



Sex Work as a Mediator Between Female Gender and Incident HIV Infection Among People Who Inject Drugs in Tijuana, Mexico

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Abstract

We studied mechanisms driving gender differences in HIV incidence among 651 women and men who inject drugs (PWID) in Tijuana, Mexico, hypothesizing that sex work will mediate the association between female gender 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 1.16–2.66, vs. 0.95 per 100 PY, 95% CI 0.62–1.47). 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 (84.3%) of the association between female gender and HIV incidence. Interventions should target female PWID who engage in sex work to reduce gender-related disparities in HIV incidence.

Keywords HIV incidence · People who inject drugs · Sex work · Mediation · Mexico

Resumen

Estudiamos los mecanismos que impulsan las diferencias de género en la incidencia del VIH entre 651 mujeres y hombres que se inyectan drogas (PQID) en Tijuana, México. Nuestra hipótesis es que el trabajo sexual puede ser una variable mediadora entre la asociación del género femenino y la incidencia del VIH. Entre 2011 y 2018 ocurrieron 43 seroconversiones de VIH: 8.8% fueron entre mujeres y 5.2% entre hombres. La densidad de incidencia del VIH fue significativamente mayor entre las mujeres en comparación con los hombres (1.75 por 100 personas años [PY], IC 95% = 1.16–2.66, vs. 0.95 por 100 PY, IC 95% = 0.62–1.47). Los factores con una asociación significativa con la seroconversión del VIH fueron: trabajo sexual (razón de riesgo ajustada [aHR] = 2.25, IC 95% = 1.05–4.80); inyección de metanfetamina (aHR = 2.30, IC 95% = 1.12–4.73); y la coinyección de metanfetamina y heroína en los últimos seis meses (aHR = 2.26, IC 95% = 1.23–4.15). En los análisis de mediación, el trabajo sexual medió una proporción sustancial (84.3%) de la asociación entre el género femenino y la incidencia del VIH. Intervenciones deben ser dirigidas a las mujeres PQID que participan en el trabajo sexual para reducir la incidencia del VIH relacionada con las disparidades de género.

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Abbreviations

PWID People who inject drugs
FSW Female sex workers
LMICs Low and middle-income countries

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 mediated by behavior and shaped by factors beyond 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, gender-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, a dependence on male partners to obtain and inject the drugs, 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 and macro level risk factors which increase HIV risk among PWID in Tijuana include: its placement along a major drug trafficking route (*macro physical*), exposure to physical, sexual, and drug cartel related violence (*micro physical*), ample access to drugs (*micro social*), punitive policing practices (e.g. 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 substance use, violence, 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 (FSW-PWID) are more likely than other female sex workers 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 both unprotected sex and the use of 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]. In addition, limited access to sterile syringes, police confiscation of syringes, and client perpetrated violence similarly impede FSW-PWID's ability to engage in safer injection practices [26, 27].

While several studies have demonstrated the disparate burden of HIV among female PWID, there is still a need to decompose gender-related disparities in HIV incidence by testing the mediating role of known risk factors. The objectives of the present study were to; [1] calculate HIV incidence density among PWID and compare incidence density rates by gender (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 gender and incident HIV infection. We hypothesized that HIV incidence would be significantly higher among female PWID, and that sex work would mediate the association between female gender and HIV incidence.

Methods

Study Population

From 2011 to 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 and completed at least one follow-up visit ($N=651$). All participants received \$5.00 US dollars for completing the screening process regardless of eligibility.

Recruitment methods

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

Surveys

The study protocol is described in full detail elsewhere [28]. 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) [9]. Data were collected using computer-assisted participant interview software [29]. 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 [30]. 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 [28].

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 [28]. 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 one tested HIV-negative and the first date one tested HIV-positive.

Sociodemographic Characteristics

Data collected on sociodemographics included: self-reported gender (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 drug 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.

Informed by the risk environment framework [9, 31] we considered several influences in the physical, social, economic and policy domains. 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 measures included in the analysis were: life-time forced sex which was defined as ever being coerced into having sex by someone who used physical or emotional pressure (yes/no), 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 measures included in the analysis were: sex work in the past six months, which was a dichotomous measure constructed 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 measures (i.e. variables that represent public health policies such as coverage of sterile syringes) 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.

Using baseline data, descriptive statistics including frequencies, percentages, medians and interquartile ranges (IQRs) were generated. Chi-square tests were used to compare participants who seroconverted and those who did not with respect to dichotomous variables, where the cell sizes

were less than or equal to five Fisher's exact tests were used, 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 gender.

Simple and multiple Cox regressions were used to evaluate associations between sociodemographic and substance use characteristics as well as factors in the risk environment and incident HIV infection for the whole sample. 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 [32], while controlling for the following confounders that have been identified as correlates of HIV infection in prior research; sex [33], income [20], duration of injection drug use [34], 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 [35, 36]. 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. $p \leq 0.05$) 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. Only one variable (lifetime 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., $< 10\%$) [37]. Using this novel method for mediation analysis, we calculated the total effect of female gender on incident HIV, the controlled direct effect (CDE) of female gender on incident HIV infection, the natural indirect effect (NIE) of female gender on incident HIV through sex work, and the proportion of the total effect of female gender on incident HIV infection mediated by the predictors tested as mediators. 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 [34], and the number of individuals residing in the respondent's household including the respondent [35, 36], and used 2500 bootstrap repetitions.

We also tested whether female gender moderated the relationship between the identified mediator(s) and incident HIV using both the multiplicative and additive scales. To test gender 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 gender as a moderator using the additive scale we estimated the relative excess risk due to interaction (RERI) [38] while controlling for the same set of confounders, using an algorithm recommended by Andersson and colleagues [39], $(HR_{11} - HR_{10} - HR_{01})$, where "11" represents the presence of both the moderator (e.g., female gender) 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. 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 = 0.92–1.68). Incidence density was significantly higher among females compared to males: 1.75 per 100 PY (95% CI 1.16–2.66) vs. 0.95 per 100 PY (95% CI 0.62–1.47), 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 Gender

Among females, incident cases were significantly more likely than PWID who did not seroconvert to report: methamphetamine and heroin co-injection $\geq$ twice a day (50.0% vs. 29.5%, $p = 0.04$, respectively), and syringe-mediated drug sharing (e.g. dividing and sharing 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 having their syringes confiscated by the police (27.3% vs. 12.3%, $p = 0.05$), and obtaining syringes from a needle exchange program (NEP) (27.3%

Table 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 (1.16, 2.66)	1,251.92	0.95 (0.62, 1.47)	2,189.306	1.25 (0.92, 1.68)	3,441.22	1.83 (1.01, 3.31)	0.04

PY = person years

95% CI = 95% Confidence Interval

P-value derived from Poisson regression

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, versus mean = 39.2, SD = 8.7, $p = 0.03$, respectively), and reported fewer years of injection drug use (median = 15, IQR = 10–19, vs. median = 18, IQR = 12–25, $p = 0.04$, respectively), compared to those who did not seroconvert. Male seroconverters were also significantly more likely to report injecting methamphetamine $\geq$ 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 models are presented in Table 3. In adjusted Cox models (1–4) factors that were significantly associated with HIV seroconversion include: sex work in the past six months (adjusted hazard ratio [aHR] = 2.25, 95% CI 1.05–4.80, $X^2 = 13.29$, $p = 0.03$); methamphetamine injection (aHR = 2.30, 95% CI 1.12–4.73, $X^2 = 13.09$, $p = 0.02$); and methamphetamine and heroin co-injection $\geq$ twice a day in the past six months (aHR = 2.26, 95% CI 1.24–4.15, $X^2 = 15.51$, $p < 0.01$) (Table 3).

Mediational Analyses

The following factors associated with HIV seroconversion were tested as mediators of the relationship between female gender and incident HIV; sex work in the past six months, methamphetamine injection, and methamphetamine and heroine co-injection $\geq$ twice a day or more in the past six months. Of these, sex work was the only significant mediator ($p = 0.01$), between female gender 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 gender on incident HIV was aHR = 1.84, (95% CI 0.86–3.35). The CDE of female gender on incident HIV was aHR = 1.14 (95% CI 0.52–2.22). The NIE of female gender on incident HIV through sex work was significant (aHR = 1.67, 95% CI 1.05, 2.51). Sex work mediated a substantial proportion (84.3%) of the association between female gender and incident HIV (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 insignificant (RERI = 1.34, 95% CI –0.75–3.43, $p = 0.21$). These tests provided no evidence that female gender 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%, $p = 0.01$). 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 [40]. Such findings highlight the distinct vulnerability of female PWID in Tijuana, and underscore the need

Table 2 Characteristics of females and males who inject drugs with and without incident HIV infection in Tijuana, Mexico (N = 651)

	Females				Males			
	Incident cases (n = 22)	Non-incident cases (n = 227)	Total (N = 249)	P	Incident cases (n = 21)	Non-incident cases (n = 381)	Total (N = 402)	P
<i>Sociodemographic characteristics</i>								
Mean age in years (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
<i>Substance use characteristics</i>								
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 $\geq$ twice a day +	4 (18.2)	30 (13.2)	34 (13.7)	0.51	6 (28.6)	46 (12.1)	52 (12.9)	0.02
Heroin injection $\geq$ twice a day +	19 (86.4)	187 (82.4)	206 (82.7)	0.63	21 (100)	332 (87.1)	353 (87.8)	0.07
Cocaine injection $\geq$ twice a day +	1 (4.6)	4 (1.8)	5 (2.0)	0.37	0	5 (1.3)	5 (1.3)	1.00
Methamphetamine and heroin co-injection $\geq$ twice a day +	11 (50.0)	67 (29.5)	78 (31.3)	0.04	11 (52.4)	144 (37.8)	155 (38.6)	0.18
<i>Micro-physical risk environment</i>								
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 one has lived in Tijuana (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 Tijuana because of deportation	3 (13.6)	43 (18.9)	46 (18.5)	0.77	4 (19.1)	101 (26.6)	105 (26.2)	0.61
Moved to Tijuana looking 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
<i>Micro-social risk environment</i>								
Syringe mediated drug sharing $\geq$ half of the time + 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

Table 2 (continued)

	Females				Males			
	Incident cases (n = 22)	Non-incident cases (n = 227)	Total (N = 249)	P	Incident cases (n = 21)	Non-incident cases (n = 381)	Total (N = 402)	P
Bought drugs already prepared in a syringe $\geq$ half of the time +	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
<i>Micro-economic risk environment</i>								
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
Average monthly income $\geq$ 3,500 Mexican pesos ⁶	5 (22.7)	75 (33.2)	80 (32.3)	0.31	5 (23.8)	95 (25.0)	100 (24.9)	0.90
<i>Micro-policy risk environment</i>								
Obtained syringes from a needle exchange program +	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 or clean syringes +	6 (27.3)	37 (16.3)	43 (17.3)	0.19	3 (14.3)	74 (19.)	77 (19.3)	0.55

¹Married or in a common law marriage

²Median number of year injecting drugs was calculated by taking the participants current age and subtracting it from the age they reported first injecting drugs

³Participants reported dividing drugs with someone else using a syringe more than half of the time in the past six months

⁴Lifetime forced sex was measured by asking participants if anyone has ever forced them to have sex using physical or emotional pressure

⁵Sex work includes those who reported selling sex in exchange for money or drugs in the past six months

⁶Approximately \$187.00 US dollars according to the exchange rate in 2018

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

for female-centered interventions that are designed to meet the unique needs of women who use drugs [41].

Consistent with our main hypothesis, we found that sex work accounted for more than three quarters of the total effect of female gender 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 [42], but add 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

FSW who inject drugs in Tijuana and Ciudad Juarez found that both interventions were efficacious and cost-effective in Ciudad Juarez [43]. In particular, the injection risk intervention modified the relationship between police confiscation of syringes and receptive needle sharing [44], 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 [43] at the time. Since this time however, funds from the Global Fund to End HIV, TB and Malaria ended in Mexico, which has been associated with syringe shortages and a return to high-risk behaviors [45, 46]. We recommend re-investing in proven harm reduction

Table 3 Crude and adjusted hazard ratios of characteristics and environmental risk factors associated with incident HIV infection among people who inject drugs in Tijuana, Mexico (N = 651)

Variable	HR (95% CI)	P	Model 1 ^a aHR (95% CI)	X2	P	Model 2 ^b aHR (95% CI)	X2	P	Model 3 ^c aHR (95% CI)	X2	P	Model 4 ^d aHR (95% CI)	X2	P
<i>Sociodemographic characteristics</i>														
Female sex	1.94 (1.06, 3.53)		0.03 1.65 (0.88, 3.09)	13.09	0.11	1.73 (0.92, 3.25)	15.51	0.08	1.29 (0.63, 2.64)	11.75	0.47	1.07 (0.49, 2.33)	13.29	0.84
Age in years	0.96 (0.92, 0.99)	0.01												
Number of years of education	0.98 (0.88, 1.08)	0.68												
Married ¹	1.62 (0.88, 2.97)	0.11												
<i>Substance use characteristics</i>														
Duration of injection drug use in years ²	0.96 (0.93, 0.99)		0.03 0.96 (0.93, 1.00)	13.09	0.06	0.96 (0.93, 1.00)	15.51	0.06	0.97 (0.93, 1.00)	11.75	0.12	0.97 (0.93, 1.00)	13.29	0.09
Methamphetamine injection ≥ twice a day +	2.15 (1.06, 4.35)		0.03 2.30 (1.12, 4.73) ^a	13.09	0.02									
Heroin injection ≥ twice a day +	2.00 (0.62, 6.47)	0.24												
Cocaine injection ≥ twice a day +	2.47 (0.34, 18.04)	0.37												
Methamphetamine and heroin co-injection ≥ twice a day +	1.99 (1.09, 3.63)	0.02				2.26 (1.24, 4.15) ^b	15.51	<0.01						
<i>Micro-physical risk environment</i>														
Lived in Tijuana for one's whole life	0.87 (0.47, 1.60)	0.65												
Number of years one has lived in Tijuana	0.98 (0.96, 1.00)	0.17												
Moved to Tijuana because of deportation	0.68 (0.30, 1.52)	0.34												
Moved to Tijuana looking for a better life	1.14 (0.45, 2.89)	0.78												
<i>Micro-social risk environment</i>														
Syringe mediated drug sharing ≥ half of the time ³ +	1.65 (0.91, 3.00)	0.10												
Police confiscation of syringes without arrest +	1.71 (0.76, 3.85)	0.19												
Ever forced to have sex ⁴	2.40 (1.25, 4.61)	<0.01							2.01 (0.94, 4.30) ^c	11.75	0.07			
Bought drugs already prepared in a syringe ≥ half of the time +	1.62 (0.58, 4.53)	0.35												

Table 3 (continued)

Variable	HR (95% CI)	P	Model 1 ^a aHR (95% CI)	X2	P	Model 2 ^b aHR (95% CI)	X2	P	Model 3 ^c aHR (95% CI)	X2	P	Model 4 ^d aHR (95% CI)	X2	P
Household size	0.97 (0.89, 1.06)		0.47 0.95 (0.87, 1.05)	13.09	0.38	0.95 (0.87, 1.05)	15.51	0.35	0.96 (0.87, 1.06)	11.75	0.46	0.96 (0.88, 1.05)	13.29	0.45
<i>Micro-economic risk environment</i>														
Sex work ⁵ +	2.42 (1.33, 4.41)	<0.01										2.25 (1.05, 4.80) ^d	13.29	0.03
Average monthly income ≥ 3,500 Mexican Pesos ⁶	0.84 (0.41, 1.71)		0.63 0.82 (0.40, 1.69)	13.09	0.60	0.81 (0.39, 1.67)	15.51	0.57	0.71 (0.34, 1.47)	11.75	0.36	0.68 (0.33, 1.41)	13.29	0.31
<i>Micro-policy risk environment</i>														
Obtained syringes from a needle exchange program +	1.98 (0.83, 4.71)	0.12												
Found it hard to get new or clean syringes +	1.24 (0.59, 2.59)	0.56												

¹ Married or in a common law marriage² Number of year injecting drugs was calculated by taking the participants' current age and subtracting it from the age they reported first injecting drugs³ Participants reported dividing drugs with someone else using a syringe more than half of the time in the past six months⁴ Lifetime forced sex was measured by asking participants if anyone has ever forced them to have sex using physical or emotional pressure⁵ Sex work includes those who reported selling sex in exchange for money or drugs in the past six months⁶ Approximately \$187.00 US dollars according to the exchange rate in 2018

Past six months +

HR = hazard ratio derived using simple Cox regression

aHR = adjusted hazard ratio derived using multiple Cox regression

P-values were derived from Cox regression

All models (1–4) controlled for sex, income, duration of injection drug use and household size

^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 4 Direct and indirect effects of female gender on incident HIV infection testing sex work as a mediator among people who inject drugs in Tijuana, Mexico (N=651)

Effect	Estimate	Standard Error	95% Confidence interval
Controlled direct effect	1.14	0.44	0.52, 2.22
Natural indirect effect	1.67	0.37	1.05, 2.51
Total effect	1.84	0.63	0.86, 3.35

Mediation analyses used 2500 bootstrap repetitions, and controlled for: income, duration of injection drug use and household size

Proportion of female gender on incident HIV mediated by sex work = 84.3%

interventions such as NEP and opiate agonist therapy, 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 [47]. For instance, relationship and power dynamics surrounding drug use that limit women's ability to negotiate male condom use [25, 48], gender-based violence [49], and economic inequality [20] are all 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 [47]. Moreover, interventions that integrate structural approaches by reducing barriers to resources [50, 51] and designing policy initiatives to promote safer sex including access to free condoms and pre-exposure prophylaxis (PrEP) [52, 53], have shown promise in reducing HIV among high-risk women in other settings [54], and should be tested among female PWID in Tijuana.

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 gender 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 [32, 37]. 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 would also like to acknowledge that this study cannot determine which aspects of sex work confer 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, 55]. 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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Compliance with ethical standards

Conflict of interest The authors have no competing interests.

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