 Sexual transmission of HIV-1 among injection drug users in San Francisco, USA: risk-factor analysis

Alex H Kral, Ricky N Bluthenthal, Jennifer Lorvick, Lauren Gee, Peter Bacchetti, Brian R Edlin

Summary

Background Many new HIV-1 infections in the USA occur in injection drug users (IDUs). HIV-1 seroconversion of IDUs is mainly associated with injection-related risk factors. Harm-reduction programmes concentrate on injection-risk behaviour. We aimed to establish whether injection or sexual risk factors, or both, were associated with HIV-1 antibody seroconversion of street-recruited IDUs in San Francisco, from 1986 to 1998.

Methods IDUs were enrolled every 6 months from four community sites. We did a nested case-control study comparing 58 respondents who seroconverted between visits with 1134 controls who remained seronegative. Controls were matched with cases by sex and date. Adjusted odds ratios and 95% CI were calculated for men and women by use of conditional logistic regression.

Findings Men who had sex with men were 8·8 times as likely to seroconvert (95% CI 3·7–20·5) as heterosexual men. Women who reported having traded sex for money in the past year were 5·1 times as likely as others to seroconvert (95% CI 1·9–13·7). Women younger than 40 years were more likely to seroconvert (95% CI 0·11–0·92). Women who reported having a steady sex-partner who injected drugs were less likely to seroconvert than other women (0·32 [0·11–0·92]).

Interpretation HIV-1 seroconversion of street-recruited IDUs in San Francisco is strongly associated with sexual behaviour. HIV-1 risk might be reduced by incorporation of innovative sexual-risk-reduction strategies into harm-reduction programmes.

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Introduction

A large proportion of new HIV-1 cases in the USA are injecting drug users (IDUs). 1 HIV-1 seroconversion of IDUs is mainly associated with injection-related risk factors. 2,3 However, few seroconversion studies have been done since 1992 and in only two was an association seen between sexual risk factors and seroconversion. 4,5 Researchers commonly concentrate on injection-related risk factors and ignore sexual risk. 6

In comparison with other US cities, HIV-1 prevalence among IDUs in San Francisco is moderate and has been stable at 10–14% since 1987. 7,8,9 HIV-1 prevalence among men who have sex with men in this city is high (30%). 10 In San Francisco, HIV-1 incidence among IDUs in methadone clinics in the late 1980s was 1·9%, 11 which was similar to an estimate for 15 other US cities at that time, 12 and to another for 17 US cities in the mid-1990s (1·5%). 13 Estimates of HIV-1 incidence in San Francisco for men who have sex with men are also similar to those of IDUs (1·2–2·8%). 13,14

San Francisco has adopted a harm-reduction philosophy 14 for prevention of HIV-1 in IDUs, which started with community-health outreach programmes in 1985, so-called bleach and teach programmes in 1986, a syringe-exchange programme in 1988, and a policy of drug treatment on demand in 1997. Harm-reduction programmes are controversial in the USA, because workers help drug users to reduce risks whether they intend to enter drug treatment or not. These programmes have reduced injection-related risks even in regions where they are illegal. 15 Few harm-reduction programmes in San Francisco have attempted to reduce sexual risk.

We assessed data from the Urban Health Study to establish risk factors for HIV-1 seroconversion among street-recruited IDUs.

Methods

Recruitment

Active IDUs were recruited for the Urban Health Study in three inner-city communities in San Francisco from 1986, and in a fourth from 1996. 6-monthly surveys included 170–250 IDUs in each community. We assessed data from 23 surveys done from 1986 to 1998. Respondents were recruited in natural settings with targeted sampling methods. 17 Communities selected had high concentrations of IDUs according to drug-treatment admission data, police arrest data, direct observation, and earlier ethnographic studies. Respondents were not recruited from institutional locations such as drug-treatment programmes, homeless shelters, correctional facilities, clinics, or hospitals. The eligibility criterion was recent intravenous drug use (past 30 days). New respondents were screened for visible signs of recent subcutaneous or intravenous drug use (so-called tracks, or recently punctured veins). Respondents were permitted to participate in subsequent surveys irrespective of whether they had continued to inject drugs. Repeat respondents were identified by checking information against that held in a database on a lap-top computer. Every 6 months, a new sample was recruited; previous participants were not helped to return to the study. This method
allowed us to assess new cases of HIV-1 infection from repeat visits of participants. Procedures

Eligible respondents had a private interview and counselling session with a trained interviewer and counsellor. All participants gave informed consent before a structured questionnaire was given by the interviewer. Questionnaires included: demographic factors (ethnic origin, age, eduction, homelessness, and neighbourhood); drug use (sharing syringes and drug cookers, injection frequency, number of years of injecting, injection drug of choice, crack-cocaine use, alcohol use, and sources of syringes); sexual practices (number of sex partners, number of male sex-partners, men who have sex with men, sex for money, safe sex [no sex or condom use at all times during vaginal or anal sex]), steady sex-partner, steady sex-partner who injected drugs, and self-reported sexually transmitted diseases, including gonorrhoea, chlamydia, syphilis, and genital herpes); and use of services (syringe-exchange use, including usual source of needles, substance-abuse treatment, contact with outreach workers, number of previous HIV-1-test results, and number of previous Urban Health Study visits).

Most questions referred to the previous year, although some were about the past 6 months (safe syringe source), past month (sharing syringes, sharing drug cookers, injection frequency, and syringe-exchange use), or current behaviour (steady sex-partner, steady sex-partner who injected drugs, homelessness, and substance-abuse treatment). 20 participants who were interviewed during 1986–88 were not asked about sex work in the past year; they were classed as having done sex work in the past year if they reported sex work in the past 5 years and more than two male sex-partners in the past year.

After interview, respondents were advised about their risk behaviours, given HIV-1 pretest counselling, and referred to medical and social services as needed. Phlebotomists took blood for HIV-1-antibody testing. Participants were paid US$15 and asked to return for HIV-1-test results and counselling 4 weeks (1986–94) or 2 weeks (1995–98) after interview. Methods were approved by the Committee on Human Subjects Research at University of California, San Francisco.

Blood samples were analysed for HIV-1 antibodies by ELISA. Positive specimens were further tested by western blot, and were confirmed as positive if results showed reactive bands at two of the following locations: p24 or gp41; and gp120 or gp160.18 Cases were participants who seroconverted, controls who did not. Controls were matched to cases of the same sex. All controls who were tested in the same surveys in which a seroconverter had their last negative and first positive test results (but were not tested in between those times) were matched to that case. Each control was matched to one case, with an algorithm that selected the least common of all possible observation windows for each control.

Statistical analysis

Participants were not required to give their names, hence a retrospective and systematic approach was used to link more than one observation of the same individual. First, a list of possible links was generated from identifying information: date of birth, sex, ethnic origin, the first two (1986–93) or four (1993–98) letters of the mother’s maiden name, and US state or country of birth. Links were verified by checking names and addresses from a contact-details form (volunteered by about half of all respondents) or by identifying information from the questionnaires that should remain constant—such as year of tattoos, pregnancies, or jail sentences. Individuals who were HIV-1 positive at baseline were excluded, the remainder were eligible for the case-control study. A crude incidence rate was calculated for eligible participants with person-years of observation as the denominator.

Cases were defined as initially HIV-1-negative participants who then had a positive HIV-1-antibody-test result in our study. We excluded those who had a gap in observation (observation window) of more than 3 years between their last negative HIV-1-antibody-test result and their first positive result, to ensure that risk factors that led to seroconversion were likely to have been ascertained in our interviews.

We compared our case-control sample with all HIV-1-antibody-negative participants by Fisher’s exact and Kruskal-Wallis tests. We used behavioural-risk data from the first follow-up interviews after positive HIV-1-antibody-test result, and the corresponding interviews for controls, to assess risk factors for HIV-1 seroconversion. Since cases and controls were matched by observation window and sex, we did regression analysis conditioned on observation window and stratified all analyses by sex. Conditional logistic regression for matched data was done for bivariate and multivariate analyses with Statistical Analysis System software (version 8.00, SAS Institute; Cary, NC, USA). In all analyses, odds ratios and adjusted odds ratios with 95% CI were calculated. All variables associated with seroconversion in bivariate analysis (p<0·10) were assessed for inclusion in multivariate analysis. Only significant variables (p<0·05) were retained in multivariate models. Interactions between all main effects were taken into account in each model.

Results

We did 13 099 interviews and HIV-1-antibody tests. We identified 6115 different participants, of whom 2120 took part more than once. 1865 individuals were eligible for the case-control study. Mean (SD) number of observations per eligible person was 4·0 (2·8). 70 participants were classed as cases, of whom nine were excluded. The median observation time of the nine excluded seroconverters was 5·5 years (range 3·5–9·0). We excluded two cases for whom controls could not be found and one whose sex we did not know. 58 participants became cases, and 1134 controls. Table 1 shows the observation windows in which seroconversion occurred for cases included in our analysis. Table 2 shows the number of controls per case. The average number of controls per case was 19·6 (median 12, range 1–96).

Seroconverters were distributed evenly throughout the Table 1: Number of years between last HIV-negative and first HIV-positive test result

<table>
<thead>
<tr>
<th>Years</th>
<th>Cases (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–5</td>
<td>22</td>
</tr>
<tr>
<td>1–5</td>
<td>14</td>
</tr>
<tr>
<td>1–9</td>
<td>7</td>
</tr>
<tr>
<td>2–5</td>
<td>8</td>
</tr>
<tr>
<td>2–9</td>
<td>4</td>
</tr>
<tr>
<td>≥3</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 2: Number of controls matched per case

<table>
<thead>
<tr>
<th>Number of controls per case</th>
<th>Number of cases represented (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2–5</td>
<td>15</td>
</tr>
<tr>
<td>6–10</td>
<td>10</td>
</tr>
<tr>
<td>11–30</td>
<td>16</td>
</tr>
<tr>
<td>31–96</td>
<td>16</td>
</tr>
</tbody>
</table>
The crude incidence rate among multiple-visit participants was 1·2% per year (95% CI 1·0–1·5). The case-control sample were also less likely than those excluded to: be homeless (357/1142 [31%] vs 1703/4123 [41%], p<0·0001); have injected cocaine in the past year (408/1078 [38%] vs 2164/4683 [46%], p=0·035); have injected speedball (heroin plus cocaine or amphetamines) in the past year (624/1107 [56%] vs 2430/4350 [56%], p=0·021); have shared syringes in the past 30 days (279/1156 [24%] vs 2034/4848 [42%], p<0·0001); and be in drug treatment (204/973 [21%] vs 1122/4293 [26%], p=0·001). Sex, sexual preference, sex work, heroin injection in the past year, and amphetamine injection in the past year did not differ significantly between groups.

Nearly half the case-control sample were African American, more than half were 40 years or older, and a third were homeless (table 3). Most used more than one substance (heroin, cocaine, or crack cocaine) and fewer than a fifth were in substance-abuse treatment at follow-up or baseline interview.‡None of the 16 male respondents who reported chlamydia was a seroconverter (p=0·99).

Several variables were significantly associated (p<0·05) with seroconversion in bivariate analysis: demographic factors (race, neighbourhood, and age), sexual risk factors (men who have sex with men, sex work, number of sex partners, having a steady sex-partner who injected drugs, and self-report of chlamydia), drug preference, and duration of injection behaviour (table 4). The only factors significantly associated with HIV-1 seroconversion in both men and women were: being African American, shorter duration of injection behaviour, and number of sex partners. For men, having a steady sex-partner who injected drugs increased the likelihood of seroconversion, whereas for women the likelihood was decreased. For men and women, having no steady sex-partner and having a steady

### Table 3: Risk factors assessed at first follow-up interview after positive HIV-antibody-test result and corresponding control interview

<table>
<thead>
<tr>
<th>Injected drugs</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection years</td>
<td>20 (71%) 250 (35%)</td>
<td>20 (83%) 175 (52%)</td>
</tr>
<tr>
<td>Heroin injection in past year</td>
<td>19 (61%) 624 (82%)</td>
<td>22 (81%) 286 (80%)</td>
</tr>
<tr>
<td>Cocaine injection in past year</td>
<td>15 (48%) 278 (36%)</td>
<td>14 (52%) 100 (28%)</td>
</tr>
<tr>
<td>Amphetamine injection in past year</td>
<td>18 (58%) 211 (28%)</td>
<td>9 (33%) 63 (18%)</td>
</tr>
<tr>
<td>Smoked crack cocaine in past year</td>
<td>18 (64%) 428 (61%)</td>
<td>18 (75%) 226 (67%)</td>
</tr>
<tr>
<td>Currently in substance-abuse treatment</td>
<td>4 (13%) 124 (16%)</td>
<td>5 (19%) 71 (20%)</td>
</tr>
</tbody>
</table>

### Table 4: Risk factors for HIV seroconversion in bivariate analysis

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category</td>
<td>Men</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td>White</td>
</tr>
<tr>
<td></td>
<td>African American</td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td>White</td>
</tr>
<tr>
<td>Recruited in Tenderloin neighbourhood</td>
<td>3.80 (1.70-8.50)</td>
</tr>
<tr>
<td>Age &lt;40 years</td>
<td>2.10 (0.96-4.40)</td>
</tr>
<tr>
<td>Homeless*</td>
<td>2.10 (0.54-2.70)</td>
</tr>
</tbody>
</table>

### Table 5: Risk factors for HIV seroconversion in multivariate analysis

<table>
<thead>
<tr>
<th>Independent factor</th>
<th>Adjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category</td>
<td>Men</td>
</tr>
<tr>
<td>Trade sex for money in past year</td>
<td>5.10 (1.90-13.70)</td>
</tr>
<tr>
<td>Age &lt;40 years</td>
<td>2.80 (1.05-7.60)</td>
</tr>
<tr>
<td>Unprotected vaginal sex in past year</td>
<td>4.50 (1.50-13.90)</td>
</tr>
</tbody>
</table>

* p<0·05. ** p<0·005.
sex-partner who did not inject drugs, were combined with the category of having a steady sex-partner who injected drugs, because they had similar risk.

Table 5 shows multivariate analysis of risk factors for HIV-1 seroconversion, stratified by sex. The only significant variable for men was having sex with men in the past year. Significant risk factors for women were: traded sex for money in the past year, and being younger than 40 years. Women who reported having a steady sex-partner who injected drugs were less likely to seroconvert than those who did not.

Since our results indicate that gay men, and women who exchange sex for money, are at increased risk of seroconversion, we assessed the risk behaviours of the 14 gay male seroconverters and 17 female sex-worker seroconverters. Of the 14 gay male seroconverters, ten reported more than one male sex-partner in the past year, 13 reported not always using condoms, seven reported having shared a syringe in the past year, and one reported having shared a drug cooker in the past year. Of the 17 female sex-workers who seroconverted, five reported more than 30 male sex-partners in the past year, nine reported between five and 30 male sex-partners, 12 reported not always using condoms for vaginal sex, five reported sharing syringes, and three reported sharing drug cookers.

There was no significant interaction between time (March, 1986, to June, 1990; July, 1990, to June, 1994; and July, 1994, to January, 1998) and each variable in table 5. Furthermore, there was no significant interaction between observation window (≤1 year vs >1 year) and each variable listed in table 5. Analyses that excluded the six seroconverters who knew they had seroconverted before their follow-up visits gave similar results to those in table 5. Nearly two-thirds of participants reported syringe exchange as their usual source of syringes (480/774 [62%] men and 245/370 [66%] women). Use of syringe-exchange programmes and HIV-1 seroconversion were not significantly linked in men (adjusted odds ratio 0.78 [95% CI 0.32–1.90]) or women (1.70 [0.51–5.90]).

Discussion

Our results show that the main risk factors for IDUs are sexual behaviours. The strongest predictor of HIV-1 seroconversion for men was having sex with men, whereas among women the strongest predictor was trading sex for money. These risk factors were reported by 53% of seroconverters. Stratified and colleagues also showed that sexual risks among IDUs were associated with seroconversion. These results suggest that HIV-1 prevention should be concentrated on sexual risk among IDUs.

The results of our study differ from those of other longitudinal studies of IDUs in that we did not find any strong evidence that injection risk factors were associated with seroconversion in multivariate analyses. Our results suggest that San Francisco’s HIV-prevention programmes for IDUs have been successful at reducing injection-related risk behaviours. However, they do not suggest that injection risk can be ignored. Upper confidence limits on injection-related risk factors were still high, even though these estimates were not significant. Furthermore, injection risk could become more important if prevention efforts were relaxed. HIV-1 transmission might be reduced by incorporation of new sexual-risk-reduction strategies into existing programmes.

Even in the age of HIV and AIDS, IDUs have been slow to reduce their sexual risk. Sexual risk interventions for IDUs based on research, have used psychological models to guide single-person, peer-based small-group, and community-level programmes. Some of these interventions have had success among non-IDU populations, but fewer have been successful for IDUs. Furthermore, when proven successful, research-driven sexual interventions have rarely been used by community-based organisations, because they can be impractical or expensive. Collaboration between organisations and researchers would improve the practicality of interventions.

Gay male IDUs are thought to be at high risk because of high HIV-1 prevalence among the people with whom they engage in risky behaviours. We could not find any published assessments of sexual interventions for these individuals. Thus, we suggest that research and harm-reduction programmes should be aimed at gay male IDUs. Research on gay male IDUs might help us to apply the work done on sexual-risk reduction among gay men to these people.

Our results confirm those of other studies in that female sex-workers are at high risk of HIV-1. Female sex-workers can be infected with HIV-1 by having unprotected sex with a large number of partners, even if most of their partners are uninfected. San Francisco has several HIV-prevention programmes for such workers, including community health outreach, HIV testing, support groups, and workshops. Strategies to enable female sex-workers to practise safe sex, including client education, might help reduce HIV risk.

In our study, young IDU women were more likely than older IDUs to seroconvert, which was also shown in a study in Baltimore, USA. These results suggest that young, female IDUs need HIV-prevention programmes. Female IDUs, who reported that they had a steady sex-partner who was an IDU, were less likely than other women to seroconvert—possibly because women in stable sexual relationships with other IDUs are less likely to engage in risky drug use or sex with other people.

Many researchers have studied the effectiveness of syringe-exchange programmes. These programmes are designed to decrease injection-related risks, which were not strongly associated with HIV-1 seroconversion in our study. Hence, we were not surprised that there was no significant association between syringe-exchange use and HIV-1 seroconversion. We applied multivariate models to the same dataset and found that among IDUs who shared syringes at baseline, those who used syringe-exchange programmes were more likely than those who did not to have stopped sharing syringes at follow-up. Those findings support others that indicate that syringe exchange is an effective HIV-1-prevention programme. Paone and colleagues suggested that sexual-risk interventions could be done at syringe-exchange programmes.

Our study has some limitations. First, the targeted sampling technique used to recruit respondents made it impossible to generalise our findings to all IDUs in San Francisco. Because drug use is illegal, no sampling technique can randomly select drug users. Further, we cannot derive true refusal rates, since IDUs who did not wish to participate did not come to our field sites, and therefore cannot be counted. An estimated 17 000 IDUs live in San Francisco, and during the 12 years of our study we interviewed 6115. However, although a substantial proportion of IDUs in San Francisco participated, we cannot know whether our study has a participation bias. Furthermore, retention bias might affect our results. 35% of participants returned for a follow-up visit. Our study was not designed as a cohort study—ie, participants returned of their own accord. Individuals who returned differed slightly from those who did not in ethnic origin, age, homelessness, cocaine use, speedball use, sharing of syringes, drug exchange, and sexual risk behaviours.
treatment, and number of years of injection behaviour. Another limitation is the possibility of bias in self-reported data because of social desirability, poor recall, and intoxication. However, multicentre-survey research has shown that self-report is very reliable among drug users not recruited in clinical settings. Because most of our cases did not know that they had seroconverted when they were interviewed, we do not believe that cases and controls differed in self-report validity. Finally, our matched case-control design prevented us from estimating HIV-incidence rates or examining time as a risk factor.

We recommend that various settings, including streets, syringe-exchange programmes, drug-treatment programmes, prisons, and hospitals are looked at as appropriate venues for sexual-risk prevention programmes for IDUs. Workers in existing programmes, in which they help IDUs to reduce their injection-related-risks, should continue their efforts and think about implementing sexual-risk prevention as well.

Contributors
Alex Kral, Jennifer Lorvich, and Richy Bluthenthal devised the report. Alex Kral, Richy Bluthenthal, Peter Bacchetti, and Brian Edlin designed the study. Jennifer Lorvich was responsible for data acquisition. Alex Kral did the main statistical analyses. Richy Bluthenthal, Lauren Gee, Peter Bacchetti, and Brian Edlin contributed to analyses. Alex Kral wrote the manuscript. All investigators commented on and amended report drafts.

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References
20 Rhodes T, Simonov GV, Quirk A. Sex, drugs, intervention, and research: from the individual to the social. Subst Use Misuse 1996; 31: 375–407.