetamine use in Tijuana (contrasted with the higher prevalence of cocaine use in Ciudad Juarez on a

cocaine trafficking route to the east<sup>9</sup>), trans-shipment of heroin and other opiates through Central Asia and of cocaine through Western Africa have been connected to increasing prevalence of local consumption of these substances.<sup>10</sup>

As drug production regions and trans-shipment routes shift in response to environmental, economic, and policy changes, there is a need to pay attention to spillover effects into local drug consumption markets, particularly in lesser developed regions with unstable governments and large numbers of migrants.<sup>8</sup> To enable this kind of surveillance of drug related harms and their reduction will require unprecedented levels of cooperation between national and international agencies traditionally focused on interdiction and public health oriented researchers and organizations. This cooperation will require a major shift towards harm reduction approaches, especially in light of growing agreement in international circles that the global War on Drugs has been unsuccessful.

## **LIMITATIONS**

### **Response Biases**

Despite numerous strengths of this study including a relatively large sample of hard to research populations, comparable measures across two studies of PWID in two countries, in depth assessment of substance use behaviors and HIV risk behaviors, and longitudinally collected data, these findings should be considered in the context of several limitations. First, as noted in the previous chapters, all data other than HIV laboratory-confirmed tests were obtained from self-report of behaviors. Nevertheless, previous studies of demonstrated the validity of PWID self-report<sup>11</sup> and participants were assured of the confidentiality of their responses and all were already admitted drug users to be eligible for the two studies. Furthermore, any

differences in recall or social desirability biases are not expected to be different across subgroups of polydrug users.

### **Unmeasured Confounders**

Second, several factors found in the literature that may further explain relationships between polydrug use and related harms were not assessed in these studies, such as psychiatric assessments of level of dependence and co-occurring mental disorders, as well as more in depth questions regarding quantity of use or alcohol use. However, these studies were designed primarily as infectious disease and policy evaluation studies and such assessments were not within the scope of their aims. Additionally, many assessment tools for psychiatric comorbidities have been validated mainly with U.S. English speaking populations and assess symptoms whose expression may vary across cultural contexts and backgrounds. Further research is needed on the appropriateness of existing assessment tools among Spanish speaking marginalized populations in Mexico with varying levels of acculturation into U.S. culture and its idioms of distress.<sup>12</sup>

### **Inferential Cautions and Generalizability**

Lastly, several inferential cautions should be noted. Chapters 2 and 3 (Aims 1 and 2) were cross-sectional analyses that determined associations but not causal processes. Chapter 4 (Aim 3) was conducted with longitudinal data, but also with a small sample size for this complex analysis, 20% attrition at follow up, conflicting fit indices for model selection, and unavailability of standard error estimates to determine uncertainty around transition probabilities. Latent class and transition analyses used in Chapters 3 and 4 (Aims 2 and 3) are exploratory non-parametric techniques for attempting to create a more parsimonious view of the

complex relationship between multiple correlated behaviors, but there is likely to be misclassification of individuals into specific subgroups to achieve this parsimony. For example, not everyone in the primarily heroin injecting subgroups were truly only injecting heroin, which may limit the ability to detect differences between this and other subgroups. Therefore latent classes/statuses/subgroups should be interpreted probabilistically rather than deterministically. Additionally, specific findings may have limited generalizability to PWID in other times and places with different historical, cultural, political, and economic contexts that influence substance use behaviors and related harms.

## **FUTURE RESEARCH IN GLOBAL HEALTH**

In addition to the need for improved harm reduction service coverage and research on the appropriateness of various psychometric tools for culturally diverse populations, future research aims in the multidisciplinary field of Global Health on the relationship of polydrug use to drug related harms may be drawn from the intersection of Epidemiology with the fields of Medical Anthropology, Psychology, and Political Science.

The “Pharmaceutical self” is described by Psychological Anthropologist Janis Jenkins<sup>13</sup> as the aspect of self—the “sum of processes by which the subject is oriented to the world and toward other people”—by and toward pharmaceutical drugs. Like medicines, drugs more broadly are material with the “power to transform,” for motives that may be therapeutic, non-therapeutic, or recreational. They may be taken to alleviate personal and social suffering or to “merely mask and dislocate the source of such suffering.” The pharmaceutical selves of PWID may reflect attempts to alleviate or mask the suffering caused by detrimental life course experiences and

their risk environment. Further research is needed on why and how people who use drugs choose to use these substances with very differing effects; how these substances used together affect physiological functioning; and how PWID may selectively use specific substances and routes of administration to simultaneously manage competing risks of drug use, subjective psychological experiences, and structural risk environments. Future research should also focus on acquiring a more comprehensive understand of how PWID manage competing priorities (food, shelter, relationships) with risks (infection, overdose, violence) over their life course.

In recognition of connections between systems of inequality and criminalization of drug use, in recent years several countries have taken steps to decriminalize the possession of small amounts of drugs and numerous U.S. states have decriminalized or legalized marijuana use.<sup>14</sup> In April 2016 the United Nations will hold a General Assembly Special Session on the World Drug Problem in response to increasingly widespread and vocal calls to amend current system of global drug control by enacting global drug policy reforms that implement evidence based policies that do not cause more harm than the consumption of drugs themselves. Future research should continue to evaluate ongoing reforms and conduct longitudinal and qualitative inquiries into trends and lived experiences of substances users in order determine how to best structure policies and services to modify risk environments and reduce harmful drug use.

## **CONCLUSIONS**

Findings from this dissertation research expand current knowledge about variety and prevalence of use of multiple substances through multiple routes among PWID in the U.S.-Mexico border region, as well as the associations of specific

patterns of use with drug-related harms of HIV and overdose. Results suggest that polydrug and polyroute users are at higher risk of acquiring HIV and are also in greater need of harm reduction services. Findings highlight the heterogeneity in substance use patterns among PWID in Tijuana and San Diego and demonstrate that polydrug and polyroute users are a high-risk subgroup who may require more tailored prevention and treatment interventions.

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