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Behavioral and contextual factors shaping HIV risk environments among people who inject drugs in Tijuana, Mexico: implications for prevention and treatment

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

Doctor of Philosophy

in

Interdisciplinary Research on Substance Use

by

Jennifer P. Jain

Committee in Charge:

University of California San Diego

Professor Steffanie A. Strathdee, Chair
Professor Eileen V. Pitpitan, Co-Chair
Professor Thomas L. Patterson

San Diego State University

Professor Mark B. Reed
Professor María Luisa Zúñiga

2019

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The Dissertation of Jennifer P. Jain is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

Chair

Co-Chair

University of California San Diego

San Diego State University

2019

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Chapter 2, “Sex work as a mediator between female sex and incident HIV infection among people who inject drugs in Tijuana, Mexico”, has been submitted to the journal of AIDS and Behavior and is under review. Coauthors on this manuscript include; Daniela Abramovitz, Steffanie A. Strathdee, Patricia Gonzales-Zuniga, Brooke S. West, and Eileen V. Pitpitan.

Chapter 3, “Economic risk factors and drug use behaviors driving HIV seroconversion among people who inject drugs in Tijuana, Mexico”, in part is currently being prepared for submission to the journal of PLOS ONE. Coauthors on this manuscript include; Steffanie A. Strathdee, Patricia Gonzales-Zuniga, Gudelia Rangel, and Eileen V. Pitpitan.

Chapter 4, “Sex differences in the psychological and environmental correlates of injection risk behaviors among people who inject drugs in Tijuana, Mexico, has been submitted to the journal Drug and Alcohol Dependence and is under review (revise and resubmit). Coauthors on this manuscript include; Steffanie A. Strathdee, Brooke S. West, Patricia Gonzalez-Zuniga, Gudelia Rangel, and Eileen V. Pitpitan.

VITA AND PUBLICATIONS

VITA

2019 Doctor of Philosophy in Interdisciplinary Research on Substance Use
University of California San Diego and San Diego State University
(San Diego, CA)

2014 Master of Public Health
San Francisco State University
(San Francisco, CA)

2008 Bachelor of Arts (Political Science)
Humboldt State University
(Arcata, CA)

PUBLICATIONS

Peer Reviewed Publications

1. Patrick R, **Jain JP**, Smith D, Harvey-Vera A, Semple S, Rangel G, Patterson TL, and Pines HA. Perceived barriers to pre-exposure prophylaxis use among HIV-negative men who have sex with men in Tijuana, Mexico: a latent class analysis. PLOS ONE. 2019 Aug;22.

2. **Jain JP**, Strathdee SA, Patterson TL, Semple S, Harvey-Vera A, Magis-Rodriguez C, Martinez G, and Pines HA. Perceived barriers to pre-exposure prophylaxis use and the role of syndemic factors among female sex workers in the Mexico-United States border region: a latent class analysis. AIDS Care. 2019 Jun;4.

3. Batchelder AW, Moskowitz JT, **Jain JP**, Cohn M, Earle M, Carrico, AW. A novel technology-enhanced internalized stigma and shame intervention for HIV-positive persons with substance use disorders. Cognitive and Behavioral Practice. 2019 Apr;16.

4. **Jain JP**, Bristow CC, Pines HA, Harvey-Vera A, Rangel G, Staines H, Patterson TL, Strathdee SA. Factors in the HIV risk environment associated with bacterial vaginosis among HIV-negative female sex workers who inject drugs in the Mexico-United States border region. BMC Public Health. 2018 Dec;18(1):1032.

5. Carrico AW, Gómez W, **Jain JP**, Shoptaw S, Discepola M V, Olem D, et al. Randomized controlled trial of a positive affect intervention for methamphetamine users. Drug Alcohol Depend. 2018;192:8–15.

6. Mirzazadeh A, Shokoohi M, Navadeh S, Danesh A, **Jain JP**, Sedaghat A, et al. Underreporting in HIV-Related High-Risk Behaviors: Comparing the Results of Multiple Data Collection Methods in a Behavioral Survey of Prisoners in Iran. Prison Journal. 2018 Jan 24;98(2):213-28.

7. Mirzazadeh A, Evans JL, Hahn JA, **Jain JP**, Briceño A, Shiboski S, Lum PJ, Bentsen C, Davis G, Shriver K, Dimapasoc M. Continued transmission of HIV among young adults who inject drugs in San Francisco: Still room for improvement. AIDS and Behavior. 2018 Apr 1;22(4):1383-94.

8. **Jain JP**, Santos GM, Scheer S, Gibson S, Crouch PC, Kohn R, Chang W, Carrico AW. Rates and correlates of syphilis reinfection in men who have sex with men. LGBT Health. 2017 Jun 1;4(3):232-6.

9. Carrico AW, **Jain JP**, Discepola MV, Olem D, Andrews R, Woods WJ, Neilands TB, Shoptaw S, Gómez W, Dilworth SE, Moskowitz JT. A community-engaged randomized controlled trial of an integrative intervention with HIV-positive, methamphetamine-using men who have sex with men. BMC Public Health. 2016 Dec;16(1):673.

10. **Jain JP**, Evans JL, Briceño A, Page K, Hahn JA. Comparison of phosphatidylethanol results to self-reported alcohol consumption among young injection drug users. Alcohol and Alcoholism. 2014 Jun 17;49(5):520-4.

11. Carrico AW, Flentje A, Gruber VA, Woods WJ, Discepola MV, Dilworth SE, Neilands TB, **Jain JP,** Siever MD. Community-based harm reduction substance abuse treatment with methamphetamine-using men who have sex with men. Journal of Urban Health. 2014 Jun 1;91(3):555-67.

<u>Submitted and Under Review</u>

1. **Jain JP**, Strathdee SA, West BS, Gonzalez-Zuniga P, Rangel G, and Pitpitan EV. Sex differences in the psychological and environmental correlates of injection risk behaviors among people who inject drugs in Tijuana, Mexico. (Revise and resubmit, under review in Drug and Alcohol Dependence).

2. **Jain JP**, Abramovitz D, Strathdee SA, Gonzalez-Zuniga P, Rangel G, West BS, and Pitpitan EV. Sex work as a mediator between female sex and incident HIV infection among people who inject drugs in Tijuana, Mexico. (Under review in AIDS and Behavior).

3. Carrico AW, Neilands T, Dilworth S, Evans J, Gómez W, **Jain JP**, Gandhi M, et al. Positive Affect Intervention to Reduce HIV Viral Load Among Methamphetamine-Using Sexual Minority Men: A Randomized Controlled Trial. (Revise and resubmit, under review in JAMA Psychiatry).

ABSTRACT OF THE DISSERTATION

Behavioral and contextual factors shaping HIV risk environments among people who inject drugs in Tijuana, Mexico: implications for prevention and treatment

by

Jennifer P. Jain

Doctor of Philosophy in Interdisciplinary Research on Substance Use

University of California San Diego, 2019

San Diego State University, 2019

Professor Steffanie A. Strathdee, Chair
Professor Eileen V. Pitpitan, Co-Chair

Background: HIV prevalence among people who inject drugs (PWID) in Tijuana, Mexico is 22 times higher than that among the general population. Among PWID, HIV transmission is shaped by factors in the physical, social, economic and policy risk environments. This dissertation explored factors associated with incident HIV infections sex differences in HIV-related risk factors and their potential underlying mechanisms among PWID in Tijuana, Mexico.

Methods: Data were drawn from a prospective cohort study of PWID in Tijuana, (N=651) chapters 2 and 3, and (N=734) chapter 4. Chapter 2 assesses sex work as a mediator in the association between female sex and elevated HIV incidence using modern mediational analyses. Chapter 3 identifies factors associated with time to HIV seroconversion using Cox regression and assesses the robustness of these

associations using novel sensitivity analyses. Chapter 4 explores sex differences in the environmental and psychological correlates of injection risk, using generalized linear regression.

Results: Chapter 2 demonstrates that HIV incidence is significantly higher among female PWID (1.75 per 100 person years [PY], 95% confidence interval [CI] 1.2-2.7, vs. 0.95 per 100 PY, 95% CI=0.6-1.4), and that sex work mediates the association between female sex and HIV incidence (proportion mediated=86.0%, p=0.01). Chapter 3 highlights sex work (adjusted hazard ratio [aHR]=2.20, 95% CI=1.03-4.68); methamphetamine injection (aHR=2.13, 95% CI=1.04-4.35); and methamphetamine and heroin co-injection (aHR=2.09, 95% CI=1.13-3.85) as drivers of HIV seroconversion, and shows that these associations are relatively robust to unmeasured confounding. In chapter 4 among both sexes, using syringes from a safe source, and safe injection self-efficacy were associated with lower injection risk (b=0.87, 95% CI=0.82-0.94, and b=0.80, 95% CI=0.76-0.84, respectively). Among females, incarceration (b=1.22, 95% CI=1.09-1.36) and syringe confiscation (b=1.16, 95% CI=1.01-1.33) were associated with elevated injection risk, whereas, among males sex work (b=1.16, 95% CI=1.04-1.30), and polysubstance use (b=1.22, 95% CI=1.13-1.31) were associated with elevated injection risk.

Conclusions: Interventions should be sex-specific, incorporate sexual risk reduction, consider drug use behaviors, and address environmental influences of HIV risk among PWID in Tijuana.

CHAPTER 1: INTRODUCTION

OVERVIEW

The risk of acquiring HIV and hepatitis C virus (HCV) among people who inject drugs (PWID) is shaped by several dynamic social and structural influences in the physical, social, economic and policy environments in which risk is produced. Many sociocultural influences also shape HIV and HCV risk environments in ways that often place female PWID at higher risk of acquiring HIV and HCV compared to their male counterparts. The importance of identifying more proximal or individual-level correlates of risk behavior in addition to broader sociostructural influences is emphasized by theoretical models such as the Social Ecological Model (SEM), which recognizes five levels of influence (e.g., individual, interpersonal, institutional, community, and policy) on human behavior. Certain individual-level influences such as self-efficacy to avoid HIV and HCV risk have been identified as key psychological factors associated with injection and sexual risk reduction among PWID in higher income settings such as the United States (US) (1). However, less is known about the underlying mechanisms driving sex disparities in HIV incidence, the causal contribution of factors associated with time to HIV seroconversion, and any potential sex differences in the psychological (e.g., self-efficacy) and environmental correlates of injection risk behaviors among PWID in low- and middle income countries (LMICs) like Mexico.

The overall purpose of this dissertation is to further our understanding of how micro physical, social, and economic risk environments increase HIV risk, and contribute to sex disparities in HIV incidence (AIMS 1-2), as well as how psychological and environmental factors shape injection risk behaviors and are differentially

associated with sex (AIM 3) among male and female PWID in Tijuana, Mexico. This dissertation is guided by the following three primary aims: (1) to calculate and compare HIV incidence density rates by sex, examine potential mediators between female sex and incident HIV infection, and calculate the attributable risk of HIV incidence due to the the identified mediator(s), among PWID in Tijuana, (2) to identify the micro physical (e.g. personal safety concerns), and social (e.g. anticipation of arrest for syringe or drug possession), factors associated with HIV seroconversion, and assess how robust these associations are to unmeasured confounding, and (3) to identify sex differences in the intrapersonal (e.g., safe injection self -efficacy), interpersonal (e.g., sex work), institutional (e.g., incarceration and police confiscation of syringes), and policy level (e.g., limited access to new/sterile syringes) correlates of injection risk behaviors among male and female PWID in Tijuana, Mexico.

To meet these aims, I utilized data from an ongoing prospective cohort study of PWID in Tijuana, to calculate HIV incidence density and apply novel mediation analysis methods to survival data to identify mechanisms driving elevated HIV incidence among female PWID compared to males (AIM 1), to identify factors associated with time to HIV seroconversion, and assess how robust these associations are to unmeasured confounding using a novel sensitivity analysis method designed for observational research (AIM 2), and to apply generalized linear regression and stratification by sex to identify sex differences in the psychological and environmental correlates of injection risk behaviors. This dissertation aims to contribute to our understanding of behavioral mechanisms driving sex disparities in HIV incidence, the robustness (e.g., robust to unmeasured confounding) of factors associated with incident HIV infection, and

environmental factors that increase injection risk as well as individual/behavioral determinants of safer injection practices among male and female PWID. Results from this dissertation will contribute to the development of sex-specific interventions designed to reduce HIV and HCV transmission among PWID by targeting environmental risk factors and increasing safe-injection self-efficacy. Furthermore, this work may improve our understanding of where to prioritize limited HIV and HCV prevention resources for PWID in Tijuana, Mexico and other LMICs.

BACKGROUND

While the national prevalence of HIV and HCV remain low in Mexico, HIV and HCV prevalence are high among PWID (2). As of 2016, the prevalence of HIV among PWID in Mexico was 12.5 times higher than that among the general population (2.5% vs. 0.2%) (3). This disparity is even more pronounced in Tijuana, a large Mexico-United States (US) border city where HIV prevalence among PWID is approximately 22 times higher than that among the general population (4.4% vs. 0.2%) (2–4). Furthermore, the cumulative AIDS incidence rate in this region is 65% higher than Mexico's national average (140 per 100,000 vs. 85 per 100,000), respectively (5). Similarly, 96% of PWID in Tijuana are living with hepatitis C virus antibodies (anti-HCV) (6), which is nearly twice as high as the estimated prevalence of PWID living with HCV-antibodies worldwide (52.3%) (7), and approximately 91 times higher than anti-HCV prevalence among the general population in Mexico (0.1%-2.0%. vs. 96%) (8).

In Tijuana, HIV prevalence is significantly higher among female PWID compared to male PWID (10.2% vs. 3.5%, p=0.001) and (8% vs. 3%, p=0.01), respectively (9,10).

This trend is consistent with findings from international research, which demonstrate that even though female PWID represent a smaller proportion of PWID globally (3.5 million out of 13 million), they tend to have a higher HIV prevalence compared to males worldwide; Latin America (38.5% vs. 34.6%), Eastern Europe (33.0% vs. 27.9%), and the United States (34.5% vs. 31.3%) (11,12). Similarly, data drawn from studies conducted across nine European countries demonstrated that overall female PWID have a higher prevalence of HIV compared to males (13). Further, findings from a systematic review that analyzed data from 117 studies across 14 countries found that female PWID had a higher odds of HIV infection compared to males (odds ratio [OR]=1.18, 95% confidence interval [CI]=1.10,1.26)(11). Likewise, HCV incidence tends to be significantly higher among female PWID compared to male PWID worldwide (14,15).

According the risk environment framework (16), HIV and HCV transmission among PWID is largely driven by individual and behavioral factors such as sexual and injection risk behaviors that are influenced by micro and macro level influences in the physical, social, economic and policy risk environments (16–18). For example, Tijuana's risk environment is shaped by a unique set of factors including: it's placement along a well-established drug trafficking route (macro-physical) (19), high rates of illicit drug use consumption that are nearly three times the national average (14.7% vs. 5.5%) (19), (micro-social), a large population of PWID (20) (micro-social), punitive policing practices (micro-social), a thriving sex trade industry (macro-policy), participation in sex work (micro-economic) (21), limited access to sterile syringes, and HIV and HCV testing and

treatment (micro-policy) (22). Together, these are some of the key multifaceted and interactive factors which comprise the risk environment for PWID in Tijuana.

Sex disparities in HIV and HCV infection are often shaped by underlying sex and gender-related risk factors such as; economic vulnerability and limited access to power and resources that make substance-involved women vulnerable to engaging in sexual and injection related risk behaviors (23,24). For instance, many female PWID in the Mexico-US border region, report entering into sex work out of economic necessity (23,25–27). Female PWID who engage in sex work (FSW-PWID) are more likely than other female sex workers who do not inject drugs (FSW) to engage in unsafe sex and drug injection practices with clients and intimate partners. This places them at risk of acquiring HIV infection through two transmission routes (e.g., unprotected sex and contaminated syringes), and increases their likelihood of acquiring HCV (11,21,28,29). It is also known that economically marginalized substance-involved women, often experience a diminished capacity to negotiate male condom use due to being under the influence of drugs and alcohol, experiencing the urgency of drug related withdrawal, and being susceptible to incentives (e.g., larger payments, drugs or alcohol) for condomless sex from clients or partners (30). Consequently, in the Mexico-US border region, HIV prevalence among female PWID who engage in sex work is two times higher than that among other FSW (12.3% vs. 6%), and 61 times higher than that among the general population (21,31).

Understanding the psychological correlates of risk behavior in addition to the broader sociostructural factors that influence risk, is also crucial for designing comprehensive HIV and HCV prevention strategies that recognize different levels of HIV

and HCV risk (32,33). The Social Ecological Model (SEM) recognizes individual, sociostructural, and policy-level factors that influence human behavior and may act as determinants of HIV and HCV vulnerabilities among PWID (33). We know from Social Cognitive Theory (SCT) (34) that one of the most important factors to consider in the individual/intrapersonal domain is self-efficacy (35). Self-efficacy can be defined as the confidence to exercise control over events in one's life (36), such as using one's own syringe regardless of experiencing withdrawal or injecting with intimate partners. Research among PWID in the United States (US) has identified a relationship between perceived self-efficacy to avoid HIV and HCV risk, and drug use and injection risk reduction (1,37), suggesting that self-efficacy is an important individual-level correlate of behavioral risk reduction among PWID. However, less is known about the impact of this individual level determinant on injection risk behaviors, and whether this effect differs by sex (e.g., male vs. females) among PWID in LMICs. More research is needed to identify sex differences in the correlates of risk reduction among PWID in Tijuana, in order to inform future interventions designed to reduce HIV and HCV transmission among PWID in this setting. This is especially important in the Mexico-US border region, where sex-related risk factors (e.g., stigma and discrimination toward female substance users) may reduce one's self-efficacy to avoid HIV and HCV risk (38,39).

GAPS IN RESEARCH ADDRESSED BY THIS DISSERTATION

This dissertation research will address several important gaps in research. First, HIV incidence density estimates are needed among PWID in the Mexico-US border region to continue to monitor the progression of the epidemic in this hard to reach

population. Several studies have identified risk factors for HIV infection among PWID, but there is a serious lack of HIV incidence data disaggregated by sex in this population. Therefore, there is also a need to identify sex related trends and disparities in HIV incidence. This dissertation (AIM 1) will address these gaps in research *by calculating HIV incidence density rates overall and by sex (males vs. females), adding to the body of literature on longitudinal trends and sex disparities in HIV infection among PWID in LMIC's (AIM 1).*

Many studies have measured HIV prevalence among PWID and revealed the impact of sex work on HIV risk, but to our knowledge no studies have assessed whether sex work mediates an association between female sex and incident HIV infection among PWID (38,40,41). Thus, there is a need to decompose sex disparities in HIV incidence using modern mediation analyses designed to illuminate the underlying determinants of health inequities. This dissertation research (AIM 1) will reduce this gap in knowledge by identifying the mechanisms driving elevated HIV incidence among female PWID using modern mediation analyses designed for survival data with a rare outcome (e.g., <10%). As such, the present research (AIM 1) may enhance our understanding of the importance of sex work as a causal driver of HIV among female PWID.

There is also is an urgent need to identify the fundamental causes of HIV infection among PWID in Tijuana, given the state of the epidemic in this population. In order to accomplish this it is necessary to estimate how robust the identified associations are to unmeasured confounding. This is especially important in the context of observational research where it is often not feasible to measure all potential

confounders, and randomization of the exposure tends to be impossible and or unethical. Therefore, it is recommended by leading experts in the field of epidemiology (42) to assess how robust associations are to unmeasured confounders. An unmeasured confounder can be defined as a factor that is related to both the treatment and the outcome, but is not measured. Assessing how robust measured associations are to unmeasured confounders helps more objectively determine the true causal contribution of these associations.

Recently, novel sensitivity analysis methods have been developed for this purpose (42). For example, the “E-value” quantifies the strength of association that an unmeasured confounder would need to have with both the treatment and the outcome in order to “explain away” an observed association, conditional on the measured covariates (e.g., variables that have been controlled for) (42). This approach is consistent with Bradford Hill’s criterion “strength of association” in determining whether or not an association is causal (43). Applying this sensitivity analysis to data drawn from observational research conducted in the Mexico-US border region is especially important because HIV prevention resources are limited in this setting and therefore must be prioritized. This dissertation (AIM 2) will help address this gap in research by utilizing Cox regression to identify predictors of time to HIV seroconversion, and applying the E-value to assess how robust the identified estimates are to unmeasured confounding.

Considering how risk environments are shaped distinctly for male and female PWID, which likely differentially impacts their self-efficacy to avoid risk, there is a need to identify potential sex differences in the environmental and personal-level correlates of

injection risk. Such methods may identify different levels of HIV and HCV risk and help inform multi-level prevention strategies that target both broader environmental risk factors (e.g., police confiscation of syringes) as well as personal-level determinants (e.g., self-efficacy) of behavior change. As such, these approaches are more comprehensive and thus potentially more effective in reducing the burden of HIV and HCV among PWID. This dissertation research (AIM 3) will contribute to the literature in this area by analyzing sex differences (e.g., male vs. female) in the environmental and psychological correlates of risk behavior, and add to the body of literature on sex differences in the multi-level correlates of injection risk behaviors among PWID in the Mexico-US border region.

Taken together, this dissertation research aims to advance existing knowledge by: (1) yielding HIV incidence density estimates, and testing whether sex work mediates an association between sex and incident HIV infection; (2) identifying micro environmental risk factors for incident HIV infection; and (3) examining sex differences in the environmental and psychological correlates of injection risk behaviors among PWID in Tijuana, Mexico.

CONCEPTUAL AND THEORETOCAL FRAMEWORKS

This dissertation research (AIM 1-2) is guided by the HIV 'risk environment' framework as described by Rhodes and colleagues (18) (Figure 1.1). This framework examines how individuals and environments interact and produce HIV and HCV risk (16). This framework considers micro and macro level influences in the physical, social, economic and policy risk domains. Environmental influences such as gendered risk

factors and easy access to drugs are hypothesized to increase one's vulnerability to acquiring HIV and HCV especially in the context of injection drug use (44).

The use of the HIV risk environment framework in this dissertation is appropriate because of its emphasis on several micro-environmental factors that are hypothesized to increase HIV and HCV risk in this research (AIMS 1-3). For instance, this framework acknowledges how sex and gender inequalities and risk factors shape micro economic exposures such as sex work that increase one's vulnerability of acquiring HIV (AIM 1). This framework also recognizes how micro-physical and social factors such as violence and fear of arrest for syringe or drug possession contribute to HIV risk among PWID (AIM 2).

This research also leverages the Social Ecological Model (SEM) to guide the exploration of how personal and environmental factors impact injection risk behavior and potentially differ by sex (Figure 1.2). For instance, safe-injection self-efficacy is explored as a primary psychological correlate of risk behavior in addition to several environmental factors such as incarceration, police confiscation of syringes, and access to harm reduction programs (e.g., needle exchange). Injection risk was measured using an "injection risk score" created from a similar index of injection risk behaviors that was developed for the Drug Users Intervention Trial (37). Injection risk indicators (e.g., sharing of needles and other paraphernalia) were measured, summed and averaged to create an "injection risk score" ranging from 1-5 where higher scores represents higher risk.

This research (AIM 3) aims to contribute to our understanding of the multi-level determinants of HIV and HCV vulnerabilities among PWID in Tijuana (45). Developing a

more in depth understanding of the different levels of HIV and HCV risk may help inform the development of multi-level prevention strategies for PWID in LMICs. This dissertation research will also assess sex as a moderator of these associations, thereby expanding our understanding of the heterogeneity in injection risk among PWID in LMICs (Figure 1.2).

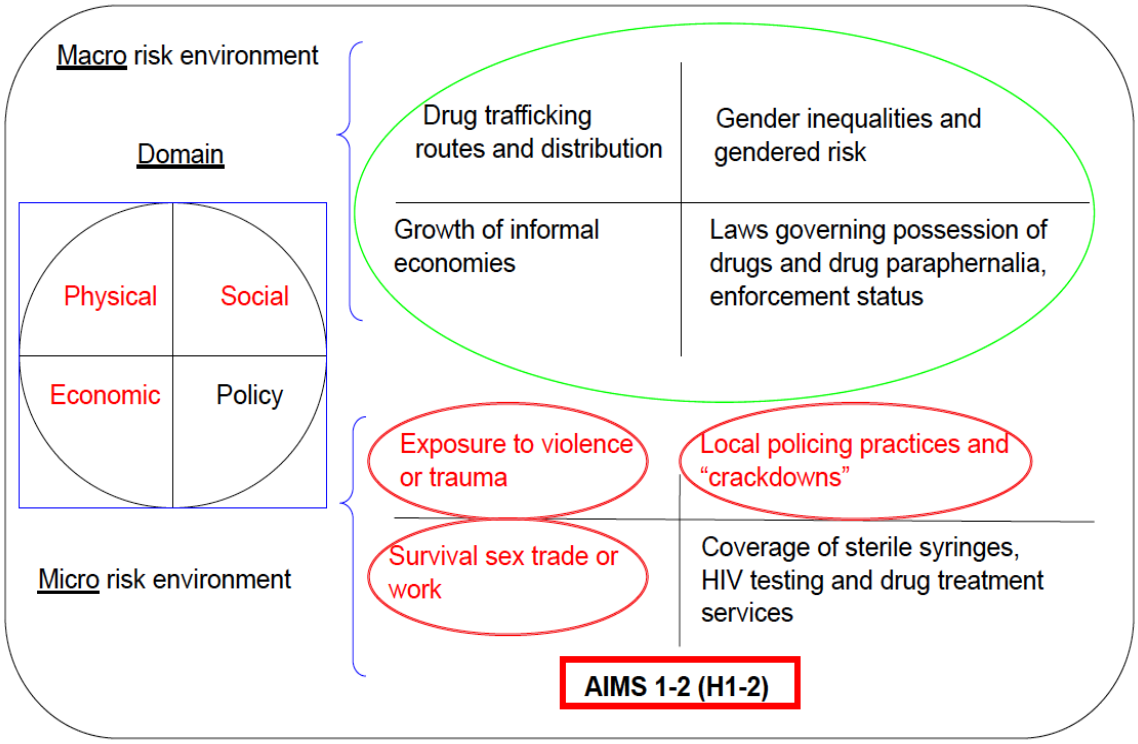

Figure 1.1: The HIV risk environment framework applied to understand environmental risk factors associated with HIV among PWID in Tijuana, Mexico, adapted for dissertation aims 1 and 2.

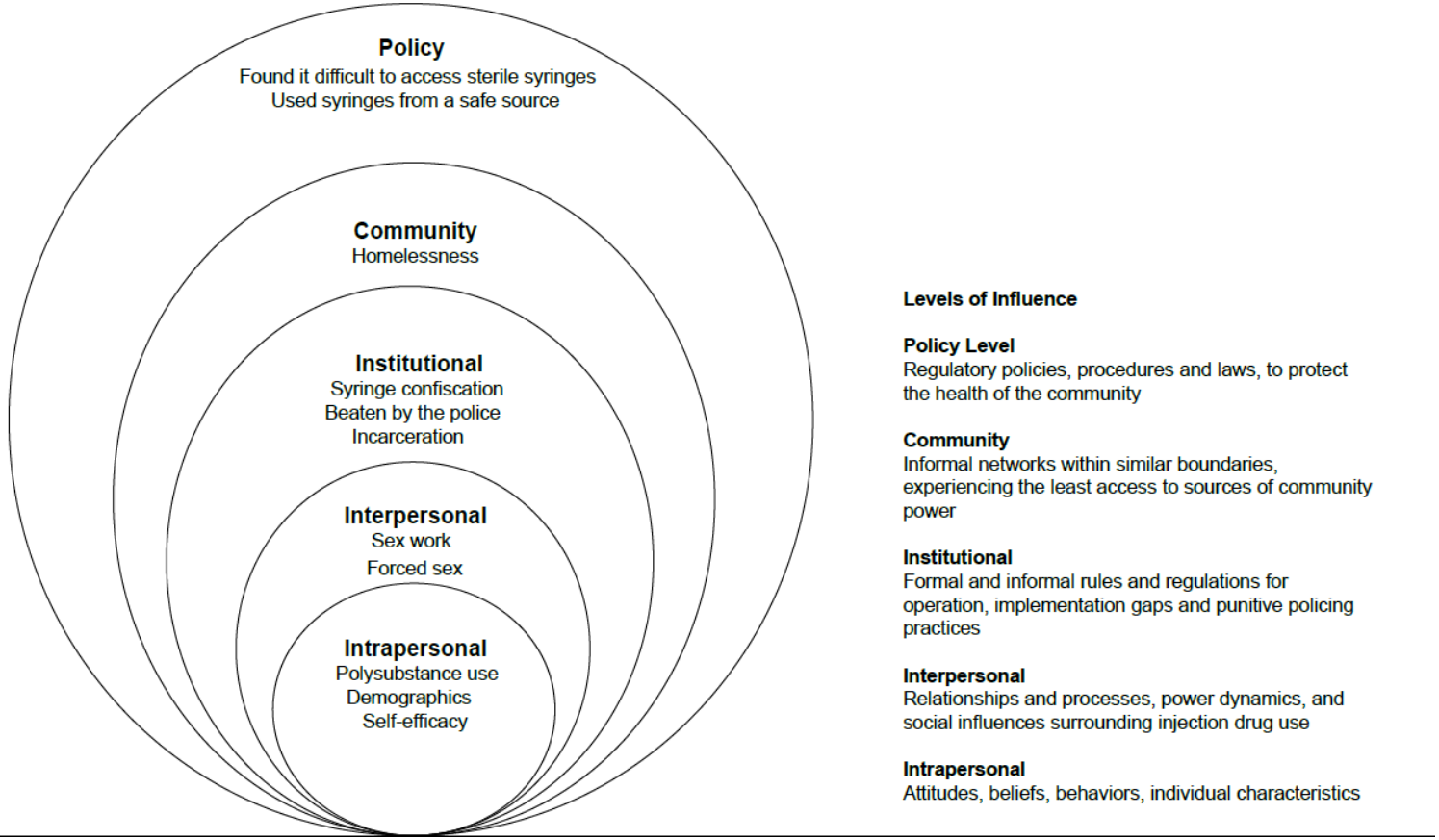

Figure 1.2: The social ecological model applied to understand the psychological and environmental factors associated with average injection risk scores among male and female PWID in Tijuana, Mexico, adapted for dissertation aim 3.

AIMS AND HYPOTHESES

The overall purpose of this dissertation is to further our understanding of how micro physical, social, and economic risk environments increase HIV risk, and contribute to sex disparities in HIV incidence (AIMS 1-2), as well as how psychological and environmental factors shape injection risk behaviors and are differentially associated with sex (AIM 3) among male and female PWID in Tijuana. Informed by the HIV risk environment framework, the social ecological model, and a review of the literature on HIV and HCV risk among male and female PWID in Tijuana, this dissertation is guided by the following three primary aims.

AIM 1: To calculate and compare HIV incidence density rates by sex, examine potential mediators between female sex and incident HIV infection, and calculate the attributable risk of HIV incidence due to the identified mediator(s), among people who inject drugs (PWID) in Tijuana, Mexico. *Hypothesis 1 (1):* Sex work and sexual violence will mediate an association between female sex and being diagnosed with HIV, among PWID in Tijuana, Mexico. *Hypothesis 1 (2):* A significant percent of HIV incidence will be attributed to sex work, among PWID in Tijuana, Mexico.

AIM 2: To identify the micro physical (e.g. personal safety concerns), and social (e.g. anticipation of arrest for syringe or drug possession), predictors of time to HIV seroconversion, and assess how robust the identified predictors of time to HIV seroconversion are to unmeasured confounding. *Hypothesis 2 (1):* PWID with a higher average score for “anticipation of arrest for syringe/drug possession” will have a significantly higher hazard rate of incident HIV infection compared to PWID with a lower average score for “anticipation of arrest for syringe or drug possession”. *Hypothesis 2*

(2): PWID with a higher average score for “safety concerns” will have a significantly higher hazard rate of incident HIV infection compared to PWID with lower average scores for “safety concerns”.

AIM 3: To identify sex differences in the psychological (e.g. safe injection self - efficacy), micro social (e.g. incarceration and police confiscation of syringes), policy (e.g. limited access to new/sterile syringes) and economic (e.g. sex work) correlates of injection risk behaviors among male and female people who inject drugs (PWID) in Tijuana, Mexico. *Hypothesis 3 (1):* The impact of safe injection self-efficacy on injection risk reduction will be greater among males compared to females in Tijuana, Mexico. *Hypothesis 3 (2):* The impact of incarceration, police confiscation of syringes, finding it difficult to access new/sterile syringes and sex work on injection risk will be greater among females compared to males in Tijuana, Mexico.

GLOBAL PUBLIC HEALTH IMPLICATIONS

This dissertation research has several global public health implications. This research will yield updated HIV incidence density estimates among male and female PWID in the Mexico-US border region (AIM 1), which will contribute to HIV surveillance efforts in this hard to reach population and low-and middle-income setting. This study will also disaggregate these data by sex, which will help illuminate sex-related trends in HIV incidence and identify the most at risk subgroup(s), which is crucial in resource-constrained settings (AIM 1). By identifying the most at risk subgroups, we can utilize limited resources wisely and maximize public health efforts to reduce HIV incidence.

Furthermore informed by the HIV 'risk environment' framework (44), using novel mediation analysis methods (46,47), this study will test sex work as a mediator in the association between female sex and incident HIV infection (AIM 1). A notable strength of mediation analysis is the ability to decompose sex-related health disparities. As such, results from this research may improve our understanding of the underlying mechanisms driving elevated HIV incidence among female PWID compared to males in the Mexico-US border region, and may contribute to our understanding of how to develop effective sex-specific interventions for PWID in this region.

Guided by the HIV 'risk environment' framework (44), this dissertation research will also utilize a novel sensitivity analysis method for observational research (42), in conjunction with Cox regression and causal modeling techniques (48), to identify the key drivers of HIV seroconversion among male and female PWID in Tijuana (AIM 2). This analysis will also examine how certain drug use behaviors such as frequent methamphetamine injection and methamphetamine and heroin co-injection (e.g., polysubstance use), are associated with time to HIV seroconversion. In doing so, this research aims to contribute to our understanding of how the co-occurrence of environmental risk factors and drug use behaviors increase the risk of acquiring HIV among PWID in Tijuana.

This research also leverages the SEM to examine the impact of psychological and environmental factors on injection risk behaviors among male and female PWID (AIM 3). Identifying multilevel (e.g., individual and environmental) factors associated with risk behavior may help inform comprehensive HIV prevention programs and

policies designed to address different levels of HIV and HCV risk among PWID in Mexico, and potentially other LMICs.

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CHAPTER 2: SEX WORK AS A MEDIATOR BETWEEN FEMALE SEX AND INCIDENT HIV INFECTION AMONG PEOPLE WHO INJECT DRUGS IN TIJUANA, MEXICO

Abstract

We studied mechanisms driving sex differences in HIV incidence among 651 women and men who inject drugs (PWID) in Tijuana, Mexico, hypothesizing that sex work may mediate an association between female sex and HIV incidence. Of 43 HIV seroconversions occurring between 2011 and 2018, 8.8% were among females and 5.2% among males. HIV incidence density was significantly higher among females versus males (1.75 per 100 person years [PY], 95% CI 1.2, 2.7, vs. 0.95 per 100 PY, 95% CI=.0.60-1.4). Factors significantly associated with HIV seroconversion were: sex work (adjusted hazard ratio [aHR]=2.25, 95% CI=1.05-4.80); methamphetamine injection (aHR=2.30, 95% CI=1.12-4.73); and methamphetamine and heroin co-injection in the past six months (aHR=2.26, 95% CI=1.23-4.15). In mediation analyses, sex work mediated a substantial proportion (86.0%, p=0.01) of the association between female sex and HIV incidence. Interventions should target female PWID who engage in sex work to reduce sex-related disparities in HIV incidence.

Introduction

In Tijuana, HIV prevalence among people who inject drugs (PWID) is 22 times higher than that among the general population in Mexico (4.4% vs. 0.2%, respectively) (1–3). In this region, HIV prevalence is also significantly higher among female PWID compared to males (10.2% vs. 3.5%, p=0.001, respectively) (4). This is consistent with findings from international research, which demonstrate that while female PWID represent a smaller proportion of PWID globally (3.5 million out of 16 million) (5), they tend to have higher HIV prevalence compared to males: (Latin America (38.5% vs. 34.6%), Eastern Europe (33.0% vs. 27.9%), and the United States (34.5% vs. 31.3%) (6,7).

Among PWID, HIV transmission is behaviorally mediated and shaped by factors that are exogenous to the individual (8). According to the risk environment framework vulnerability to HIV infection among PWID is produced by micro and macro level factors in the physical, social, economic and policy domains (8,9) Also, sex-related inequalities shape HIV risk environments in ways that place female PWID at greater risk of acquiring HIV compared to males (6). Sociostructural factors including heightened stigma among female PWID, physical and sexual violence, dependence on male partners for drug acquisition, preparation and injection, and participation in sex work, all exacerbate HIV risk among female PWID (10–16).

Tijuana's HIV risk environment is shaped by a unique set of physical, social, economic and policy related factors. Micro level exposures that contribute to HIV risk among PWID in Tijuana include exposure to physical violence (*micro physical*), punitive policing practices such as police confiscation of syringes (*micro social*), engagement in

sex work *(micro economic),* and limited coverage of HIV testing and treatment services (*micro policy*) (17,18). As a result, Tijuana has become an epicenter of violence, substance use, and elevated incidence of HIV and other sexually transmitted infections (STIs).

Among female PWID in Tijuana, there is significant overlap between injection drug use and sex work (19). Given women's lower economic status and limited access to resources especially in low-and middle-income countries (LMICs) like Mexico, many female PWID in this setting report selling sex out of economic necessity to support themselves, their families, and/or their drug use (20–22). Female PWID who engage in sex work are more likely than other female sex workers (FSW) who do not inject drugs to engage in unsafe sex and injection practices with clients and intimate partners, placing themselves at risk of acquiring HIV through two transmission routes: unprotected sex and using contaminated syringes (6,19,23,24). In many cases, this is due to social and structural barriers to condom use and negotiation including gender and power dynamics, sexual violence and limited access to condoms and safe places to practice sex work (25).

While several studies have demonstrated the disparate burden of HIV among female PWID, there is still a need to decompose sex-related health disparities in HIV incidence by testing the mediating role of known risk factors. The primary objectives of the present study were to; (1) calculate HIV incidence density among PWID and compare incidence density rates by sex (male versus females), (2) compare HIV incident cases to those who did not seroconvert with respect to sociodemographics, behavioral characteristics and factors in the risk environment among males and females

separately, (3) identify factors associated with HIV seroconversion, (4) and examine potential mediators between female sex and incident HIV infection. We hypothesized that HIV incidence would be significantly higher among female PWID, and that sex work would mediate an association between female sex and HIV incidence.

Methods

Study population. From 2011-2013, 734 male and female PWID were recruited into *'Proyecto El Cuete IV"* an ongoing prospective cohort study in Tijuana, Mexico.

Eligibility criteria. Participants were required to meet the following inclusion criteria; 1) be at least 18 years old, 2) self-report injection drug use in the past month, 3) have visual evidence of injection drug use (e.g. track marks), 4) be able to speak English or Spanish, 5) be able to provide written informed consent, 6) plan to stay in Tijuana for at least 24 months, 7) and report no current participation in an intervention study at the time of enrollment. The analysis was restricted to those who tested HIV-negative at baseline (N=651). All participants received $5.00 US dollars for completing the screening process regardless of eligibility.

Recruitment methods. Participants were recruited using targeted sampling techniques, where trained research staff conducted street-based outreach in areas of Tijuana where PWID often reside, congregate, and/or access services.

Surveys. The study protocol is described in full detail elsewhere (26). Participants completed semi-annual surveys administered by trained Spanish speaking interviewers with extensive experience working with PWID in Tijuana. Surveys included measures on sociodemographics, HIV and substance use risk behaviors, and factors in the HIV risk

environment (e.g. sexual violence, access to sterile syringes, and experiences with law enforcement officials)(9). Data were collected using computer-assisted participant interview software (27). Screening and data collection took place in a private setting. Participants were compensated $20.00 US dollars for each visit.

HIV screening and test counseling. Briefly, participants were screened for HIV antibodies at each visit via finger stick using the Advanced Quality Rapid Antibody test (InTec Products, Inc.). Participants testing HIV-positive were asked to provide a peripheral blood sample for confirmation at the San Diego Department of Public Health (28). HIV–positive participants were referred to local municipal health care centers for free treatment and follow-up care. All participants received pre and post-test counseling in accordance with the Mexican Ministry of Health guidelines (26).

Ethical considerations. All study procedures were approved by the Human and Subjects Protections Program at the University of California, San Diego and the University of Xochicalco in Tijuana (26). All participants provided written informed consent at baseline.

Measures

Outcome measure. The outcome of interest was incident HIV infection based on confirmatory test results, defined as seroconverting post-baseline. Seroconversion was assumed to have occurred at the mid-point between the last date HIV-negative and the first HIV-positive.

Sociodemographic characteristics. Data collected on socio-demographics included: self-reported sex (male/female/transsexual), age in years, number of years of education starting at first grade, and marital status.

Substance use characteristics. Participants were asked to report their age at first injection which was used to calculate the total number of years of injection drugs use, by subtracting ones current age from the age they reported first injecting drugs. We also collected data on the types of substances injected at least twice a day or more in the past six months including: methamphetamine, methamphetamine and heroin together, heroin and cocaine.

Micro-physical risk environment. Micro-physical measures included in the analysis were: the number of years one has lived in Tijuana, lived in Tijuana for one's whole life (yes/no), moved to Tijuana because of deportation (yes/no) and moved to Tijuana looking for a better life (yes/no).

Micro-social risk environment. Micro-social measures included in the analysis were: lifetime forced sex which was defined as ever being coerced into having sex by someone who used physical or emotional pressure, police confiscation of syringes (yes/no) and syringe mediated drug sharing in the past six months (yes/no), whether one had bought drugs that came prepared in a syringe at least half of the time in the past six months (yes/no), and the number of individuals residing in the respondents household including the respondent.

Micro-economic risk environment. Micro-economic measures included in the analysis were: sex work in the past six months, which was a dichotomous measure based on the response to the following question: "In *the last six months, how many*

people gave you something you needed in exchange for having sex with them?" We also asked participants to report their average monthly income in Mexican pesos.

Micro-policy risk environment. Micro-policy measures included in the analysis were: whether the participant reported obtaining syringes from a needle exchange program (yes/no) and whether the participant reported finding it hard to get new syringes in the past six months (yes/no).

Statistical Analysis

Data from 16 research visits over a 90-month period, ranging from March of 2011 to October of 2018, were used to calculate HIV incidence density. Time spent at risk was calculated by subtracting the baseline interview date from the date when the participant was assumed to have seroconverted. For those who did not seroconvert during the follow-up period, time at risk in person years (PY) was calculated by subtracting the date of their last assessment from the date of their baseline interview (e.g. right censored). Next, we compared females and males with respect to HIV incidence by using Poisson regression with the log of time spent at risk as an offset term (Table 1).

Using baseline data, descriptive statistics including frequencies, percentages, medians and interquartile ranges (IQRs) were generated (Table 2). Chi-square tests were used to compare participants who seroconverted and those who did not with respect to dichotomous variables, and, depending on distributional assumptions, either t-tests or Wilcoxon Rank Sum tests were used for comparisons involving continuous variables. These analyses were stratified by sex.

Simple and multiple Cox regression were used to evaluate associations between sociodemographic and substance use characteristics as well as factors in the HIV risk environment and incident HIV infection for the whole sample (Table 3). In bivariate analyses primary exposures that yielded a p-value ≤0.05 were examined further in multivariable Cox models, and each primary effect was modeled separately as recommended by Greenland and colleagues (29), while controlling for the following confounders that have been identified as correlates of HIV infection in prior research; sex (30), income (20), duration of injection drug use (31), and the number of individuals residing in the respondents household including the respondent, which served as a proxy for the number of dependents one has (32,33). We compared nested Cox models using the Likelihood Ratio test to arrive at parsimonious models, and in adjusted analyses exposures which yielded a p-value ≤0.05 derived from Cox regression, were selected for further exploration in subsequent mediation analyses. The proportional hazards assumption was assessed for all factors significantly (e.g. p≤0.05) associated with incident HIV in bivariate analyses as follows: for continuous variables, we examined plots of Schoenfeld residuals against the time variable, and for categorical variables, we examined plots of log-minus-log of the survival function against the time variable. Additionally, interactions terms between predictors and time were included and tested in the models by using likelihood ratio tests. Only one variable (forced sex) did not meet the proportional hazard assumption, in which case, Allison suggests interpreting its effect as an average effect over the period at risk (30).

Mediational analyses using Cox proportional hazard models were implemented using the SAS Mediation Macro designed for survival data with a rare outcome (e.g.,

<10%) developed by VanderWeele and Valeri (34). Using this novel method for mediation analysis, we calculated the total effect of female sex on incident HIV, the controlled direct effect (CDE) of female sex on incident HIV infection while controlling for sex work, and the natural indirect effect (NIE) of female sex on incident HIV through sex work. In these mediational analyses we controlled for the following confounders that have been identified as correlates of HIV infection in prior research; income (20), duration of injection drug use (31), and the number of individuals residing in the respondent's household including the respondent (32,33), and used 2,500 bootstrap repetitions. The proportion of the total effect of female sex on incident HIV infection mediated by the predictors tested as mediators was estimated using the SAS Mediate Macro designed for survival data with a rare outcome while controlling for the same set of confounders (35).

We also tested whether female sex moderated the relationship between the identified mediator(s) and incident HIV using both the multiplicative scale and the additive scale. To test sex as a moderator using the multiplicative scale we included an interaction term in each multivariable Cox model while controlling for the aforementioned confounders. To test sex as a moderator using the additive scale we estimated the relative excess risk due to interaction (RERI) (36) while controlling for the same set of confounders, using the algorithm recommended by Andersson and colleagues (37), (HR_{11}-HR_{10}-HR_{01}), where "11" represents the presence of both the moderator (e.g., female sex) and the risk factor (e.g., sex work).

Finally, the attributable risk percent (ARP) of HIV incidence due to the significant mediator(s) was calculated along with corresponding p-value(s), derived from Fisher's

exact tests. The ARP was calculated by subtracting the proportion of exposed PWID with incident HIV from the proportion of unexposed PWID with incident HIV, and then dividing this by the proportion of exposed PWID with incident HIV and multiplying this value by 100. Finally, the population attributable risk percent (PAR%) was calculated to estimate the expected reduction in HIV incidence if the sample were not exposed to the significant mediator(s). PAR% was calculated by subtracting the proportion of PWID with incident HIV from the proportion of unexposed PWID with incident HIV, dividing this by the proportion of PWID with incident HIV and multiplying this value by 100. All analyses were performed in SAS 9.4 and Stata 14.2.

Results

HIV incidence density. Of 651 PWID (males: 402, females: 249), 43 seroconversions occurred between 2011 and 2018, 8.8% among females and 5.2% among males, yielding a cumulative incidence density of 1.25 per 100 person-years (PY) (95% CI=0.9-1.6). Incidence density was significantly higher among females compared to males: 1.75 per 100 PY (95% CI=1.6-2.7) vs. 0.96 per 100 PY (95% CI=0.60-1.5), with a female to male incidence rate ratio of 1.83 (95% CI=1.01-3.31, p=0.04) (Table 1).

Comparison of participants who did and did not seroconvert by sex. Among females, incident cases were significantly more likely than PWID who did not seroconvert to report: methamphetamine and heroin co-injection ≥ twice a day (50.0% vs. 29.5%, p=0.04, respectively), and syringe-mediated drug sharing (e.g. dividing drugs with a syringe) more than half of the time in the past six months (59.1% vs. 30.5%,

p=0.01). Female incident cases were also more likely to report police confiscation of syringes (27.3% vs. 12.3%, p=0.05), and obtaining syringes from a needle exchange program (NEP) (27.3% vs. 10.1%, p=0.02), in the past six months. Finally, among females, incident cases were significantly more likely to report sex work in the past six months compared to those who did not seroconvert (86.4% vs. 65.2%, p=0.04) (Table 2).

Among males, incident cases were younger on average (mean=35.2, standard deviation [SD]=7.2 verses mean=39.2, SD=8.7, p=0.03, respectively), and reported fewer years of injection drug use (median=15 vs. median=18, p=0.04, respectively), compared to those who did not seroconvert. Male seroconverters were also significantly more likely to report injecting methamphetamine ≥ twice a day in the past six months (28.6% vs. 12.1%, p=0.02), compared to those who did not seroconvert (Table 2).

Multivariable Cox regression. Results from the bivariate Cox regression are presented in Table 3. In adjusted Cox models (1-4) factors that were significantly associated with HIV seroconversion included: sex work in the past six months (adjusted hazard ratio [aHR]=2.25, 95% CI=1.05-4.80; methamphetamine injection ≥ twice a day in the past six months (aHR=2.30, 95% CI=1.12-4.73); and methamphetamine and heroin co-injection ≥ twice a day in the past six months (aHR=2.26, 95% CI=1.24-4.15) (Table 3).

Mediational analyses. The following factors associated with HIV seroconversion were tested as mediators of the relationship between female sex and incident HIV; sex work in the past six months, methamphetamine injection ≥ twice a day, and methamphetamine and heroine co-injection ≥ twice a day or more in the past six

months. Sex work was the only significant mediator (p=0.01), between female sex and HIV seroconversion (Table 4).

Mediating effect of sex work. Using Cox proportional hazard models and controlling for the aforementioned confounders, the TE of female sex on incident HIV was aHR=1.87, (95% CI=0.90, 3.39). The CDE of female sex on incident HIV was aHR=1.15 (95% CI=0.54, 2.18). The NIE of female sex on incident HIV through sex work was significant (aHR=1.68, 95% CI=1.05, 2.60). Sex work mediated a substantial proportion (86.0%, p=0.01) of the association between female sex and incident HIV infection (Table 4).

Moderation analyses. Results from the multiplicative interaction analysis were insignificant (aHR=2.57, 95% CI=0.45-14.49, p=0.29). Similarly results from the RERI test using the additive scale were also insignificant (RERI=1.34, 95% CI= -0.75-3.43, p=0.21). These tests provided no evidence that female sex moderated the relationship between sex work and incident HIV infection.

Attributable and population attributable risk percentages. The percent of HIV incidence that can be attributed to sex work (e.g. attributable risk percent) was: 57.2% (95% CI=23.9%-75.9%, p=0.006). The expected percent reduction in HIV incidence (e.g. population attributable risk percent) if the entire sample were not exposed to sex work was 29.3%.

Discussion

In this study of PWID in Tijuana, females were nearly twice as likely to undergo HIV seroconversion relative to males over the 7-year follow-up period. Few studies have

presented data illustrating consistently elevated HIV incidence rates among female PWID, especially in LMICs like Mexico (38). Such findings highlight the distinct vulnerability of female PWID in Tijuana, and underscore the need for female-centered interventions that are designed to meet the unique needs of women who use drugs (39).

Consistent with our main hypothesis, we found that sex work accounted for more than three quarters of the total effect of female sex on HIV incidence, and that a significant proportion of HIV seroconversions could be attributed to sex work among PWID in our sample. Our findings are consistent with previous work which describes an association between sex work and HIV infection among females who use drugs globally (40), but adds to this body of literature by demonstrating that sex work is a key underlying determinant of elevated HIV incidence among female PWID in Tijuana.

A previous study evaluating two brief interventions that aimed at reducing both injection and sexual risks among FSWs who inject drugs in Tijuana and Ciudad Juarez found that both interventions were efficacious and cost-effective in Ciudad Juarez (41). In particular, the injection risk intervention modified the relationship between police confiscation of syringes and receptive needle sharing (42), suggesting that this intervention could buffer negative influences in the risk environment. However, neither the sexual or injection risk interventions were efficacious in Tijuana, which may have been due to the fact that considerable resources had been invested in condom and syringe distribution (41) at the time. Since this time, however, funds from the Global Fund to End HIV, TB and Malaria ended in Mexico, which was subsequently associated with syringe shortages and a return to high-risk behaviors (43,44). We recommend re-

investing in proven harm reduction interventions such as NSP and OAT, as well as implementing these interventions at scale.

Future interventions should also address other underlying factors that may increase sexual risk taking behavior among female PWID (45). For instance, relationship and power dynamics surrounding drug use that limit women's ability to negotiate male condom use (25,46), gender-based violence (47), and economic inequality (20) are potential drivers of risky sexual practices in the context of sex work. HIV prevention strategies should address these factors by amending social and cultural norms, and increasing access to employment opportunities for women who use drugs by providing training programs and working to decrease stigma among female substance users (45). Moreover, interventions that integrate structural approaches by reducing barriers to resources (48,49) and designing policy initiatives to promote safer sex including access to free condoms and PrEP (50,51), have shown promise in reducing HIV among high-risk women in other settings (52), and should also be tested among female PWID in Tijuana given that this sub-population remains especially vulnerable to HIV infection.

Although this study provides important insight into the underlying mechanisms driving HIV seroconversion among female PWID in Tijuana, our findings should be interpreted in the context of certain limitations. The relatively small number of incident cases precluded stratification by sex in Cox regression models. The observational nature of this study limits our ability to draw causal inferences, however the assumption of temporal precedence was met in our mediation analysis, and we used prospective data and causal modeling building techniques (29,34). The low prevalence of sex work

among male PWID may be due to differential misclassification that can arise from the stigma associated with sex work among males. We did not use time-updated covariates in this analysis, future methodological advances are needed to enable such analyses. We would also like to acknowledge that this study cannot determine which aspects of sex work confers risk of HIV acquisition (e.g., trading sex for drugs or sharing syringes with clients). The study population was sampled using non-probability recruitment methods, which limits the generalizability of our findings to PWID in other settings. Finally we relied on self-report of several sensitive behaviors, which may have led to socially desirable reporting. However, it should be noted that our outcome of interest (incident HIV infection) was based on confirmatory test results.

Conclusion

Despite these limitations, this study illustrates that sex work is an important underlying mechanism explaining elevated HIV incidence among female PWID in Tijuana, Mexico. Our findings highlight sex work as a central driver of HIV seroconversion among female PWID, and underscore the urgent need for HIV prevention programs to incorporate sexual risk reduction counseling, promote policy initiatives that endorse safer sex, and offer PrEP in order to mitigate the sexual transmission of HIV among female PWID (21,53). Further, creative interventions to address the underlying drivers of sex work (e.g., economic vulnerability and relationship and power dynamics surrounding drug use) should be developed for female PWID in Tijuana. In conclusion, female-centered harm reduction interventions that recognize

multiple HIV transmission routes (e.g., unprotected sex and using contaminated syringes), are needed in the Mexico-US border region.

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Table 2.1: Incidence density rates of human immunodeficiency virus infection among females and males who inject drugs in Tijuana, Mexico (N=651)

	Females (n=22)		Males (n=21)		Overall (n=43)		Females vs. Males	
	Cases/100 PY, (95% CI)	Observed PY Females	Cases/100 PY, (95% CI)	Observed PY Males	Cases/100 PY, (95% CI)	Total PY	Incidence Rate Ratio (95% CI)	P-value
HIV	1.75 (1.2, 2.7)	1,251.92	0.95 (0.6, 1.4)	2,189.306	1.25 (0.9, 1.6)	3,441.22	1.83 (1.01, 3.31)	0.04

Notes:

PY=person years
95% CI=95% Confidence Interval
P-value derived from Poisson regression

Table 2.2: Characteristics of females and males who inject drugs with and without incident HIV infection in Tijuana, Mexico (N=651)

	Females				Males			
Sociodemographic characteristics	Incident Cases (n=22)	HIV-negative (n=227)	Total (N=249)	*P*	Incident Cases (n=21)	HIV-negative (n=381)	Total (N=402)	*P*
Mean age (Standard deviation=SD)	33.18 (8.69)	35.03 (9.04)	34.86 (9.01)	0.35	35.23 (7.19)	39.21 (8.68)	39.01 (8.65)	0.03
Median number of years of education (Interquartile range=IQR)	7.5 (5,9)	8 (6,11)	8 (6,11)	0.11	7 (6,10)	8 (6,9)	8 (6,9)	0.76
Married[1]	15 (68.2)	129 (56.8)	144 (57.8)	0.30	10 (47.6)	143 (37.5)	153 (38.1)	0.35
Substance use characteristics								
Median duration of injection drug use in years (IQR)[2]	11 (7,15)	12 (5,20)	12 (5,20)	0.98	15 (10,19)	18 (12,25)	18 (12,25)	0.04
Methamphetamine injection++	4 (18.2)	30 (13.2)	34 (13.7)	0.51	6 (28.6)	46 (12.1)	52 (12.9)	0.02
Heroin injection++	19 (86.4)	187 (82.4)	206 (82.7)	0.63	21 (100)	332 (87.1)	353 (87.8)	0.07
Cocaine injection++	1 (4.6)	4 (1.8)	5 (2.0)	0.37	0	5 (1.3)	5 (1.3)	0.59
Methamphetamine/heroin co-injection++	11 (50.0)	67 (29.5)	78 (31.3)	0.04	11 (52.4)	144 (37.8)	155 (38.6)	0.18
Micro-physical risk environment								
Lived in Tijuana for one's whole life	7 (31.8)	77 (33.9)	84 (33.7)	0.84	10 (47.6)	161 (42.3)	171 (42.5)	0.63
Median number of years lived in TJ (IQR)	19.6 (5,31)	18 (7.5, 30)	18.3 (7.1,30)	0.94	26 (11,34)	25.6 (12,36.5)	25.8 (12,36)	0.48
Moved to TJ because of deportation	3 (13.6)	43 (18.9)	46 (18.5)	0.54	4 (19.1)	101 (26.6)	105 (26.2)	0.44
Moved to TJ for a better life	4 (19.1)	26 (11.5)	30 (12.2)	0.31	1 (4.7)	38 (10.3)	39 (10.0)	0.41
Micro-social risk environment								
Drug sharing++[3]	13 (59.1)	69 (30.5)	82 (33.1)	0.01	7 (33.3)	146 (38.4)	153 (38.2)	0.64
Police confiscation of syringes+	6 (27.3)	28 (12.3)	34 (13.7)	0.05	1 (4.7)	38 (9.9)	39 (9.7)	0.43
Ever forced to have sex[4]	11 (50.0)	80 (35.2)	91 (36.5)	0.17	2 (9.5)	12 (3.2)	14 (3.5)	0.12
Bought drugs prepared in a syringe++	3 (13.6)	13 (5.8)	16 (6.5)	0.15	1 (4.8)	21 (5.5)	22 (5.5)	0.88
Median household size (IQR)	2 (1,4)	2 (2,4)	2 (2,4)	0.66	2 (2,4)	3 (2,5)	3 (2,5)	0.31

Table 2.2: Characteristics of females and males who inject drugs with and without incident HIV infection in Tijuana, Mexico (N=651), continued

	Females				Males			
Micro-economic risk environment	Incident Cases (n=22)	HIV-negative (n=227)	Total (N=249)	*P*	Incident Cases (n=21)	HIV-negative (n=381)	Total (N=402)	*P*
Sex work+[5]	19 (86.4)	144 (65.2)	163 (67.1)	0.04	3 (14.3)	37 (9.7)	40 (9.9)	0.49
Monthly income ≥$3, 500[6]	5 (22.7)	75 (33.2)	80 (32.3)	0.31	5 (23.8)	95 (25.0)	100 (24.9)	0.90
Micro-policy risk environment								
Obtained syringes from a NEP+[7]	6 (27.3)	23 (10.1)	29 (11.6)	0.02	0	24 (6.3)	24 (5.9)	0.24
Found it hard to get new syringes+	6 (27.3)	37 (16.3)	43 (17.3)	0.19	3 (14.3)	74 (19.)	77 (19.3)	0.55

Notes:
[1]Married or in a common law marriage
[2]Median number of year injecting drugs was calculated by taking the participant's current age and subtracting it from the age they reported first injecting
[3]Participants reported dividing drugs with someone else using a syringe more than half of the time in the past six months
[4]Lifetime forced sex was measured by asking participants if anyone has ever forced them to have sex using physical or emotional pressure
[5]Sex work includes those who reported selling sex in exchange for money or drugs in the past six months
[6] Average month income in Mexican Pesos, approximately $187.00 US dollars according to the exchange rate in 2018
[7]Needle exchange program
+Past six months
++At least twice a day in the past six months
P-values were calculated using Chi2 tests for categorical predictors, Wilcoxon Ranksum tests where medians were compared and T-tests where means were compared for continuous exposures
All percentages were rounded up to the nearest tenths percent
Some percentages are based on denominators smaller than the N listed in the column heading this is due to missing data.

Table 2.3: Crude and adjusted hazard ratios of characteristics and environmental risk factors for incident HIV infection among people who inject drugs in Tijuana, Mexico (N=651)

Variable	HR	95% CI	Model 1[a] aHR (95% CI)	Model 2[b] aHR (95% CI)	Model 3[c] aHR (95% CI)	Model 4[d] aHR (95% CI)
Sociodemographic characteristics						
Female sex	1.94*	1.06, 3.53				
Age in years	0.96*	0.92, 0.99				
Number of years of education	0.98	0.88, 1.08				
Married[1]	1.62	0.88, 2.97				
Substance use characteristics						
Duration of injection drug use in years[2]	0.96*	0.93, 0.99				
Methamphetamine injection++	2.15*	1.06, 4.35	2.30* (1.12, 4.73)[a]			
Heroin injection++	2.00	0.62, 6.47				
Cocaine injection++	2.47	0.34, 18.04				
Methamphetamine/heroin co-injection++	1.99*	1.09, 3.63		2.26** (1.24, 4.15)[b]		
Micro-physical risk environment						
Lived in TJ for one's whole life	0.87	0.47, 1.60				
Number of years one has lived in TJ	0.98	0.96, 1.00				
Moved to TJ because of deportation	0.68	0.30, 1.52				
Moved to TJ looking for a better life	1.14	0.45, 2.89				
Micro-social risk environment						
Drug sharing[3]++	1.65	0.91, 3.00				
Police confiscation of syringes+	1.71	0.76, 3.85				
Ever forced to have sex[4]	2.40**	1.25, 4.61			2.01 (0.94, 4.30)[c]	

Table 2.3: Crude and adjusted hazard ratios of characteristics and environmental risk factors for incident HIV infection among people who inject drugs in Tijuana, Mexico (N=651), continued

Variable	HR	95% CI	Model 1[a] aHR (95% CI)	Model 2[b] aHR (95% CI)	Model 3[c] aHR (95% CI)	Model 4[d] aHR (95% CI)
Bought drugs prepared in a syringe ++	1.62	0.58, 4.53				
Household size	0.97	0.89, 1.06				
Micro-economic risk environment						
Sex work[5]+	2.42**	1.33, 4.41				2.25* (1.05, 4.80)[d]
Average monthly income ≥$3,500[6]	0.84	0.41, 1.71				
Micro-policy risk environment						
Obtained syringes from a NEP[7]+		0.83, 4.71				
Found it hard to get new syringes+	1.24	0.59, 2.59				

Notes:
[1]Married or in a common law marriage
[2]Number of year injecting drugs was calculated by taking the participant's current age and subtracting it from the age they reported first injecting
[3]Participants reported dividing drugs with someone else using a syringe more than half of the time in the past six months
[4]Lifetime forced sex was measured by asking participants if anyone has ever forced them to have sex using physical or emotional pressure
[5]Sex work includes those who reported selling sex in exchange for money or drugs in the past six months
[6] Average monthly income in Mexican pesos, approximately $187.00 US dollars according to the exchange rate in 2018
[7] Needle exchange program
+Past six months
++At least twice a day in the past six months
HR=hazard ratio
aHR=adjusted hazard ratio
p-values derived from Cox regression are denoted as follows; ≤0.05* and ≤0.01**
All models controlled for sex, income, duration of injection drug use and number of people in the respondent's household including the respondent
[a]Total effect of methamphetamine injection on HIV incidence after adjusting for the aforementioned confounders
[b]Total effect of methamphetamine and heroin co-injection on HIV incidence after adjusting for the aforementioned confounders
[c]Total effect of forced sex on HIV incidence after adjusting for the aforementioned confounders
[d]Total effect of sex work on HIV incidence after adjusting for the aforementioned confounders
Some percentages are based on denominators smaller than the N listed in the column heading this is due to missing data.

Table 2.4: Direct and indirect effects of female sex on incident HIV infection among people who inject drugs in Tijuana, Mexico (N=651)

Effect	Estimate	Standard Error	95% Confidence Interval
Controlled direct effect	1.15	0.43	0.54, 2.18
Natural indirect effect	**1.68**	**0.39**	**1.05, 2.60**
Total effect	1.87	0.64	0.90, 3.39

Notes:
2,500 bootstrap repetitions used
Controlled for: income, duration of injection drug use and number of people in the respondent's household including the respondent

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CHAPTER 3: ECONOMIC RISK FACTORS AND DRUG USE BEAHVIORS DRIVING HIV SEROCONVERSION AMONG PEOPLE WHO INJECT DRUGS IN TIJUANA, MEXICO

Abstract

Introduction: A concentrated epidemic of HIV persists among people who inject drugs (PWID) in Tijuana, Mexico. Among PWID in this region, HIV transmission is often exacerbated by environmental risk factors. Utilizing the HIV 'risk environment' framework, we studied PWID in Tijuana to identify predictors of time to HIV seroconversion, hypothesizing that environmental risk factors would predominate as predictors of HIV seroconversion and be robust to unmeasured confounding.

Methods: From 2011-2013, HIV-seronegative PWID aged ≥18 were enrolled into an ongoing prospective cohort study in Tijuana, and completed semi-annual HIV tests and behavioral interviews through 2018. Using multivariable Cox regression, we identified predictors of time to HIV seroconversion controlling for age, education, income, sex and lifetime residence in Tijuana. Finally, we tested how robust our findings were to unmeasured confounding using E-value sensitivity analysis.

Results: Of 651 PWID (males: 402, females: 249), 43 seroconversions occurred, 8.8% among females and 5.2% among males. Factors independently associated with time to HIV seroconversion were: baseline engagement in sex work (adjusted hazard ratio [aHR]=2.20, 95% CI=1.03-4.68); methamphetamine injection ≥ twice/day (aHR=2.13, 95% CI=1.04-4.35); and methamphetamine and heroin co-injection ≥ twice/day, in the past six months (aHR=2.09, 95% CI=1.13-3.85). E-values for these

point estimates were: sex work (E=4.62), methamphetamine injection (E=4.45), and heroin and methamphetamine co-injection (E=4.38).

Conclusions: Sex work and drug use behaviors were independently associated with time to HIV seroconversion in this cohort of PWID. These factors were moderately robust to unmeasured confounding, therefore strong confounding associations are needed to diminish these effects. Interventions should address stimulant injection and stimulant/depressant co-injection, as well as the sexual transmission of HIV among PWID in Tijuana, in order to reduce HIV incidence.

Introduction

Tijuana is a large Mexico-United States (US) border city where HIV prevalence among people who inject drugs (PWID) is 17.5 times higher than that among the general population in Mexico (3.5% vs. 0.2%) (1). According the HIV 'risk environment' framework (2–5), HIV transmission among PWID is driven by micro and macro risk factors that are exogenous to the individual in the physical, social, economic and policy domains (6). For instance, micro policy influences such as punitive policing practices (e.g., police confiscation of syringes and or drugs for personal use), exacerbate HIV risk by dissuading PWID from carrying their own syringes and or drugs, which can lead to syringe and injection equipment sharing, as well as drug sharing practices (7).

Other environmental factors that likely influence HIV transmission among PWID in Tijuana include its placement along a prominent drug trafficking route (macro physical); high rates of community violence (micro physical); a large sex trade industry (macro economic); and limited access to harm reduction services (e.g., needle exchange programs, and free HIV testing and treatment) (micro policy) (2). Tijuana is also a key transit route for heroin and methamphetamine entering the US, which contributes to the availability of these substances and fuels the local drug consumption market (8). As such, Tijuana has one of the highest rates of heroin and methamphetamine consumption, and one of the largest populations of PWID in Mexico (9). Furthermore, in Tijuana alone there are roughly 9,000 female sex workers (FSW) who can legally participate in the sex trade industry (10). In addition, very few harm reduction services exist in Tijuana, leaving those who use illicit substances and or engage in sex work without access to necessary health and social services (11).

In light of the continuing HIV epidemic among PWID in Tijuana, there is an urgent need to identify the drivers of HIV transmission in order to inform HIV prevention programs. In observational research, where randomization of the exposure is not possible and often not ethical, there is a need to assess how robust measured associations are to unmeasured confounding in order to rule out alternative explanations and identify causal factors. However, it is often not feasible to measure all potential confounders and therefore impossible to take them into account in statistical analyses.

Recently, novel sensitivity analysis methods for observational research such as the “E-value” have been developed precisely for this purpose (12). The E-value quantifies the strength of association that an unmeasured confounder would need to have with both the treatment and outcome variables in order to “explain away” an observed association, after taking into consideration the measured covariates (12). This approach highlights the importance of Bradford Hill’s criterion “strength of association” in determining whether or not an association is causal (13). This is especially important in low-and middle-income countries (LMICs) like Mexico, where limited HIV prevention resources must be prioritized.

HIV transmission among PWID in Tijuana has multiple contributing determinants. Prior research in this region has identified several potential risk factors for HIV in this population including younger age (14), female sex (14), length of residence in Tijuana (15), greater number of injecting partners (15), deportation from the US (15), and police confiscation of syringes (7). While these studies identified important risk factors for HIV

among PWID, they did not assess how robust these associations were to unmeasured confounding.

In order to address these gaps in research, we utilized data from a large cohort of PWID in Tijuana, and identified factors in the HIV risk environment and drug use behaviors associated with incident HIV infections. We also assessed how robust these estimates were to unmeasured confounding using the E-value (12). We hypothesized that micro environmental risk factors including personal safety concerns and feeling concerned about the safety of friends and family, and anticipation of arrest for syringe or drug possession would predominate as predictors of HIV seroconversion, and be robust to unmeasured confounding.

Methods

Study population. The study protocol is described in full detail elsewhere (16). From 2011-2013, 734 male and female PWID were recruited into *'Proyecto El Cuete IV"* an ongoing prospective cohort study in Tijuana, Mexico, of which 651 were HIV-negative at baseline and included in this analysis.

Eligibility criteria. Participants were required to; 1) be at least 18 years old, 2) self-report injection drug use in the past month, 3) have visual evidence of injection drug use (e.g. track marks), 4) be able to speak English or Spanish, 5) be able to provide written informed consent, 6) have no plans to leave Tijuana for at least 24 months, 7) and report no current participation in an intervention study at the time of enrollment. All participants received $5.00 US dollars for completing the screening process.

Recruitment. Participants were recruited using targeted sampling techniques, which involved trained research staff conducting street-based outreach in areas of Tijuana where PWID often reside, and/or access services (e.g., public health clinics and shooting galleries).

Baseline survey. Participants completed semi-annual surveys administered by trained Spanish speaking interviewers with extensive experience working with PWID in Mexico. Surveys included measures on sociodemographics, HIV and substance use risk behaviors, and factors in the HIV risk environment (e.g., experiences with law enforcement, sense of personal safety, sexual violence, and access to sterile syringes) (2). To enhance reliability and validity, data were collected using computer-assisted participant interview software (17), and data collection took place in a private setting. Participants were compensated $20.00 US dollars for each visit.

HIV screening. Participants were screened for HIV antibodies at each visit via finger stick using the Advanced Quality Rapid Antibody test (InTec Products, Inc.). Participants testing HIV-positive were asked to provide a peripheral blood sample for confirmation at the San Diego Department of Public Health (18). HIV–positive participants were referred to local municipal health care centers for free treatment and follow-up care. All participants received pre and post-test counseling in accordance with the Mexican Ministry of Health guidelines (16).

Ethical considerations. All study procedures were approved by the Human and Subjects Protections Program at the University of California, San Diego and the University of Xochicalco in Tijuana (16). All participants provided written informed consent at baseline.

Measures

Outcome. The outcome of interest was incident HIV infection based on confirmatory test results, defined as seroconverting post-baseline. Seroconversion was assumed to have occurred at the mid-interval point between the last date one tested HIV-negative and the first date one tested HIV-positive.

Sociodemographics. Data were collected on socio-demographics including: self-reported sex (male/female/transsexual), age in years, number of years of education starting at first grade, and marital status (married/common law marriage vs. single/divorced/widowed).

Substance use characteristics. Participants were asked to report their age at first injection which was used to calculate the total number of years of injection drugs use, by subtracting ones current age from the age they reported first injecting drugs. We also collected data on the types of substances injected at least twice a day or more in the past six months including: methamphetamine, methamphetamine and heroin together, heroin and cocaine.

Micro-physical risk environment. Informed by Rhode's risk environment (3) we measured safety concerns using a two item index created from (1) *"On a scale of 1 to 5, with 1 being not at all concerned and 5 being extremely concerned, how concerned were you generally about your personal safety?"* (2) *"On a scale of 1 to 5 with 1 being not at all concerned and 5 being extremely concerned, how concerned were you generally about the safety of your family and friends?"* Responses for the two items were averaged to create an average safety concerns score (Cronbach's alpha=0.88), which ranged from 1-5. Other micro physical risk factors measures were: the number of

years one has lived in Tijuana; lived in Tijuana for one's whole life (yes/no); moved to Tijuana because of deportation (yes/no) and moved to Tijuana looking for a better life (yes/no).

Micro-social risk environment. Informed by Rhode's risk environment framework (3) we measured anticipation of arrest for syringe/drug possession using a six item index created from several variables: (1) *"How likely do you think it is that you could get arrested for drug possession if you are stopped by the police when you are carrying drugs?"* (2) *"How likely do you think it is that you could get arrested for paraphernalia possession if you are stopped by the police when you are carrying new, unused syringes?"* (3) *"How likely do you think it is that you could get arrested for paraphernalia possession if you are stopped by the police when you are carrying used syringes?"* (4) *"How likely do you think it is that police would demand a bribe from you if they stop you when you are carrying new, unused syringes?"* (5) *"How likely do you think it is that police would demand a bribe from you if they stop you when you are carrying used syringes?"* (6) *"How likely do you think it is that you will be arrested just because you look like a drug user?"* Responses for the six items were averaged to create an average anticipation of arrest for syringe/drug possession score (Cronbach's alpha=0.97), which ranged from 1-4. Other micro-social risk factors measured were: lifetime forced sex which was defined as ever being coerced into having sex by someone who used physical or emotional pressure *("Has anyone ever forced you to have sex with them using either physical force or emotional pressure?");* police confiscation of syringes in the past six months (yes/no); syringe mediated drug sharing in the past six months (yes/no); whether one had bought drugs that came prepared in a syringe at least half of

the time in the past six months (yes/no); and the number of people in the respondents household including the respondent.

Micro-economic risk environment. Micro-economic measures included in the analysis were: sex work in the past six months, which was a dichotomous measure created from the following two variables: *"Has anyone ever given you anything you needed (such as money, drugs, alcohol, shelter, food, transportation or protection) in exchange for sex? (yes/no)" and "In the last six months, how many people gave you something you needed in exchange for having sex with them?"* We also asked participants to report their average monthly income in Mexican pesos and created a dichotomous variable for those who earned at least 3,500 pesos on average each month versus those who did not.

Micro-policy risk environment. Data on measures which reflect harm reduction policy (e.g., access to harm reduction services) in Tijuana were also collected including the following: whether the participant reported obtaining syringes from a needle exchange program (yes/no) and whether the participant reported finding it difficult to get new syringes in the past six months (yes/no).

Statistical Analysis

Data from 16 research visits over a 90-month period, from March 2011 to October, 2018 were used to measure incident HIV infection. Time spent at risk was calculated by subtracting the baseline interview date from the date when the participant was assumed to have seroconverted, with seroconversion assumed to have occurred at the mid-interval point between the last date one tested HIV-negative and the first date

one tested HIV-positive. For those who did not seroconvert during the follow-up period, time at risk was calculated by subtracting the date of their last assessment from the date of their baseline interview (e.g., right censored).

Using baseline data, descriptive statistics including frequencies, percentages, medians and interquartile ranges (IQRs) were generated (Table 1). Chi-square tests were used to compare participants who seroconverted and those who did not with respect to dichotomous variables, and, depending on distributional assumptions, either T-tests or Wilcoxon Rank Sum tests were used for comparisons involving continuous variables. Analyses were stratified by incident HIV status (e.g., incident cases versus those who did not seroconvert over the follow up period).

Simple and multiple Cox regression were used to identify factors associated with incident HIV infection for the study sample (Table 1). We compared nested Cox models using the Likelihood Ratio test to arrive at parsimonious models, and in unadjusted analyses variables which yielded a p-value ≤0.05 were selected for further exploration in multivariable Cox models. Consistent with the causal inference framework, in multivariable Cox regression analyses each predictor (e.g., primary effect measure) was modeled separately, in order to avoid confusing direct effect estimates with total effect estimates (19). All adjusted models controlled for the following confounders that have been identified as risk factors for HIV in previous research (15): sex, age, education, income, and lifetime residence in Tijuana (Table 2). Correlations between the confounders were examined to rule out multicollinearity. The proportional-hazards assumption was assessed for all variables examined using plots of Schoenfeld residuals (20).

Moderation analyses were conducted to assess whether sex moderated the relationship between each primary effect measures and incident HIV infection. Moderation was assessed using the multiplicative and additive scales. To test sex as a moderator using the multiplicative scale, we included an interaction term in each multivariable Cox model while controlling for the aforementioned confounders. To test sex as a moderator using the additive scale, we estimated the relative excess risk due to interaction (RERI) (21) while controlling for the same set of confounders. To calculate the RERI we used the following algorithm recommended by Andersson and colleagues (22), (HR_{11}-HR_{10}-HR_{01}).

Finally, sensitivity analyses were conducted by computing the E-value (12) for each adjusted point estimate and the lower limit of the corresponding confidence interval (CI) (Table 3). All analyses were conducted using Stata 14.2.

Results

Of 651 PWID (males: 402, females: 249), 43 seroconversions occurred during the study period, 22 (8.8%) among females and 21 (5.2%) among males. Relative to PWID who remained seronegative, incident cases were significantly younger (mean=34.18 [SD=7.97] vs. mean=37.65 [SD=9.04], p =0.01). Incident cases reported significantly fewer years of injecting drugs compared to those who did not seroconvert (median=14 [IQR=8-19] vs. median=16 [IQR=9-23], p=0.04). A greater proportion of incident cases compared to those who did not seroconvert reported methamphetamine injection (23.3% vs. 12.5%, p=0.04), and methamphetamine and heroin co-injection ≥ twice a day in the past six months (51.1% vs. 34.7%, p=0.03) (Table 1).

Comparisons of PWID who seroconverted to those who did not. Relative to PWID who remained seronegative, incident cases were significantly more likely to report engaging in sex work in the past six months (51.1% vs. 30.0%, p=<0.01). Incident cases were also significantly more likely to report ever being forced into having sex compared to those who did not seroconvert (30.2% vs. 15.1%, p=0.01) (Table 1).

Cox regression. After adjusting for potential confounders, factors independently associated with incident HIV were: sex work in the past six months (aHR=2.20, 95% CI=1.03-4.68), methamphetamine injection ≥ twice a day in the past six months (aHR=2.13, 95% CI=1.04-4.35), and methamphetamine and heroin co-injection ≥ twice a day in the past six months (aHR=2.09, 95% CI=1.13-3.85) (Table 2).

Moderation analyses. Results from the multiplicative interaction analyses were insignificant (sex work*sex, p=0.29), (methamphetamine injection*sex, p=0.35), and (methamphetamine and heroin co-injection*sex, p=0.55). Similarly, results from the additive interaction test/RERI were insignificant (RERI for sex work*sex, p=0.19), (RERI for methamphetamine injection*sex, p=0.62), and (RERI for methamphetamine and heroin co-injection*sex, p=0.26). These tests demonstrate no evidence that sex moderates the relationship between these primary effects and HIV seroconversion.

E-values for all aHRs and the lower limit of the corresponding CIs are presented in Table 3. The observed aHR for sex work in the past six months of 2.20 (95% CI=1.03-4.68) had and E-value of 4.62, and an E-value for the lower limit of the CI of 1.72, meaning that an unmeasured confounder would need to be associated with the treatment and outcome with a aHR of 4.62 or greater in order annul the effect of sex work on HIV. The observed aHR for methamphetamine injection ≥ twice a day in the

past six months of 2.13 (95% CI=1.04-4.35) had an E-value of 4.45, and an E-value for the lower limit of the CI of 1.75. The observed aHR for methamphetamine and heroin co-injection ≥ twice a day in the past six months of 2.09 (95% CI=1.13-3.85) had an E-value of 4.38, and an E-value for the lower limit of the CI of 2.00 (Table 3).

Discussion

This study of factors associated with time to HIV seroconversion among PWID in Tijuana identified several important findings. At baseline, engagement in sex work and certain drug use behaviors including injecting methamphetamine alone and in combination with heroin was associated with significantly higher HIV incidence. We also found that the parameter estimates for each of these predictors of time to HIV seroconversion were moderately robust to unmeasured confounding, suggesting that relatively strong confounding associations would be needed to “explain away” these observed associations. These findings highlight the importance of developing interventions informed by harm reduction that offer both behavioral treatment and pharmacotherapies for substance use disorder, and address the sexual transmission of HIV among PWID in this region.

Globally, HIV transmission among sex workers has received a great deal of attention; however, the sexual transmission of HIV among PWID has received less attention (23). In our study the strong association between sex work and HIV seroconversion contributes to the literature on the potential for the sexual transmission of HIV among PWID, and highlights the need to address the social and structural conditions surrounding sex work that contribute to sexual and injection related risk

behaviors in the context of sex trade among PWID. For instance, the co-occurrence of several socio-structural conditions including economic vulnerability (24), sexual violence (25–27), and limited access to harm reduction programs and other health and social services (11,28), exacerbate HIV risk and shape health-related inequalities among PWID who engage in sex work in Tijuana. As a result, female sex workers who inject drugs bear the highest burden of HIV in the Mexico-US border region with an estimated HIV prevalence of 12.3% (10).

The adjusted point estimate for sex work was moderately robust to unmeasured confounding, suggesting that relatively strong confounding associations would be needed to diminish the observed association between sex work and HIV seroconversion (12). According to the E-value methodology (12), the appropriate interpretation of these results is that the evidence for causality in the association between reporting sex work at baseline and subsequent HIV seroconversion is moderately strong. In particular, the E-value maps onto Hill's criterion "strength of association" which discusses the importance of strong associations (13). However, several other criteria for causality exit including: consistency, specificity, temporality, biologic gradient, plausibility, coherence, experimental evidence, and analogy (29). In addition to these the counterfactual framework discusses the following three main assumptions; exchangeability, positivity, and consistency, which also need to be met in order to infer causality (29). While several of these including: consistently, temporality, plausibility, coherence, and analogy were met in this study other assumptions (e.g., exchangeability and positivity) remain potentially violated. Future studies should utilize inverse probability weighting methods in conjunction with the E-value to address these limitations.

However, this finding still has important implications for HIV prevention in Tijuana amidst prominent co-occurring sex and drug trade industries. In Tijuana, sex work is legal in certain districts (e.g., the red light district or *"la zona roja")* provided that sex workers operate with a permit and undergo routine HIV and other STI screening (30). However, many sex workers including those that use illicit substances, inject drugs, and or practice street-based sex work, are less visible to local authorities enforcing such regulations, and often cannot afford the payments associated obtaining sex work permits (31). Interventions should seek to engage sex workers who inject drugs by utilizing proven strategies that address the co-occurrence of sexual and injecting risk behaviors (32).

We also found that those who reported frequent methamphetamine injection at baseline had a significantly higher hazard rate of HIV seroconversion compared to those who did not report frequent methamphetamine injection at baseline. This finding was also supported by a moderately strong E-value, suggesting that this association is relatively robust to unmeasured confounding. Several studies have found an association between methamphetamine injection and HIV infection largely driven by increased sexual and injecting risk behaviors such as multiple sex partners, condomless sex, and syringe sharing (33–38). These risk behaviors are often driven by an increase in sexual arousal induced by methamphetamine and an increase in the frequency of injection, compared to those who inject other substances (39). In the Mexico-US border region methamphetamine injection is also associated with engagement in sex work, and is exacerbated by methamphetamine production and trafficking in this region (10,40,41).

In Mexico, methamphetamine production has increased drastically over the past two decades, with Mexico now supplying an estimated 70-90% of the entire US supply of methamphetamine (42–44). The large-scale production of methamphetamine in Mexico, and trafficking of methamphetamine through Tijuana has created a classic "spillover" effect that has fueled the local drug consumption market (8). Our finding supports this previous work suggesting that methamphetamine use in Tijuana is an ongoing concern and contributes to HIV transmission among PWID. Findings from other studies (33,34,45) that have tested cognitive and behavioral therapies for methamphetamine dependent individuals have shown that participants post treatment have reduced their stimulant use and engagement in HIV-related risk behaviors. However, there is still an urgent need to develop effective medication treatments for methamphetamine dependence and deliver these in conjunction with cognitive and behavioral therapies to PWID in Tijuana (46).

This study also found a strong association that was moderately robust to unmeasured confounding, between frequent methamphetamine and heroin co-injection at baseline and HIV seroconversion over the follow-up. This finding is consistent with literature discussing the connection between polysubstance use and HIV-related risk behaviors in the Mexico-US border region (47,48). Previous studies in this region also found that those reporting methamphetamine and heroin co-injection reported greater difficulty finding new/sterile syringes, and reported a significantly greater need for drug treatment compared to those who did not report methamphetamine and heroin co-injection (48). These findings highlight the need to expand access to medication-assisted treatments (MAT) (e.g., methadone, buprenorphine and naloxone) for opioid

use disorder in the Mexico-US border region. Although MAT is approved for use Mexico access remains severely limited (49). For instance, there are only two government clinics and sixteen private clinics offering MAT in all of Mexico (49). As such, there is an need to increase access to MAT for PWID in Tijuana who use opioids alone and in conjunction with other substances in order to reduce the burden of HIV in this population as well as to address the other health consequences (e.g., fatal overdose and hepatitis C) associated with opioid dependence.

Limitations

Although this study identified important risk factors for HIV seroconversion which were moderately robust to unmeasured confounding among a hard to reach population of PWID in Tijuana, findings from this study should be interpreted in the context of certain limitations. First, we utilized data from an observational study, which limits our ability to draw causal inferences. However, we applied a novel sensitivity analysis method designed for observational research to test how robust our findings were to unmeasured confounding. We also used causal modeling building techniques (19) and prospective data. Although these methods were used, future studies should utilize inverse probability weighting to estimate average causal effects in conjunction with the E-value to further assess whether the associations identified here are in fact causal. We only identified baseline predictors of time to HIV seroconversion, due to the small number of incident cases and the amount of missing data over the follow up period. This limits our ability to understand whether the impact of these factors on HIV seroconversions vary over time. We also relied on self-reported data of several

sensitive behaviors including sexual and injecting risk behaviors, which may have led to socially desirable reporting likely pushing the bias towards the null. However, it should be noted that our outcome of interest (incident HIV infection) was based on confirmatory test results. We also used non-probability recruitment methods (targeted sampling) to recruit individuals into the study, which limits the generalizability of our findings to other PWID in Tijuana who were not included in this study as well as PWID in other settings.

Conclusion

Despite these limitations, this large study of factors associated with HIV seroconversion among PWID in Tijuana highlights sex work, the injection of stimulants and the co-injection of stimulants and opiates as key drivers of HIV transmission. These findings underscore the urgent need to develop pharmacotherapeutic strategies for methamphetamine dependence, increase access to MAT for opioid use disorder, and integrate cognitive behavioral strategies into interventions that utilize medication treatments for substance use disorder. In addition, harm reduction programs that address the sexual transmission of HIV driven by the social and structural conditions surrounding sex work are needed to reduce HIV transmission among PWID in this region.

Tables

Table 3.1: Factors in the HIV risk environment, drug use behaviors and demographics characteristics associated with HIV seroconversion among people who inject drugs, with and without HIV in Tijuana, Mexico (N=651)

Sociodemographic characteristics	Incident Cases (n=43)	HIV-negative Cases (n=608)	*P*	Total (N=651)	HR	95% CI	*P*
Female sex	22 (51.2)	227 (37.3)	0.07	249 (38.3)	1.94	1.06-3.53	0.03
Mean age (Standard deviation=SD)	34.18 (7.97)	37.65 (9.04)	0.01	37.42 (9.00)	0.96	0.92-0.99	0.02
Median number of years of education (Interquartile range=IQR)	7 (5, 10)	8 (6, 10)	0.44	8 (6, 10)	0.97	0.88-1.08	0.68
Married or common law marriage[1]	25 (58.1)	272 (44.7)	0.08	297 (45.6)	1.62	0.88-2.97	0.11
Drug use behaviors							
Median number of years of injecting drugs (IQR)[2]	14 (8, 19)	16 (9, 23)	0.04	16 (9, 23)	0.96	0.93-0.99	0.03
Bought drugs already prepared in a syringe^+	4 (9.3)	34 (5.6)	0.32	38 (5.8)	1.61	0.57-4.53	0.35
Methamphetamine injection++	10 (23.3)	76 (12.5)	0.04	86 (13.2)	2.15	1.06-4.35	0.03
Injected heroin++	40 (93.0)	519 (85.4)	0.16	559 (85.8)	2.00	0.61-6.47	0.24
Injected cocaine++	1 (2.3)	9 (1.4)	0.66	10 (1.5)	2.46	0.33-18.04	0.37
Heroin/methamphetamine co-injection++	22 (51.1)	211 (34.7)	0.03	233 (35.7)	1.99	1.09-3.63	0.02
HIV risk environment							
Micro-physical risk environment							
Lived in TJ for one's whole life	17 (39.5)	238 (39.1)	0.96	255 (39.1)	0.86	0.47-1.60	0.65
Moved to TJ because of deportation	7 (16.2)	144 (23.7)	0.26	151 (23.2)	0.67	0.30-1.52	0.34
Moved to TJ looking for a better life	5 (11.9)	64 (10.7)	0.81	69 (10.8)	1.13	0.44-2.89	0.78
Average personal safety concern (SD)	3.58 (1.43)	3.35 (1.47)	0.33	3.37 (1.46)	1.06	0.86-1.30	0.60
Micro-social risk environment							
Drug sharing++[3]	20 (46.5)	215 (35.4)	0.14	235 (36.2)	1.65	0.90-3.00	0.10
Police confiscation of syringes+	7 (16.2)	66 (10.8)	0.27	73 (11.2)	1.71	0.76-3.85	0.19
Average anticipation of arrest (SD)	3.35 (1.15)	3.44 (0.94)	0.55	3.43 (0.96)	0.93	0.70-1.24	0.63
Ever forced to have sex[4]	13 (30.2)	92 (15.1)	0.01	105 (16.1)	2.41	1.25-4.61	0.01

Table 3.1: Factors in the HIV risk environment, drug use behaviors and demographics characteristics associated with HIV seroconversion among people who inject drugs, with and without HIV in Tijuana, Mexico (N=651), continued

Micro-economic risk environment	Incident Cases (n=43)	HIV-negative Cases (n=608)	*P*	Total (N=651)	HR	95% CI	*P*
Sex work+[5]	22 (51.1)	181 (30.0)	<0.01	203 (31.4)	2.42	1.33-4.41	<0.01
Average monthly income ≥$3,500[7]	10 (23.2)	170 (28.0)	0.49	180 (27.7)	0.84	0.41-1.70	0.63
Micro-policy risk environment							
Obtained syringes from a NEP+[6]	6 (13.9)	47 (7.7)	0.14	53 (8.1)	1.98	0.83-4.7	0.12
Found it hard to get new or clean syringes+	9 (20.9)	111 (18.3)	0.67	120 (18.4)	1.24	0.59-2.58	0.56

Notes:
[1]Married or in a common law marriage
[2]Median number of year injecting drugs was calculated by taking the participants current age and subtracting it from the age they reported
first injecting drugs
[3] Syringe mediated drug sharing was defined as dividing drugs with someone else using a syringe
[4]Lifetime forced sex was defined as ever being forced into having sex by someone who used physical or emotional pressure
[5]Sex work includes those who reported selling sex in exchange for money, drugs, food, shelter or protection
[6]NEP, needle exchange program
[7] Average monthly income in Mexican pesos, approximately $187.00 US dollars according to the exchange rate in 2018
+Past six months
++ At least twice a day in the past six months
^+More than half of the time in the past six months
P-values were calculated using Chi2 tests for categorical predictors, Wilcoxon Rank sum tests where medians were compared, T-tests
where means were
compared for continuous exposures, and p-values associated with hazard ratios (far right) were derived using Cox regression
Some percentages are based on denominators smaller than the N listed in the column heading this is due to missing data.

Table 3.2: Factors independently associated with time to HIV seroconversion among people who inject drugs in Tijuana, Mexico (N=651)

Variable	Model 1[a] aHR (95% CI)	Model 2[b] aHR (95% CI)	Model 3[c] aHR (95% CI)
Sex work+[1]	2.20 (1.03-4.68)[a]		
Methamphetamine injection++		2.13 (1.04-4.35)[b]	
Heroin/methamphetamine co-injection++			2.09 (1.13-3.85)[c]

Notes:
[1]Sex work includes those who reported selling sex in exchange for money, drugs, food, shelter or protection in the past six months
+Past six months
++At least twice a day in the past six months
Each model controlled for: sex, age, education, income, and lifetime residence in Tijuana
Models 1-3 were built modeling each exposure separately
[a]Total effect of sex work in the past six months on HIV seroconversion while controlling for the aforementioned confounders
[b]Total effect of methamphetamine injection at least twice a day in the past six months on HIV seroconversion while controlling for the aforementioned confounders
[c]Total effect of heroin and methamphetamine co-injection at least twice a day in the past six months on HIV seroconversion while controlling for the aforementioned confounders

Table 3.3: E-values for the point estimates and the lower confidence interval limits of factors independently associated with incident HIV infection among people who inject drugs in Tijuana, Mexico (N=651)

Variable	E-value for the Adjusted Point Estimate	E-value for the lower limit of the 95% Confidence Interval
Sex work+	4.62	1.72
Methamphetamine injection++	4.45	1.75
Heroin and methamphetamine co-injection+ +	4.38	2.00

Notes:
[1]Sex work includes those who reported selling sex in exchange for money, food, drugs, shelter, transportation or protection in the past six months
+Past six months
++At least twice a day in the past six months

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CHAPTER 4: SEX DIFFERENCES IN THE PSYCHOLOGICAL AND ENVIRONMENTAL CORRELATES OF INJECTION RISK BEHAVIORS AMONG PEOPLE WHO INJECT DRUGS, IN TIJUANA, MEXICO

Abstract

Background: HIV and HCV transmission among people who inject drugs (PWID) is fueled by injection risk behaviors. We studied PWID in Tijuana, Mexico to identify potential sex differences in the psychological and environmental correlates of injection risk.

Methods: From 2011-2013 734 PWID (female: 277, male: 457) were enrolled into an observational cohort study in Tijuana. At baseline, participants completed interviews on injection and sexual risks. Utilizing baseline data, we conducted multiple generalized linear models stratified by sex to identify factors associated with injection risk scores (e.g., the frequency of injection risk behaviors).

Results: For males and females, difficult access to sterile syringes was associated with elevated injection risk (*b*=1.24, 95% confidence interval [CI]=1.16-1.33), using syringes from a safe source (e.g., needle exchange programs) was associated with lower injection risk (*b*=0.87, 95% CI=0.82-0.94), and for every one-unit increase in safe injection self-efficacy we observed a 20% decrease in injection risk (*b*=0.80, 95% CI=0.76-0.84). Females had a higher safe injection self-efficacy score compared to males (median=2.83 Interquartile range [IQR]=2.2-3 vs. median=2.83 [IQR=2-3], p=0.01). Among females, factors associated with elevated injection risk were: recent

incarceration (*b*=1.22, 95% CI=1.09-1.36), and police confiscation of syringes in the past six months (*b*=1.16, 95% CI=1.01-1.33). Among males, factors associated with elevated injection risk were: sex work (*b*=1.16, 95% CI=1.04-1.30), and polysubstance use in the past six months (*b*=1.22, 95% CI=1.13-1.31).

Conclusions: Interventions to reduce injection risk among PWID in Tijuana should be sex-specific and address different levels of HIV and HCV risk to enhance safe injection self-efficacy.

1. Introduction

The rate of illicit drug use consumption in Tijuana, Mexico is nearly three times the national average (14.7% vs. 5.5%), and this region hosts one of the largest populations of people who inject drugs (PWID) in all of Mexico (1–3). The prevalence of HIV among PWID in Tijuana is approximately 17.5 times higher than that among the general population in Mexico (3.5% verses 0.2%) (4). Further, according to prior research 96% of PWID in Tijuana are living with hepatitis C (HCV) antibodies (anti-HCV) (5), which is nearly twice as high as the estimated prevalence of PWID living with anti-HCV worldwide (52.3%) (Degenhardt et al., 2014). The spread of HIV and HCV among PWID is largely driven by the dynamic interplay between personal and environmental factors (7,8).

The social ecological model (SEM) is a widely accepted theoretical framework that considers how individuals interact with their environments (8–10). This framework acknowledges five levels of influence on human behavior ranging from the most proximal, the intrapersonal level, to the most distal, the policy level (Figure 1). As such, the multi-layered and interactive effects of individual and environmental-level factors are well captured by the SEM due to its comprehensive nature (10,11). Given the increasing recognition of several levels of HIV and HCV risk and the need to create multilevel prevention strategies, we selected this framework to guide our research (Figure 1).

Research among PWID guided by broader environmental frameworks such as the risk environment framework (12) have shown that the transmission of HIV and HCV among PWID is exacerbated by various, social, economic and political influences (13,14). For instance in Tijuana, HIV and HCV risk among PWID is shaped in part by

limited access to harm reduction services (e.g., needle exchange programs and HIV/HCV testing and treatment) (15), and punitive policing practices (e.g., syringe confiscation and incarceration of substance users) (16). Other factors to consider are the sociostructural conditions surrounding sex work among PWID in this region that increase sexual and injecting risk taking behaviors (17), and high rates of illicit drug consumption that is fueled by this city's placement along a well-established drug trafficking route (1).

It is also important to acknowledge that social, economic and political influences often place females at elevated risk of acquiring HIV and HCV compared to their male counterparts (18). This is evidenced by the fact that worldwide, HIV prevalence (19) and HCV incidence (20,21), tend to be significantly higher among female PWID compared to male PWID. These disparities are often driven by sex-related risk factors such as physical and sexual violence (22) and economic vulnerability which can fuel participation in sex work, and a dependence upon male partners for drug acquisition, preparation and injection (23). However, more research is needed to identify sex differences in different levels (e.g., psychological/personal and environmental) of HIV and HCV risk to inform comprehensive prevention packages among PWID in low-and middle-income countries (LMICs) like Mexico. Understanding the psychological correlates of safer injection or risk reduction in conjunction with broader environmental risk factors may help inform the development of such prevention strategies.

We know from social cognitive theory (SCT) (24) that one of the most important factors to consider at the intrapersonal level of the SEM is self-efficacy. Self-efficacy can be defined as the ability or confidence to exercise control over events in one's life,

and is a key determinant of healthy behavior change and marker of behavioral resilience (25). Research in the United States (US) among PWID has identified a close relationship between perceived self-efficacy to avoid HIV risk, and drug use and injection risk reduction (26,27). However, more research is needed to examine the impact of safe injection self-efficacy on injection risk and assess whether this effect differs by sex, in order to inform future interventions to reduce HIV and HCV transmission in addition to other drug related harms among male and female PWID in LMICs. This is especially important in Tijuana, where several sex-related risk factors such as sexual violence, economic vulnerability, and limited access to power and resources, are prevalent and may reduce one's safe injection self-efficacy as seen in other settings (22,28).

To address these gaps in research, we leveraged the SEM and studied female and male PWID in Tijuana to identify sex differences in the psychological and environmental correlates of injection risk behaviors. We hypothesized that the impact of intrapersonal (e.g., safe injection self-efficacy), interpersonal (e.g., sex work and forced sex), institutional (e.g., incarceration, police confiscation, ever beaten by the police), community (e.g., homelessness), and policy (e.g., finding it difficult to access sterile syringes) level factors would differ by sex such that females would experience greater barriers to practicing risk reduction compared to males. As such, this research will add to the body of literature on sex differences in the psychological and sociostructural correlates of injection risk behaviors, and may help inform future multilevel HIV and HCV preventions strategies for PWID in Mexico and other LMICs.

2. Methods

Baseline data were drawn from *'Proyecto El Cuete'* an ongoing observational research study of PWID in Tijuana, Mexico. A detailed description of the study protocol has been published elsewhere (29). All study procedures were approved by Institutional Review Boards at the University of California, San Diego, and the University of Xochicalco in Tijuana, Mexico. All participants completed written informed consent at baseline.

2.1. Design

2.1.1. Recruitment, screening and enrollment.

A total of 734 individuals were enrolled between 2011 and 2013. Participants were recruited using targeted sampling techniques where trained staff performed street-based outreach in areas of Tijuana where PWID often congregate or access services. Eligible participants were required to: 1) be at least 18 years old, 2) self-report injection drug use in the past month, 3) have visual evidence of injection drug use (e.g. track marks), 4) be able to speak English or Spanish, 5) be able to provide written informed consent, 6) have no plans to leave Tijuana for 24 months, 7) and report no current participation in an intervention study. All participants received $5.00 US dollars (USD) for completing the screening process.

2.1.2. Baseline survey.

Participants completed a baseline assessment that lased approximately 90 minutes and was administered by trained bilingual and bicultural interviewers with extensive experience working with PWID in Mexico. To enhance the reliability and validity of self-reported sensitive behaviors (e.g., HIV risk behaviors), data were collected using computer-assisted participant interview software (30) and conducted in a private setting. Participants were compensated $20.00 USD for their baseline visit.

2.1.3. Measures

Outcome. The primary outcome of interest was an "injection risk score" which was modeled after a measure created for the Drug User's Intervention Trial (27), and has been used widely in other research (31) but has not yet been formally validated. The injection risk score was calculated from an index of five injection risk indicators including the following five likert-scaled variables assessing the frequency of injection risk behaviors in the past six months: (1) *"Of the times you injected in the last six months, how often did you use a syringe that you knew or suspected that it had used before by someone else?"* (2) *"Of the times you injected in the last six months, how often did you divide up drugs with somebody else by using a syringe?"* (3) *"Of the times you injected in the last six months, how often did you use a cooker, cotton, or water with someone or after someone else used it?"* (4) *"Of the times you injected in the last six months, how often did you buy drugs that came already prepared in a syringe?"* and (5) *"Of the times you injected in the last six months, how often did you inject with a new, sterile syringe?"* The likert-scaled responses for these five items were*; never, sometimes, about half of the time, often, and always,* and were averaged to create an

average injection risk score ranging from 1-5 with higher scores representing higher injection risk, (Cronbach's alpha=0.72).

Intrapersonal level factors. Age in years, self-reported sex (female sex/male sex), number of years of education completed starting at first grade, marital status (married/common law marriage verses single/divorced/separated or widowed), income in Mexican pesos indicating whether one earned at least 3,500 pesos on average each month (yes/no), the number of years lived in Tijuana, and the ability to speak English. Participants were also asked to report their age at first injection which was used to calculate the total number of years of injection drugs use, by subtracting each participant's current age from the age they reported first injecting drugs. We also collected data on the types of substances injected at least twice a day or more in the past six months including: methamphetamine and heroin together, and methamphetamine alone.

We considered 'safe injection self-efficacy' as the primary psychological exposure using a six-item index that has been tested and validated among PWID in several settings (Garfein et al., 2007): (1) *"I can avoid injecting with a needle someone else has used, even if I am injecting with people I know well."* (2) *"I can avoid injecting with a needle someone else used even if I am dope sick or in withdrawal."* (3) *"I can avoid using cookers, cottons, or rinse water that someone else used, even if I am injecting with people I know well."* (4) *"I can avoid using my injecting partner's needle, even if we have shared needles before."* (5) *"I can avoid using my injecting partner's cooker, cotton, or rinse water, even if we've shared them before."* (6) *"I can avoid injecting with a needle someone else used, even if I have had sex without condoms with*

that person." The likert-scaled responses for these six items ranged from *"absolutely sure I cannot"* to *"absolutely sure I can",* and were averaged to create an average safe injection self-efficacy score (Cronbach's alpha=0.94) ranging from 1-4.

Interpersonal level factors. Sex work in the past six months (yes/no), was defined as receiving something one needed (e.g., money, drugs, food etc.) in exchange for sex in the past six months. Forced sex (yes/no) was defined as ever having been forced into sex by someone using physical or emotional pressure.

Institutional level factors. Incarceration in the past six months, police confiscation of syringes without arrest in the past six months (yes/no), and reporting having ever been beaten by law enforcement.

Community level factors. Homelessness (e.g., sleeping in abandoned buildings and/or on the street) in the past six months (yes/no).

Policy level factors. Used syringes from a 'safe source' (e.g., pharmacies, needle exchange programs (NEPs), doctors, hospitals or clinics) (yes/no), and finding it hard to access new/sterile syringes in the past six months (yes/no). These variables serve as proxy's for access to harm reduction services.

2.2. Statistical analyses

Utilizing baseline data, we compared females and males with respect to factors in each level of the SEM (e.g., intrapersonal, interpersonal, institutional, community, and policy), using chi-square tests for dichotomous variables and depending on distributional assumptions T-tests or Wilcoxon Ranksum Tests for continuous variables (Table 1). Then, simple generalized linear regression models with a lognormal

distribution stratified by sex were used to identify correlates of injection risk by sex. Each exposure in bivariate analyses with a p-value ≤0.05 was included in subsequent multiple linear regression analyses.

Multiple generalized linear regression models with a lognormal distribution stratified by sex were performed to estimate the association of statistically significant exposures from bivariate models with injection risk scores by sex, while controlling for identified confounders to reduce bias (Table 3). We controlled for the following factors that have been associated with injection risk among PWID in Tijuana in previous research (19): age, education, income, and length of residence in Tijuana. In order to avoid committing a “table two fallacy” (33,34), all primary exposures were estimated in separate models, and the secondary effects we controlled for were not reported or interpreted. A “table two fallacy” is where one adjusts for primary effect measures and mistakenly reports and interprets these coefficients as total effects instead of controlled direct effects (33). All beta coefficients were exponentiated to facilitate the interpretation of our results. Analyses were conducted using STATA 14.2.

3. Results

Of 734 PWID, 277 (37.7%) were female and 457 (62.3%) were male. The average age was 37.4 (Standard deviation [SD]=8.9), and the median age at first injection was 14 (Interquartile range [IQR]=12-16). Over a third (39.4%) of the sample reported being able to speak English. One fifth of males (21.8%) reported ever having sex with another male (MSM).

Intrapersonal level differences by sex. Baseline comparisons of female and male PWID suggested that the two groups differed with respect to some intrapersonal level factors. Females were significantly younger compared to males (35.1 [SD=8.9], vs. 38.8 [SD=8.7], p<0.001), and initiated injection drug use at a significantly older age compared to males (median 15 [IQR=13-17] vs. 14 [IQR=12-16]). Males reported living in Tijuana for significantly longer durations compared to females (median=14.4 [IQR=8-21]) vs. median=10 [IQR=4.7-17.5], p<0.001). A higher proportion of females reported earning ≥ 3,500 Mexican pesos on average each month compared to males (32.6% vs. 24.5%, p=0.02). Lastly, a significantly higher proportion of females reported being married compared to males (57% vs. 38.3%, p<0.001). Males reported a higher median number of years injecting drugs compared to females (18 [IQR=12-24] vs. 12 [IQR=5-20], p<0.001). Finally, females reported a higher median score for safe injection self-efficacy compared to males (2.83 [IQR=2.2-3] vs. 2.83 [2-3], p=0.01) (Table 1).

Interpersonal level differences by sex. Compared to males a significantly greater proportion of females reported engaging in sex work in the past six months (65.7% vs. 10.7%, p<0.001), and reported ever being forced into having sex (35.9% vs. 3.9%, p<0.001) (Table 1).

Institutional level differences by sex. A greater proportion of males reported incarceration in the past six months compared to females (43.3% vs. 30.2%, p<0.001), and a significantly greater proportion of males reported ever being beaten by the police compared to females (64.8% vs. 22.5%, p<0.001) (Table 1).

Community level differences by sex. Females were significantly more likely to report being homeless in the past six months compared to males (33.2% vs. 23.4%, p<0.01) (Table 1).

Policy level differences by sex. A significantly greater proportion of males reported using syringes from a 'safe source' (e.g., NEP) compared to females (51.9% vs. 34.7%, p<0.001) (Table 1).

After controlling for potential confounders, among both females and males finding it difficult to access new/sterile syringes was associated with a 24% increase in average injection risk scores (*b*=1.24, 95% CI=1.16-1.33). Using syringes from a 'safe source' was associated with a 13% decrease in average injection risk scores (*b*=0.87, 95% CI=0.82-0.94). Similarly, for every one-unit increase in safe injection self-efficacy we observed a 20% decrease in average injection risk scores (*b*=0.80, 95% CI=0.76-0.84).

Among females, incarceration and police confiscation of syringes in the past six months were associated with a 22% (*b*=1.22, 95% CI=1.09-1.36), and a 16% increase in average injection risk scores (*b*=1.16, 95% CI=1.01-1.33), respectively. Among males, sex work and injecting methamphetamine and heroin together ≥ twice a day in the past six months were associated with a 16% (*b*=1.16, 95% CI=1.04-1.30), and a 22% increase in average injection risk scores (*b*=1.22, 95% CI=1.13-1.31), respectively.

4. Discussion

This large study of injection risk behaviors among female and male PWID in Tijuana identified several key findings. Among both females and males, safe injection self-efficacy and using syringes from a safe source were associated with lower injection

risk scores. Also, finding it difficult to access new or sterile syringes was associated with elevated injection risk scores among both sexes. We also uncovered several risk factors that were independently associated with injection risk and varied by sex. First, sex work and polysubstance use were associated with elevated injection risk among males and not females. Second, recent incarceration and police confiscation of syringes were associated with elevated injection risk among females and not males. Together, these findings may help inform intervention that seek to address the multilevel determinants of injection risk behaviors among female and male PWID in the Mexico-US border region.

The strong association between safe injection self-efficacy and lower injection risk scores found in this study has important implications for behavioral interventions that seek to reduce injection risk among PWID. Former research discovered that an interactive sexual and injection risk reduction intervention increased safe injection self-efficacy which in turn decreased receptive needle sharing among female sex worker-PWID in the Mexico-US border region (35). This offers evidence that safe injection self-efficacy can be enhanced through behavioral intervention efforts. Based on our findings, we suggest that interventions aiming to reduce the spread of blood borne infections (e.g., HIV and HCV) among PWID should utilize strategies to enhance safe injection self-efficacy. Our study contributes to existing literature (26,35), by showing that safe injection self-efficacy is associated with risk reduction for both female and male PWID in Tijuana, which is promising as it suggests that self-efficacy acts as a buffer against injection risk equally among females and males. This study also fills an important gap in literature on the correlates of safer injection practices among PWID in LMICs.

Our study also found that using syringes from a safe source was associated with lower injection risk scores, whereas finding it difficult to access new/sterile syringes was associated with elevated injection risk scores. These policy level determinants of injection risk behavior are consistent with prior research (36,37) and underscore the importance of harm reduction programs in reducing injection risk among PWID. Harm reduction services such as NEPs are crucial social and health interventions for PWID (36–38). NEPs reduce the burden of HIV,HCV, and other poor health outcomes such as abscess wounds, among PWID through several mechanisms including providing free access to sterile injection equipment, offering risk reduction counseling and providing referrals to healthcare and substance use treatment (38).

Unfortunately, NEPs are scarce in Tijuana partially because the Global Fund for HIV, Tuberculosis and Malaria withdrew support for NEPs in 2013 due to Mexico's strengthening economy (39). As a result, the proportion of PWID accessing harm reduction services in Tijuana is suboptimal (<10%) according to the World Health Organizations standard of at least 60% of PWID accessing services (39,40). This is especially concerning in Tijuana where several thousands of PWID reside and localized epidemics of HIV and HCV exist among PWID (39). Based on our findings, we recommend: reinstating funding for NEPs; providing free HIV and HCV testing and treatment at local clinics and hospitals; and increasing access to substance use treatment such as opiate substitution therapy (36).

Interestingly, we found that sex work was associated with an increase in injection risk among males only. One possible explanation for this finding is that the majority of males in our sample who reported engaging in sex work were also MSM (data not

shown; 83.7%). Former research among MSM in the US who reported injection drug use and sex work found a close association between sex work and HIV infection (41). Further, other studies among PWID in the US found independent associations between needle sharing and homosexual and bisexual sex, which may have been explained by sex work that was underreported (42,43). Our finding underscores the need to focus on the intersection of sex work and injection drug use among male PWID, and acknowledge the co-occurrence of these factors as potential drivers of injection risk in this population.

This study also found that the impact of polysubstance use on injection risk was greater among male PWID compared to females. Earlier research among PWID in Estonia and Russia found that opiate and stimulant injection was associated with both injection and sexual risk behaviors, but no heterogeneity by sex was reported (Tavitian-Exley et al., 2018). Similarly, research among PWID in Tijuana found that polydrug use was independently associated with sexual and injection risk practices, but no differences by sex were found (44,46). Findings from our study are consistent with this research but add to this body of literature (44–46) by demonstrating sex differences in the relationship between polysubstance use and injection risk. Future interventions in Tijuana should scale-up access to medication-assisted treatments (e.g., methadone and buprenorphine) for opioid use disorder (47), and develop effective pharmacotherapies for stimulant use disorder (48). Furthermore, medication treatments should be offered in conjunction with behavioral therapies (49) in order to more effectively reduce injection risk among polysubstance users.

In our study, recent incarceration was associated with a higher injection risk scores among female PWID only. In Latin America, the number of women incarcerated nearly doubled between 2006 and 2011 when recruitment for this study began, and the vast majority (60-80%) of these women were incarcerated for non-violent drug-related crimes (50). Incarceration and the post release period have been shown to increase HIV and HCV risk among PWID in several settings (51,52), but these studies reported no evidence that the impact of incarceration on injection risk was greater among females compared to males. Findings from this study expand upon former research (51,52) by demonstrating that the impact of incarceration on injection risk is differentially associated with sex among PWID in LMICs.

The strong association between police confiscation of syringes and elevated injection risk scores among female PWID maps onto former research conducted among PWID in the Mexico-US border region, which documented that such punitive policing practices exacerbate injection risk behaviors (16,53–57). Aggressive policing practices compromise one's ability to engage in safer injection practices by reducing access to sterile injection equipment (55,58–60). In Mexico, syringe purchase and possession without a prescription is legal, therefore this finding also highlights a significant implementation gap (55,56). Our results support this previous work, suggesting that policing practices in Tijuana continue to exacerbate injection risk especially among female PWID. Interventions should aim to: enhance law enforcement's knowledge of current drug policy and the benefits of harm reduction; reduce stigma among women who use drugs; and ensure that policing practices are in accordance with international human rights law (23,61).

Although this study provides important insight into how personal, sociostructural, and policy influences shape injection risk among female and male PWID in Mexico, our study has limitations. We used non-probability sampling methods to recruit individuals into the study, which limits the generalizability of our findings to PWID in Tijuana who were not included in this study as well as PWID in other settings. We used cross-sectional data, which limits our ability to draw causal inferences and assess temporal associations. Future research should examine whether the identified correlates of injection risk predict behavior change in longitudinal analyses. Baseline data were collected between 2011 and 2013 and therefore may not be representative of current trends among PWID in Tijuana, which further limits the generalizability of our findings. Although the outcome measure for this study was modeled closely after a measure used in a large intervention trial designed to reduce sexual and injection risk among PWID (27), it has yet to been validated. However, it is important to note that this measure has strong predictive and face validity, as well as internal consistency.

In summary, findings from this study show how personal and environmental factors contribute to injection risk and differ markedly by sex among PWID in Mexico. This study also demonstrates that safe injection self-efficacy and access to harm reduction programs promote risk reduction in this population. In doing so, this study highlights several multilevel factors which shape injection risk and safer injection practices among male and female PWID. Identifying such multilevel correlates of injection risk may help inform the development of comprehensive interventions that seek to target several levels of HIV and HCV risk in order to enhance safe injection self-efficacy among PWID in Tijuana, Mexico.

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Chapter 4, in full is a reprint of the material being revised for resubmission to the Journal of Alcohol and Drug Dependence: Jennifer P. Jain, Steffanie A. Strathdee, Brooke S. West, Patricia Gonzalez-Zuniga, Gudelia Rangel, and Eileen V. Pitpitan; “Sex differences in the psychological and environmental correlates of injection risk behaviors among people who inject drugs in Tijuana, Mexico.” Jennifer P. Jain the dissertation author is the primary author of this material.

Tables and Figures

Table 4.1: Intrapersonal, interpersonal, institutional, community and policy level factors among females and males who inject drugs in Tijuana, Mexico (N=734)

	Females (n=277) n (%)	Males (n=457) n (%)	*P*	Total (n=734) N (%)
Intrapersonal level factors				
Average age (standard deviation=SD)	35.1 (8.9)	38.8 (8.7)	<0.001	37.4 (8.9)
Median age at first injection (Interquartile range [IQR])	15 (13-17)	14 (12-16)	<0.001	14 (12-16)
Married[1]	158 (57.0)	175 (38.3)	<0.001	333 (45.4)
Median number of years of education since first grade (IQR)	8 (6-11)	8 (6-9)	0.06	8 (6-10)
English speaking	116 (41.9)	173 (37.9)	0.28	289 (39.4)
Earned at least 3,500 Mexican pesos on average monthly[2]	90 (32.6)	111 (24.5)	0.02	201 (27.5)
Median number of years lived in Tijuana (IQR)	10 (4.7-17.5)	14.4 (8-21)	<0.001	12 (6-20)
Males reporting ever having sex with another male	--	160 (35.24)	--	160 (21.8)
Median number of years injecting drugs (IQR)[3]	12 (5-20)	18 (12-24)	<0.001	16 (9-22)
Methamphetamine and heroin co-injection ≥ twice a day+	86 (31.1)	171 (37.4)	0.08	257 (35.0)
Methamphetamine injection ≥ twice a day+	38 (13.7)	58 (12.7)	0.70	96 (13.1)
Median safe injection self-efficacy score (Range: 1-4) (IQR)[4]	2.83 (2.2-3)	2.83 (2-3)	0.01	2.83 (2-3)
Median injection risk score (Range: 1-5) (IQR)[5]	2.2 (1.6-3)	2.2 (1.6-2.8)	0.01	2.2 (1.6-2.8)
Injection risk indicators				
Syringe sharing ≥ half of the time+	103 (37.2)	145 (31.7)	0.13	248 (33.8)
Syringe mediated drug sharing[6] ≥ half of the time+	95 (34.4)	172 (37.7)	0.37	267 (36.5)
Injection equipment sharing ≥ half of the time+	137 (49.6)	218 (47.8)	0.63	355 (48.5)
Bought drugs already prepared in a syringe ≥ half of the time+	16 (5.8)	26 (5.7)	0.94	42 (5.8)
Used a sterile syringe for each injection ≥ half of the time+	140 (50.9)	227 (49.8)	0.77	367 (50.2)
Interpersonal level factors				
Sex work+[7]	176 (65.7)	49 (10.7)	<0.001	225 (31.0)
Ever forced into having sex[8]	99 (35.9)	18 (3.9)	<0.001	117 (16.0)

Table 4.1: Intrapersonal, interpersonal, institutional, community and policy level factors among females and males who inject drugs in Tijuana, Mexico (N=734), continued

	Females (n=277) n (%)	Males (n=457) n (%)	*P*	Total (n=734) N (%)
Institutional level factors				
Incarceration+	83 (30.2)	198 (43.3)	<0.001	281 (38.4)
Syringe confiscation by police+	37 (13.4)	46 (10.1)	0.17	83 (11.3)
Ever beaten by the police	62 (22.5)	296 (64.8)	<0.001	358 (48.8)
Community level factors				
Homeless[9]+	92 (33.2)	107 (23.4)	<0.01	199 (27.1)
Policy level factors				
Used syringes from a safe source[10]+	96 (34.7)	237 (51.9)	<0.001	333 (45.4)
Found it hard to access new or sterile syringes+	49 (17.7)	87 (19.1)	0.63	136 (18.6)

Notes:
Past six months+
Married or common-law marriage[1]
Average monthly income of 3,500 Mexican pesos is approximately $182 USD[2]
Number of year injecting drugs was calculated by taking the participant's current age and subtracting it from the age they reported first injecting drugs[3]
Self-efficacy for safer injection practices score was created from six items assessing one's efficacy to engage in safer injection practices[4]
The injection risk score: was created from 5 index variables assessing: the how often PWID reported syringe sharing, syringe mediated drug sharing, equipment sharing, buying drugs that came prepared in a syringe, and injecting with a new/sterile syringe, in the past six months[5]
Syringe mediated drug sharing[6]
Sex work includes those who reported selling sex in exchange for money, drugs, food, shelter or transportation in the past six months[7]
Forced sex was defined as ever having been forced into having sex by someone using physical or emotional pressure[8]
Homeless includes those who slept in places mostly consistent with being homeless including: abandoned buildings and outdoors/on the street in the past six months[9]
Used needles from a safe source: pharmacy, needle exchange program, doctor, hospital or clinic in the past six months[10]
P-values were derived from Chi2 tests, Wilcoxon rank sum tests and T-tests depending on distributional patterns
Some percentages are based on denominators smaller than the N listed due to missing data

Table 4.2: Simple generalized linear model results of psychological and environmental correlates of injection risk behaviors among females and males who inject drugs in Tijuana, Mexico (N=734)

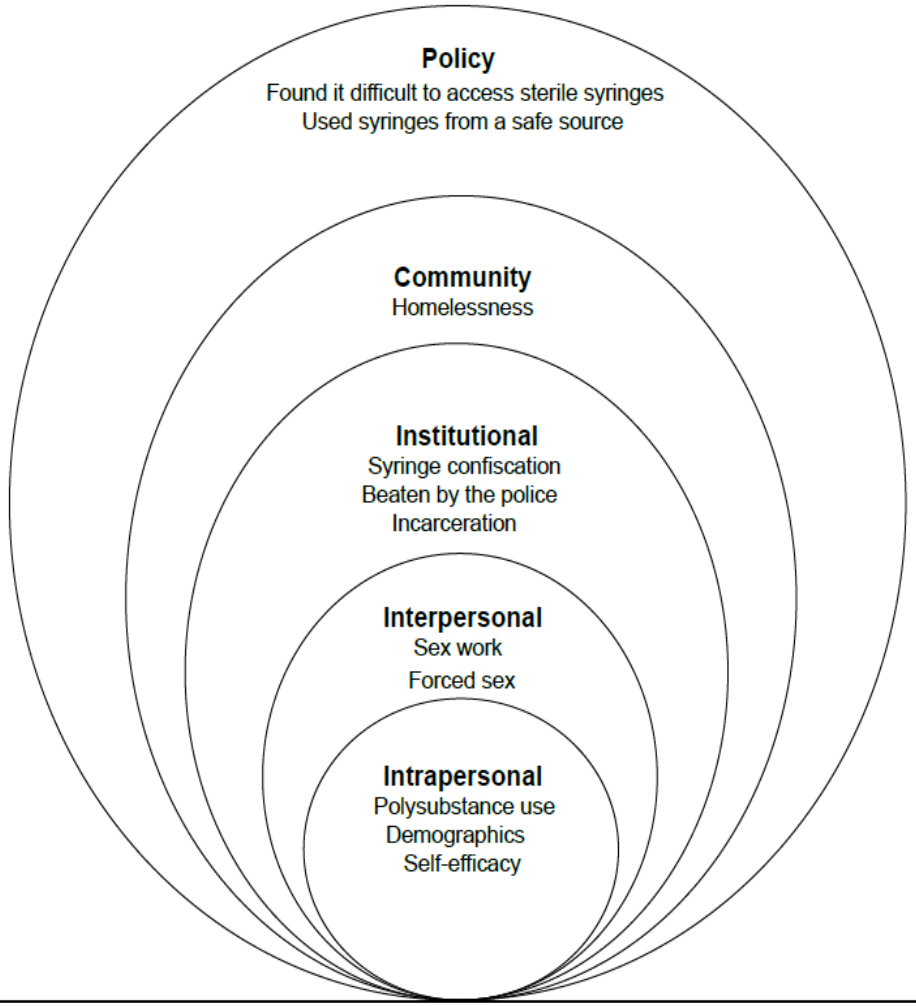
	Females (n=277)			Males (n=457)			Overall (N=734)		
Intrapersonal level factors	**β**	**95% CI**	**P**	**β**	**95% CI**	**P**	**β**	**95% CI**	**P**
Methamphetamine and heroin co-injection++	1.06	0.97-1.17	0.191	1.15	1.07-1.23	<0.001	1.11	1.05-1.17	<0.001
Methamphetamine injection ≥++	0.95	0.83-1.08	0.405	1.08	0.97-1.20	0.162	1.03	0.94-1.11	0.542
Self-efficacy for safer injection practices[1]	0.79	0.75-0.83	<0.001	0.78	0.74-0.82	<0.001	0.78	0.75-0.81	<0.001
Interpersonal level factors									
Sex work+[2]	1.14	1.03-1.25	0.012	1.26	1.16-1.38	<0.001	1.16	1.10-1.22	<0.001
Ever forced into having sex[3]	1.06	0.97-1.16	0.23	1.16	0.95-1.41	0.14	1.10	1.02-1.18	0.01
Institutional level factors									
Incarceration+	1.21	1.10-1.32	<0.001	1.18	1.11-1.26	<0.001	1.18	1.12-1.24	<0.001
Syringe confiscation by the police+	1.14	1.02-1.28	0.021	1.25	1.13-1.38	<0.001	1.2	1.12-1.30	<0.001
Ever beaten by the police+	1.06	0.95-1.19	0.237	1.07	0.99-1.15	0.067	1.03	0.97-1.09	0.235
Community level factors									
Homeless+	0.97	0.88-1.06	0.559	1.06	0.98-1.14	0.133	1.03	0.96-1.09	0.399
Policy level factors									
Used syringes from a safe source[4]+	0.86	0.79-0.95	0.002	0.83	0.77-0.88	<0.001	0.84	0.79-0.88	<0.001
Found it hard to access new/sterile syringes+	1.38	1.26-1.50	<0.001	1.21	1.13-1.31	<0.001	1.27	1.20-1.35	<0.001

Notes:
Past six months+
At least twice a day in the past six months++
Self-efficacy for safer injection practices score was created from six items assessing one's efficacy to engage in safer injection practices[1]
Sex work includes those who reported selling sex in exchange for money, drugs, food, shelter or transportation in the past six months[2]
Forced sex was defined as every having been forced into having sex by someone using physical or emotional pressure[3]
Used needles from a safe source includes; pharmacies, needle exchange programs, hospitals or clinics in the past six months[4]
Unadjusted estimates listed here represent the total effect of each exposure on average injection risk scores by sex and overall
All beta coefficients were exponentiated to facilitate interpretation

Table 4.3: Multiple generalized linear model results of psychological and environmental correlates of injection risk behaviors among females and males who inject drugs in Tijuana, Mexico (N=734)

	Females (n=277)			Males (n=457)			Overall (N=734)		
Intrapersonal level factors	**β**	**95% CI**	**P**	**β**	**95% CI**	**P**	**β**	**95% CI**	**P**
Methamphetamine and heroin co-injection ≥ twice a day+	1.05	0.94-1.17	0.378	1.22	1.13-1.31	<0.001	1.15	1.08-1.23	<0.001
Self-efficacy for safer injection[1]	0.78	0.72-0.83	<0.001	0.82	0.77-0.88	<0.001	0.80	0.76-0.84	<0.001
Interpersonal level factors									
Sex work[2]	1.10	0.96-1.25	0.169	1.16	1.04-1.30	0.008	1.14	1.04-1.24	0.004
Ever forced into having sex[3]	1.03	0.92-1.16	0.60	1.17	0.95-1.43	0.14	1.05	0.95-1.17	0.33
Institutional level factors									
Incarceration	1.22	1.09-1.36	<0.001	1.08	0.99-1.17	0.057	1.14	1.06-1.22	<0.001
Syringe confiscation by the police+	1.16	1.01-1.33	0.039	1.04	0.90-1.21	0.558	1.09	0.99-1.21	0.086
Policy level factors									
Used syringes from a safe source+[4]	0.84	0.75-0.94	0.003	0.90	0.83-0.98	0.014	0.87	0.82-0.94	<0.001
Found it hard to access new/sterile syringes+	1.34	1.21-1.48	<0.001	1.17	1.06-1.29	0.002	1.24	1.16-1.33	<0.001

Notes:
Past six months+
Self-efficacy for safer injection practices score was created from six items assessing one's efficacy to engage in safer injection practices[1]
Sex work includes those who reported selling sex in exchange for money, drugs, food, shelter or transportation in the past six months[2]
Forced sex was defined as ever having been forced into having sex by someone using physical or emotional pressure[3]
Used needles from a safe source includes; pharmacies, needle exchange programs, hospitals or clinics in the past six months[4]
Each stratified model controlled for age, education, income, and length of residence in Tijuana, Mexico
Models estimating overall effects controlled for the aforementioned confounders in addition to sex
Adjusted estimates listed here represent the total effect of each exposure on average injection risk scores by sex and overall
All beta coefficients were exponentiated to facilitate interpretation



Levels of Influence

Policy Level
Regulatory policies, procedures and laws, to protect the health of the community

Community
Informal networks within similar boundaries, experiencing the least access to sources of community power

Institutional
Formal and informal rules and regulations for operation, implementation gaps and punitive policing practices

Interpersonal
Relationships and processes, power dynamics, and social influences surrounding injection drug use

Intrapersonal
Attitudes, beliefs, behaviors, individual characteristics

Figure 4.1: The social ecological model applied to understand the psychological and environmental factors associated with average injection risk scores among male and female PWID in Tijuana, Mexico.

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CHAPTER 5: DISCUSSION

OVERVIEW

The overall purpose of this dissertation is to further our understanding of how micro physical, social, and economic risk environments increase HIV risk, and contribute to sex disparities in HIV incidence, as well as how psychological and environmental factors shape injection risk behaviors and are differentially associated with sex among male and female PWID in Tijuana, Mexico. This research addressed the following three aims: (1) calculate and compare HIV incidence density rates by sex, examine potential mediators between female sex and incident HIV infection, and calculate the attributable risk of HIV incidence due to the identified mediator(s), among PWID in Tijuana, Mexico, (2) identify the micro physical (e.g. personal safety concerns), and social (e.g. anticipation of arrest for syringe or drug possession), factors associated with time to HIV seroconversion, and assess how robust these associations are to unmeasured confounding, among PWID in Tijuana, Mexico, and (3) identify sex differences in the psychological (e.g. safe injection self-efficacy), micro social (e.g. incarceration and police confiscation of syringes), policy (e.g. limited access to new/sterile syringes) and economic (e.g. sex work) correlates of injection risk behaviors among PWID in Tijuana, Mexico. Findings from this research reduce current gaps in the literature regarding behavioral mechanisms driving elevated HIV incidence among female PWID compared to males in LMICs, environmental risk factors and drug use behaviors associated with time to HIV seroconversion among male and female PWID and the robustness of these associations to unmeasured confounding. In addition, this

research adds to existing knowledge regarding sex differences in the psychological and environmental correlates of injection risk behaviors among PWID in Tijuana, Mexico.

This dissertation research illustrates several key findings. First, findings from this research highlight that sex work is a significant pathway through which female PWID acquire HIV in this region. Second, sex work, the injection of stimulants, and the co-injection of stimulants and opiates are associated with HIV transmission among male and female PWID in Tijuana. Thirdly, this research shows how safe injection self-efficacy and access to harm reduction services are associated with risk reduction among males and females. However, other risk factors such as police confiscation of syringes, incarceration, sex work and polysubstance use (e.g., the co-injection of heroin and methamphetamine) were shown to differentially impact injection risk among males and females. Taken together, findings from this research highlight how HIV and HCV risk environments are differentially shaped for males and females who inject drugs in the Mexico-US border region.

In chapter 2 (AIM 1), among a total of 651 PWID (males: 402, females: 249), there were a total of 43 incident cases over a 7-year period ranging from 2011-2018, 8.8% among females and 5.2% among males. Incidence density was significantly higher among female PWID relative to males. This chapter also shows that sex work in the past six months mediated a substantial proportion of the association between female sex and HIV incidence (proportion mediated: 86.0%, p=0.01). Findings from this chapter suggest that sex work mediates the relationship between being a female and acquiring HIV over the follow-up period, suggesting that sex work is a significant pathway through which females acquire HIV in this region.

Applying the HIV risk environment framework and previous knowledge of the impact of certain drug use behaviors (e.g., stimulant injection and polysubstance use) on HIV risk, chapter 3 (AIM 2) identified factors associated with incident HIV among PWID in Tijuana. This chapter also applied a novel sensitivity analysis method designed for observational research (1), to estimate how robust the identified associations are to unmeasured confounding. Findings from this chapter demonstrate that sex work, methamphetamine injection and the co-injection of methamphetamine and heroin are key factors associated with incident HIV infection among PWID in Tijuana. PWID who reported engaging in any of these behaviors had a significantly higher hazard rate of HIV infection relative to those who did not report engaging in these behaviors. This chapter also shows that these factors are relatively robust to unmeasured confounding, suggesting that strong confounding associations would be needed to diminish these effects.

Leveraging the social ecological model, chapter 4 (AIM 3) describes how difficult access to sterile syringes is associated with elevated average injection risk scores, whereas using syringes from a safe source (e.g., syringe exchange program or public health clinic), and safe injection self-efficacy are associated with lower average injection risk scores among both male and female PWID in Tijuana. Also, this chapter highlights that several influences in the HIV risk environment (e.g., limited access to sterile syringes, incarceration, police confiscation of syringes, and sex work), and polysubstance use (e.g., co-injection of methamphetamine and heroin), differentially impact injection risk among males and females. Among females recent incarceration and syringe confiscation by the police were associated with elevated injection risk

scores, whereas among males, sex work and polysubstance use were associated with elevated injection risk scores. These finding suggest that intrapersonal and policy level influences impact injection risk equally among males and females. In addition, this research shows how institutional level factors pose the greatest threats to safer injection practices among females, whereas among males intrapersonal and interpersonal level factors act as barriers to risk reduction.

Overall, findings from these studies show how several dynamic behavioral and contextual factors play key roles in shaping HIV and HCV risk among PWID in Tijuana. By decomposing sex-related disparities in HIV incidence this research identifies an important pathway through which females may acquire HIV in Tijuana. This research also shows how robust certain reemerging associations with HIV are to unmeasured confounding. Finally, this dissertation highlights the multi-level determinants of HIV and HCV vulnerabilities, and underscores how these determinants differ markedly by sex.

IMPLICATIONS

This dissertation research has several important implications for global public health. Findings from chapter 2 will contribute to HIV surveillance efforts among PWID in the Mexico-US border region. Specifically, this chapter shows how female PWID are nearly twice as likely to seroconvert over a 7-year period relative to males. Few studies have provided evidence of a consistently elevated HIV incidence rate among female PWID, especially in LMICs. These findings suggest that female PWID in this region are uniquely vulnerable to acquiring HIV, and are in need of female-centered HIV prevention programs that enable them to utilize harm reduction (2).

Specifically, implementing multi-level approaches and combined HIV prevention packages that address the individual, social and structural determinants of injection and sexual risk among female PWID in Tijuana may help reduce the disparate burden of HIV in this sub-population (3). For example, behavioral interventions that address underlying mental health (e.g., depression, substance use, and trauma), conditions for female substance users may be beneficial (4). In addition, interventions that reduce social drivers such as stigma and the complex relationship and power dynamics that surround drug use and sex trade could help improve the risk environment for women in this region (4,5). Finally the structural drivers of risk such as limited access to sterile syringes, free HIV testing and treatment, and substance use treatment should be addressed by reinstating funding for proven harm reduction methods in this region (6).

Chapter 2 also utilized a novel mediation analysis method designed for survival data (7,8), to decompose the identified sex-related disparity in HIV incidence. Mediation analysis is particularly useful in illuminating the underlying determinants of health inequities (9). This study found that sex work accounted for more than three quarters of the total effect of female sex on HIV incidence, and that a significant proportion of HIV incidence among PWID in this sample could be attributed to sex work. These findings are consistent with prior research among female sex workers (FSW) globally which demonstrates a strong association between sex work and HIV infection (4), but add to this body of knowledge by showing that sex work is a key underlying determinant of sex disparities in HIV incidence among PWID in the Mexico-US border region.

A previous intervention designed to simultaneously reduce injection and sexual risk behaviors among FSW-PWID in Ciudad Juarez and Tijuana, demonstrated efficacy

in buffering influences in the HIV risk environment on injection risk, and in reducing HIV/STI incidence (10,11). For instance, among intervention participants the impact of police confiscation of syringes on injection risk was reduced significantly compared to control participants (11). While this effect was more modest for those Tijuana, participants reported greater access to sterile syringes and free condoms, suggesting that community level harm reduction programs are also powerful in reducing injection risk and HIV/STI incidence among female PWID. However, since the completion of this intervention in 2010, the Global Fund for HIV, malaria and tuberculosis has withdrawn support for harm reduction programs in Mexico due to its strengthening economy (6). Since 2010, this withdrawal has been associated with a return to high-risk behaviors among PWID (6). Findings from chapter 2 suggest the need to reinstate funding for proven harm reduction programs such as needle exchange, opiate substitution therapy (OAT) (e.g., methadone and buprenorphine, pre-exposure prophylaxis (PrEP),and implement proven behavioral interventions at scale.

Similarly, in chapter 3 the strong association between sex work and HIV seroconversion, is consistent with other literature describing the risk of acquiring HIV among sex workers globally (4,12), but contributes to our knowledge by showing that the sexual transmission of HIV among PWID is an ongoing public health concern in the Mexico-United States (US) border region. This findings highlights the importance of developing interventions informed by harm reduction that address the sexual transmission of HIV, in addition to the parenteral transmission among PWID in this region.

This study also found a strong association between frequent methamphetamine injection and HIV seroconversion. Several studies (13–18) have demonstrated an association between methamphetamine use and HIV. This association is largely due to an increase in sexual and injection risk behaviors, driven by amphetamine induced sexual drive and increased frequency of drug injection (19). Other factors that contribute to this relationship are decreased antiretroviral mediation adherence for HIV-positive methamphetamine users, and increases in the number of sexual partners while feeling the effects of methamphetamine (20). Our results support this previous work demonstrating that methamphetamine use is an ongoing concern and continues to worsen the spread of HIV infection among PWID. These findings also have important implications for substance use treatment in the Mexico-US border region.

Several studies to date (13,14,21) have tested cognitive and behavioral therapies for methamphetamine dependence and have shown that these treatments can reduce stimulant use and the engagement in HIV-related risk behaviors. However, a serious gap in research is the lack of effective pharmacotherapies for methamphetamine dependence (22). Future studies, should seek to test and develop pharmacotherapies for methamphetamine dependence in order to expand treatment options for those who experience methamphetamine dependence.

The co-injection of methamphetamine and heroin is a common form of polysubstance use in Tijuana, as heroin and methamphetamine are both regularly trafficked through this region (23). Previous studies in the Mexico-US border region found that PWID who co-injected methamphetamine and heroin, reported greater difficulty finding new or sterile syringes, and a significantly greater need for drug

treatment relative to those who did not report methamphetamine and heroin co-injection (24). Our findings, add to this previous work by showing that methamphetamine and heroin co-injection is strongly associated with a significantly higher hazard rate of HIV infection. This finding underscores the urgent need to develop effective pharmacotherapies for amphetamine dependence, and increase access to OAT such as methadone and buprenorphine to meet the needs of polysubstance users in Tijuana. Currently, OAT in Mexico is only offered through 2 government clinics and 16 private clinics which severely limits its uptake by key populations such as PWID (25). In addition to scaling-up access to OAT and developing medication treatments for methamphetamine, these pharmacotherapies should be delivered in conjunction with proven behavioral therapies such as contingency management and cognitive behavioral therapy (21).

Leveraging the social ecological model, the last study in this dissertation shows how safe injection self-efficacy and access to harm reduction programs are key determinants of risk reduction among male and female PWID. This study also found that several influences in the risk environment differentially impact injection risk among males and females. Among females institutional level factors related to punitive policing practices were key drivers of injection risk. However among males, intrapersonal and interpersonal level factors such as drug use behaviors and sex work respectively were main drivers of injection risk. These findings highlight the heterogeneous impact of personal and environmental factors on injection risk among males and females who inject drugs in Tijuana.

Identifying the multi-level correlates of HIV and HCV transmission risk behaviors may help inform the development of comprehensive interventions strategies that seek to address personal and environmental factors. For instance, interventions that utilize behavioral methods to enhance safe injection self-efficacy and aim to reduce the social and structural drivers or injection risk may more effectively reduce HIV and HCV transmission among PWID in Tijuana (26).

LIMITATIONS

Although this dissertation research provides important insight into the behavioral and contextual factors shaping HIV and HCV risk environments among male and female PWID in Tijuana, findings from this dissertation should be interpreted in the context of several limitations. First, the relatively small number of incident cases (n=43) in chapters 2 (AIM 1) and 3 (AIM 2), precluded stratification by sex in Cox regression models. Data for all three studies in chapters 2-4 were drawn from an observational research study which limits our ability to draw causal inferences and identify temporal associations.

However, in chapters 2 and 3 (AIM 1-2) the assumption of temporal precedence was met and prospective data were used. Further, in chapters 2 and 3 (AIM 1-2) causal model building techniques were used (7,27), and the outcome of interest (incident HIV infection) was based on confirmatory test results. Also, chapter 3 (AIM 2) applied a novel sensitivity analysis method specifically designed observational data, to assess how robust measured associations are to unmeasured confounding. However, there are several other criteria for causality including: consistency, specificity, temporality, biologic gradient, plausibility, coherence, experimental evidence, and analogy (28). In addition to

these the counterfactual framework discusses the following three main assumptions; exchangeability, positivity, and consistency, which also need to be met in order to infer causality (28). While several these including: consistently, temporality, plausibility, coherence, and analogy were met in chapters 1-2 other assumptions (e.g., exchangeability and positivity) remain potentially violated. Future studies should utilize methods such as inverse probability weighting to address some of these limitations including the lack of randomization of the exposure.

It is also important to note that in chapters 2-4 where sex work emerged as key covariate of interest, the low prevalence of sex work reported among male PWID, may have been due to differential misclassification bias. Differential misclassification bias can arise from the stigma associated with sex work among males, which may have attenuated our findings. Also, regarding the findings related to sex work in chapter 2 (AIM 1), it is not possible to disentangle which aspects of sex work (e.g., trading sex for drugs or sharing syringes with clients), confers risk of HIV seroconversion.

Given how HIV acquisition has multiple contributing determinants including but not limited to sex work future studies should utilize qualitative methods to better understand the contextual factors which shape risk environments for female PWID who sell sex. For instance, in the context of Tijuana several dynamic sex-specific risk factors such as income inequality (29), gender-based violence (30), punitive policing practices (11), and relationship dynamics surrounding drug use shape HIV risk pathways (31). Therefore, collecting nuanced data using mixed methods approaches is needed to disentangle all of the potential underlying causes of HIV acquisition among female PWID in this region. Such data may help inform the development of sex-specific

interventions for women who use and inject drugs in Tijuana and other low and middle-income settings (32).

In chapters 2 (AIM 1) and 3 (AIM 2), time-updated covariates were not used, due to the small number of incident cases, large amount of missing data over the follow up period, and need for methodological advances to enable such analyses in the context of mediation analysis with survival data . This limits our ability to understand how these factors impact HIV seroconversion over time. Future research should examine whether the factors associated with incident HIV infection remain significant over time.

The study population for this dissertation research was sampled using non-probability recruitment methods (e.g., targeted sampling techniques), which limits the generalizability of our findings to other PWID in Tijuana who were not included in this study, in addition to PWID in other settings. Also, this dissertation research relied on self-report of several sensitive behaviors (e.g., sexual and injection related risk behaviors), which may have led to socially desirable reporting (e.g., underreporting).

Finally, in chapter 4 (AIM 3), cross-sectional data were used which limits our ability to draw causal inferences and assess temporal associations. Future research should examine whether these correlates of injection risk and injection risk reduction predict behavior change in longitudinal analyses. Also, this chapter utilized an outcome measure of injection risk behaviors that has not yet been validated. However, the injection risk score variable utilized as an outcome in this chapter was carefully modeled after a composite variable used in a large intervention trial testing behavioral strategies to reduce injection risk among PWID in several settings in the US (33). Lastly, baseline

data utilized in chapter 4 were collected between 2011 and 2013 and therefore may not be representative of current trends among PWID in Tijuana, Mexico.

CONCLUSIONS

Despite these limitations this dissertation research provides important insight into the behavioral and contextual factors which shape HIV and HCV risk environments among male and female PWID in Tijuana, Mexico. This work shows that sex work is a key behavioral mechanism explaining elevated HIV incidence among female PWID relative to males, and suggests that female-centered HIV prevention programs which incorporate sexual risk reduction counseling, and access to free condoms and PrEP should be tested among female PWID in this region (2,34). In addition, findings from this dissertation suggest addressing the underlying drivers of risky sexual practices (e.g., economic vulnerability and relationship and power dynamics surrounding drug use), among female PWID in Tijuana.

This dissertation research also highlights the injection of stimulants and the co-injection of stimulants and depressants as key drivers of HIV transmission among male and female PWID in this region. As such, there is a need to implement interventions that utilize both behavioral and pharmacotherapeutic approaches to address drug dependence. While pharmacotherapeutic therapies exist for opioid dependence, there is still an urgent need to develop pharmacotherapeutic strategies to treat methamphetamine dependence (22).

Moreover, this dissertation research shows how various influences in the risk environment perpetuate injection risk, and demonstrates that access to harm reduction

programs (e.g., reporting the use of syringes from a needle exchange program) and safe injection self-efficacy promote risk reduction among PWID in Tijuana. This work also describes how females and males differ markedly with respect to sociodemographics, environmental risks, and drug use behaviors. As such, this research provides insight into how HIV and HCV risk environment are differentially shaped for male and female PWID. Taken together, findings from this dissertation may help inform the development of multi-level harm reduction interventions that seek to address the social and structural drivers of HIV and HCV transmission and enhance safe injection self-efficacy among PWID in Tijuana, Mexico and other similar LMICs.

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