

## ORIGINAL CONTRIBUTIONS

### High Rates of HIV Infection among Injection Drug Users Participating in Needle Exchange Programs in Montreal: Results of a Cohort Study

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Needle exchange programs (NEPs) are designed to prevent human immunodeficiency virus (HIV) transmission among injection drug users. Although most studies report beneficial effects in terms of behavior modification, a direct assessment of the effectiveness of NEPs in preventing HIV infection has been lacking. A cohort study was conducted to assess the association between risk behaviors and HIV seroprevalence and seroincidence among injection drug users in Montreal, Canada. The association between NEP use and HIV infection was examined in three risk assessment scenarios using intensive covariate adjustment for empirical confounders: a cross-sectional analysis of NEP use at entry as a determinant of seroprevalence, a cohort analysis of NEP use at entry as a predictor of subsequent seroconversion, and a nested case-control analysis of NEP participation during follow-up as a predictor of seroconversion. From September 1988 to January 1995, 1,599 subjects were enrolled with a baseline seroprevalence of 10.7%. The mean follow-up period was 21.7 months. The adjusted odds ratio for HIV seroprevalence in injection drug users reporting recent NEP use was 2.2 (95% confidence interval 1.5–3.2). In the cohort study, there were 89 incident cases of HIV infection with a cumulative probability of HIV seroconversion of 33% for NEP users and 13% for nonusers ( $p < 0.0001$ ). In the nested case-control study, consistent NEP use was associated with HIV seroconversion during follow-up (odds ratio = 10.5, 95% confidence interval 2.7–41.0). Risk elevations for HIV infection associated with NEP attendance were substantial and consistent in all three risk assessment scenarios in our cohort of injection drug users, despite extensive adjustment for confounders. In summary, in Montreal, NEP users appear to have higher seroconversion rates than NEP nonusers. *Am J Epidemiol* 1997;146:994–1002.

cohort studies; HIV; needle exchange programs; substance abuse; substance abuse, intravenous

Injection drug use is now recognized as one of the major routes for transmission of HIV infection. For the past 15 years, several strategies have been developed to reduce HIV transmission among drug users, and needle exchange programs (NEPs) have constituted one of the most favored (1). These programs aim at increasing accessibility to sterile needles and syringes and removing circulating contaminated injecting material (2).

There are many difficulties and pitfalls in trying to assess the effectiveness of NEPs in reducing HIV transmission. Accessibility to the injecting drug user

(IDU) population is difficult because of legal barriers surrounding drug use. Random assignment of participants to interventions can rarely be achieved, introducing potential for selection bias in subsequent program evaluations. NEPs are often initiated in the community along with other intervention measures, causing difficulties in the interpretation of the specific effects for each component of the entire intervention program. Such considerations have been recently and extensively reviewed by a panel of experts (3).

The first studies on NEPs were conducted in Europe, mostly among heroin users, and they showed

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Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; IDU, injection drug user; NEP, needle exchange program; OR, odds ratio.

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encouraging results. In London, England, and Glasgow, Scotland, a significant reduction in injecting behaviors was observed among recent NEP attenders (4–6). In the United Kingdom, a prospective survey between 1987 and 1988 reported higher levels of risk behaviors among nonattenders and a decrease in syringe sharing from 34 to 27 percent among attenders (7). In Australia, there was no increase of intravenous drug use due to the implementation of a NEP among clients of a methadone maintenance unit (8).

In North America, several studies have been conducted in recent years. In Hartford, Connecticut, and in New York City, NEP attenders reported decreased equipment sharing (9, 10). In Tacoma, Washington, in a case-control study among IDUs entering a methadone program, the nonuse of the NEP was associated with a significant risk for hepatitis B and hepatitis C (11, 12). A 4-year study evaluating the impact of NEPs among IDUs admitted for treatment in San Francisco, California, detected no negative consequences (13).

As stated earlier, changes in the rate of HIV infection among NEP attenders have been difficult to monitor. In Sweden, a small NEP was found useful in maintaining a low HIV seroprevalence among heroin and amphetamine IDUs (14). In the NEP of Portland, Oregon, one HIV seroconversion was observed in 162 person-years at risk (15). Kaplan and Heimer (16) used an innovative, albeit indirect, method of assessing HIV transmission by testing the returned syringes; and they estimated that incidence had declined among IDUs attending a NEP in New Haven, Connecticut. In Amsterdam, the Netherlands, where a large NEP was established in 1984, HIV seroprevalence remained at approximately 30 percent; and the seroconversion rate decreased from 9.2 percent in 1986 to 2.5 percent per year in 1992 (17). This decrease in incidence could not be directly attributed to the impact of the NEP. In two recent reviews by individuals commissioned to study the impact of NEP (1, 3), the authors concluded that such programs are generally useful in halting the progression of HIV infection in IDUs.

In Canada, implementation of NEPs started in 1989—almost simultaneously in Vancouver, Toronto, and Montreal. In 1988, our group began to accrue subjects in a cohort investigation of active IDUs in downtown Montreal. This cohort is an observational study and was not designed to study or evaluate NEPs. However, preliminary results on risk factors as predictors for HIV seroconversion among IDUs recruited in this cohort indicated a significant independent association between HIV seroconversion and the following variables: street recruitment, previous imprisonment, cocaine as drug of choice, number of injections in the last month, having two or more sharing partners in the

last month, sharing with an HIV-seropositive partner, having HIV-seropositive acquaintances, and finally, having attended a NEP at least once in the last 6 months (18). Because of the potential consequences of these findings on policies and prevention of HIV among IDUs, we present herein an extensive analysis of the association between NEP use and baseline HIV seroprevalence and cumulative seroincidence in our cohort.

## MATERIALS AND METHODS

### Subjects

Cohort members were actively recruited from three main sources. The Detoxification Unit of Saint-Luc Hospital in downtown Montreal contributed 33 percent of the recruitment, and referral from collaborating institutions catering to the needs of IDUs in the city such as shelters, private and public readaptation centers, therapeutic communities, and community-based agencies including city street workers contributed 5 percent of the cohort. With IDU groups gradually becoming aware of our ongoing investigation, direct self-referral became more and more important with 62 percent of the total recruitment. A \$10 fee (in Canadian dollars) was given at each visit as an incentive to participate in the study. Recruitment is ongoing and has been stable, with a mean of 23 new subjects enrolled each month.

IDUs were eligible if they had injected drugs within the last 6 months. After providing an informed consent at admission, subjects underwent a structured, questionnaire-based interview to elicit detailed information on sociodemographic characteristics, knowledge and attitudes concerning HIV infection, drug use, and sexual behavior. A follow-up questionnaire probed for similar information during all subsequent returns. All interviews were conducted by trained nurses with extensive experience with drug users. The first follow-up return was scheduled at 3 months and subsequent visits, every 6 months thereafter. A venous blood sample was drawn at each visit for serologic testing. Presence of anti-HIV antibodies was detected with a commercial enzyme-linked immunoassay (BioChem ImmunoSystems Inc., Montreal, Canada) and confirmed at the Quebec Provincial Public Health Laboratory by Western blot or radioimmunoprecipitation assay.

Of the 1,599 subjects enrolled from September 1988 to January 1995, 171 were seropositive at enrollment, for a seroprevalence rate of 10.7 percent. Subjects included in the cohort are those who have been followed up at least once after their initial visit. Among the initially seronegative subjects, 377 (26.4 percent)

were lost to follow-up. The present cohort analysis includes 974 HIV-negative subjects after elimination of 77 enrolled after October 1994 to ensure that all participants had been followed for at least 3 months. The mean follow-up period was 21.7 months, with a median of 15.4 months and intervals ranging from 3 months to 5 years, and with each subject contributing follow-up information since the date of entry until the date of a positive HIV serology for seroconverters or until the date of the last visit for those remaining seronegative.

### Regression analyses

Three risk assessment scenarios were used to study the association between NEP use and HIV infection. In the first scenario, as subjects were enrolled into the cohort, their initial serologic status was ascertained along with baseline questionnaire information on risk factors. NEP use in the entry questionnaire is a dichotomous variable, and the subject was asked whether he or she had attended a NEP to get his/her equipment in the past 6 months or in the past 3 months in the case of the follow-up questionnaire. This scenario is akin to a cross-sectional study of NEP use at entry as a marker associated with baseline HIV seroprevalence, and it also allowed a comparison of NEP attenders with nonattenders.

After eliminating those who were seropositive at entry, a cohort of seronegative individuals was assembled for continued surveillance. In this second scenario, NEP use reported in the entry questionnaire was treated as a possible predictor of subsequent seroconversion during follow-up.

In the third scenario, NEP participation during follow-up at the time of seroconversion was examined as a predictor of seroconversion in the cohort. A nested case-control design was used, whereby seroconverters were considered cases and up to four matched controls were randomly chosen from among those of the same gender, age (5-year groups), language (French vs. other), and year of enrollment who remained seronegative at the time their index case seroconverted. Information on NEP use was obtained from the interview at the time of the first visit, when the subject tested seropositive for cases, and from the last follow-up interview, for controls.

The odds ratio (OR), computed in unconditional logistic regression models, measured the magnitude of the association between NEP use at entry and HIV seroprevalence (first scenario) (19, 20). The hazard ratio, computed in Cox's proportional hazards regression models, was the estimate of effect for NEP use in all cohort analyses (second scenario) (21, 22). For the nested case-control analyses, due to the matched na-

ture of the data, conditional logistic regression models were computed to derive ORs for the association between NEP use and HIV risk (third scenario) (19, 20).

### Adjustment for confounders

A major concern in the assessment of a statistical association between NEP participation and risk of HIV seropositivity is the potential existence of confounders related to drug utilization and sexual practices. Confounders were identified empirically, i.e., by comparing the magnitude of the association between NEP use and HIV risk in regression models containing NEP use adjusted for the covariate of interest with that observed in crude models where NEP was the sole variable. The ratio between the adjusted and the crude estimates gauged the magnitude of the confounding effect for a given variable. An empirical confounder was considered any variable whose model produced an adjusted estimate for NEP that was either higher or lower than the crude estimate for NEP by at least two specified thresholds, 10 percent and 4 percent. Multivariate models of increasing complexity were computed by adding the confounders selected at the 10 percent level followed by those at the 4 percent level, corresponding respectively to models 2 and 3 in tables 2-5. In all analyses, covariate data were always derived from the same interview eliciting information on NEP use.

## RESULTS

### Seroprevalence analysis

Most subjects recruited in the study were male ( $n = 1,274$ , 79.7 percent). The mean age at entry was 32.2 years (median 32 years). Women were slightly younger (28.9 vs. 33 years) with half of them (162 of 325) reporting involvement in prostitution. Most participants reported consumption of multiple drugs lasting an average of 9.1 years, with cocaine the drug of choice for 64.2 percent of them; 82 percent reported having injected drugs in the previous month. Seven hundred sixty-seven (48 percent) IDUs reported NEP attendance at entry.

In table 1, the differences between NEP attenders and nonattenders are outlined, and NEP attenders are defined as those who reported having obtained their clean equipment at least once in a NEP in the 6 months before enrollment in the study. Prevalences of HIV and hepatitis B markers were significantly higher among NEP attenders; they were younger, had a lower income, and had been in treatment for addiction less frequently. They reported homo- or bisexual orientation and involvement in prostitution activities more frequently. In general, NEP attenders reported higher frequencies of risk behaviors related to drug injection.

**TABLE 1. Characteristics of subjects according to their needle exchange program (NEP) attendance at study entry among intravenous drug users in Montreal, Quebec, Canada, 1988–1995\***

Variables	NEP attenders (n = 767) (48%)	NEP non-attenders (n = 832) (53%)	<i>P</i> value†
HIV‡ seropositive	16	5.8	<0.001
anti-HBC‡ positivity	59	45.7	<0.001
Gender			
Male	81	78.5	0.22
Female	19	21.5	
Age (years)			
≤25	21.8	14.5	0.002
26–30	23	26.8	
31–35	25.8	27.8	
≥36	29.5	30.9	
Income (Canadian dollars)			
<10,000	38.7	32.4	0.003
10–24,999	32.5	30.3	
25–49,999	15.5	21.8	
≥50,000	13.4	15.5	
Homo-/bisexual reported orientation	11.1	7.5	0.01
Have ever engaged in prostitution activity	26.6	19	<0.001
Cocaine as drug of choice (vs. other)	65.4	63.2	0.6
Presently in treatment for addiction	37.4	61.3	<0.001
No. of injections previous month			
0	13.3	22.1	<0.001
1–29	24.1	28.5	
30–100	34.2	26.1	
>100	28.4	23.3	
Borrowed IV‡ equipment in the last 6 months	78.2	72.1	0.005
Disinfected IV equipment with "javel" last 6 months	57.4	25.7	<0.001
Used IV drugs in shooting galleries last 6 months	22.9	12.7	<0.001
Practiced booting in the last 6 months	25.7	18.8	<0.001
No. with three or more HIV-positive acquaintances	30.4	16.9	<0.001
Shared IV equipment with HIV-positive partner	14.7	6.9	<0.001

\* All data shown are percentages.

† Significance from chi-square test.

‡ HIV, human immunodeficiency virus; HBC, hepatitis B core antigen; IV, intravenous.

There were no significant differences between the two groups for language, living status (alone vs. with other people), schooling, number of recent sexual partners, drug of choice, drug use in prison, and number of recent intravenous users from whom they had borrowed syringes. Borrowing was defined as either borrowing a used syringe from another person or using a used syringe from an unknown origin. Borrowing

from an HIV-seropositive person is based on the reported HIV status of the lender.

In table 2, the association between NEP participation and seropositivity at entry for all subjects and for males only, with additional stratification for sexual orientation, is shown. All minimally adjusted ORs (controlling for age, entry period, gender, and language, taken as a priori confounders) indicate moderate but significant higher risks associated with NEP use that were of comparable magnitude across all sexual strata. The additional and incremental two-step adjustment for empirical confounders (10 percent threshold for OR2 and 4 percent threshold for OR3 as described in Methods) reduced the magnitude of the associations but still revealed consistent risk elevations in all subsets.

### Incidence analysis

Seronegative subjects included in the cohort study ( $n = 974$ ) were different from those lost to follow-up ( $n = 377$ ) on the following parameters: the proportion of male subjects (81 vs. 74 percent) and francophones (80 vs. 72 percent), declaring a lower income (11.5 vs. 21 percent), cocaine as drug of choice (64 vs. 57 percent), sharing in the last 6 months (78 vs. 68 percent), having more than two sharing partners in the last month (23 vs. 17 percent), and getting syringes and needles at the drug dealer (57 vs. 33 percent). Subjects lost to follow-up more often reported sharing with an HIV-positive partner (11 vs. 7 percent). There were no differences for the following variables: mean age, prostitution, getting syringes and needles from pharmacies, injecting in shooting galleries, and attending a NEP.

With 89 incident cases of HIV seroconversion during follow-up, overall incidence was 5.1 per 100 person-years (95 percent confidence interval (CI) 4.1–6.2). Incidence was 7.9 per 100 person-years (95 percent CI 6.0–10.2) among NEP attenders and 3.1 per 100 person-years (95 percent CI 2.1–4.4) among non-attenders. The cumulative probability of HIV seroconversion during follow-up according to NEP participation can be seen in figure 1. The difference between the two curves is highly significant ( $p < 0.0001$ , log rank test). In table 3, it can be seen that although the nearly threefold elevation in risk associated with NEP use at entry is considerably reduced upon adjustment by empirical confounders, hazard ratios remain significantly greater than unity for all subjects and for males only, indicating that NEP use during the 6 months before entry is a predictor for HIV seroconversion during follow-up in the cohort.

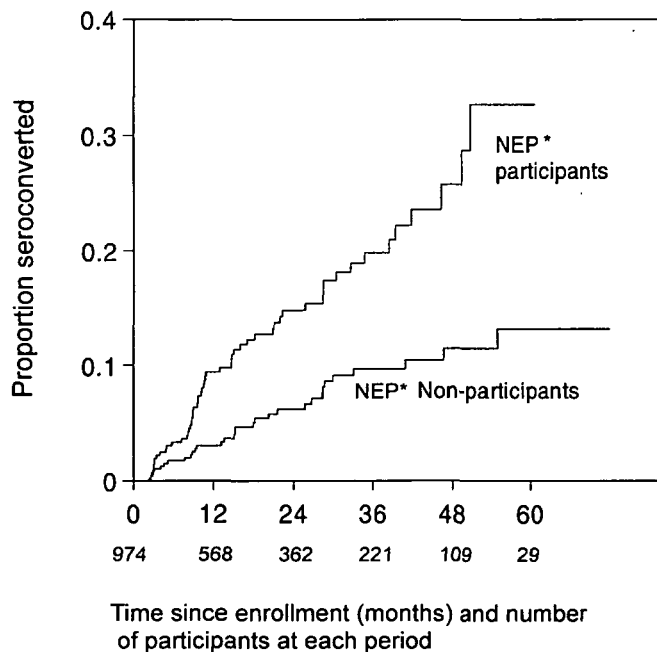
**TABLE 2. Odds ratios (ORs) and 95% confidence intervals (CIs) of human immunodeficiency virus (HIV) seropositivity among injection drug users at enrollment associated with participation in needle exchange program within the last 6 months in Montreal, Quebec, Canada, 1988–1995**

Subjects included in the analysis	No.	OR1*	95% CI	OR2†	95% CI	OR3‡	95% CI
All subjects	1,599	3.1	2.2–4.5	2.3	1.6–3.4	2.2	1.5–3.2
Heterosexuals	1,147	2.9	1.8–4.6	2.3	1.4–3.7	2.1	1.3–3.5
Homosexuals and prostitutes	447	2.7	1.5–4.8	2.0	1.1–3.7	1.9	1.0–3.6
All male subjects	1,274	3.6	2.4–5.3	2.7	1.8–4.1	2.5	1.6–3.8
Heterosexuals	1,000	3.3	2.0–5.4	2.6	1.5–4.3	2.4	1.4–4.1
Homosexuals and prostitutes	270	3.0	1.5–6.1	2.4	1.1–5.2	2.4	1.0–5.4

\* Adjusted for age, entry period, gender (for all subjects only), and language.

† Adjusted for variables above and additionally for number of acquaintances known to be HIV positive, treatment for addiction, and other sources of intravenous (IV) equipment (pharmacy, shooting gallery, dealer) in the last 6 months.

‡ Adjusted for all of the above and additionally for number of times IV drugs were used in previous month, number of times new IV equipment was used in previous month, sharing IV equipment with an HIV-positive person, living status, and drug of choice.



**FIGURE 1.** Cumulative human immunodeficiency virus seroincidence among needle exchange program (NEP\*) participants and nonparticipants in the Montreal Saint-Luc cohort, Canada, between 1988 and 1995.

### Nested case-control analysis

In table 4, the results of the nested case-control analysis can be seen, with 88 seroconversion cases and their 320 matched controls (one case that had no controls fulfilling the matching criteria was excluded) based on use of the questionnaire at the time of seroconversion. In the nested case-control analysis, participation was further categorized as exclusive or nonexclusive, depending on whether subjects also obtained their intravenous equipment from sources other than the NEP, e.g., pharmacies, dealers, friends, and in shooting galleries. There were substantial risk eleva-

tions among NEP users, both exclusive and nonexclusive, that persisted after adjustment for confounders, for all subjects, and for males only.

We also investigated whether consistency of NEP attendance influenced risk of HIV seroconversion in the cohort using the information on NEP attendance from baseline and follow-up interviews. Consistent attenders were defined as those who reported some NEP attendance at all visits, whereas those with no reported NEP attendance in any of the interviews were considered nonattenders. Those reporting intermittent NEP attendance were subdivided according to the proportion of interviews with reported NEP attendance. Consistent attenders, when compared with nonattenders and intermittent attenders at baseline, were more likely to identify cocaine as their drug of choice (84.6 percent), had injected more often in the last month (76 percent with 30 injections or more), had more sharing partners in the last month, reported more booting in the last 6 months, and reported getting their equipment less often at shooting galleries. However, they had used brand new equipment more often in the previous month and had disinfected their equipment more often in the last 6 months. As shown in table 5, there was a clear tendency for risks of seroconversion to increase with frequency of NEP use over time. Upon adjustment for confounders, significant elevations remained only among self-reported consistent users for all subjects and for males only.

In searching for interaction effects between NEP attendance and other variables, period of admission into the cohort was found to yield a marginally significant interaction with NEP ( $p = 0.06$ ). The association between HIV seroconversion and NEP attendance appears to have decreased in magnitude for those recently admitted into the cohort. After stratifying the cohort by entry periods, the following crude hazard ratios for NEP attendance were found: Septem-

**TABLE 3. Hazard ratios (HRs) and 95% confidence intervals (CIs) of becoming seropositive to the human immunodeficiency virus during follow-up associated with participation in a needle exchange program within the last 6 months at entry in a cohort of injection drug users in Montreal, Quebec, Canada, 1988–1995\***

Subjects Included in the analysis	No.	HR1†	95% CI	HR2‡	95% CI	HR3§	95% CI
All subjects	974	2.6	1.7–4.0	1.8	1.1–2.9	1.7	1.0–2.7
Males only	787	3.1	1.9–5.0	2.1	1.3–3.5	1.9	1.1–3.3

\* Results by Cox proportional hazards regression.

† Adjusted for age, entry period, gender (for all subjects only), and language.

‡ Adjusted for variables above and additionally for drug use during occasional encounters in last 6 months, ever having borrowed intravenous (IV) equipment from an HIV-positive person, treatment for addiction, and other sources of IV equipment (pharmacy, shooting gallery, dealer) in the last 6 months.

§ Adjusted for all of the above and additionally for drug of choice, number of times IV drugs were used in previous month, drugs used with regular partners in last 6 months, drug used at dealer's in previous month, number of times new IV equipment was used in previous month, number of acquaintances known to be HIV positive, living status, and practice of disinfection.

**TABLE 4. Odds ratios (ORs) and 95% confidence intervals (CIs) of becoming seropositive to the human immunodeficiency virus during follow-up in a cohort of injection drug users between 1988 and 1995, associated with participation in a needle exchange program 3 months before the last visit\***

Needle exchange program use	No.	OR1†	95% CI	OR2‡	95% CI	OR3§	95% CI
All subjects	408						
Nonusers	273	1.0	Referent	1.0	Referent	1.0	Referent
Users, nonexclusive	104	6.8	3.9–12.1	3.3	1.6–6.7	4.2	1.6–11.0
Users, exclusive	31	7.8	3.1–19.2	4.2	1.5–11.5	6.5	1.8–23.8
Males only	367						
Nonusers	240	1.0	Referent	1.0	Referent	1.0	Referent
Users, nonexclusive	96	6.1	3.4–11.1	3.5	1.6–7.5	4.2	1.5–12.2
Users, exclusive	31	7.2	2.9–17.9	4.3	1.5–12.1	10.0	2.3–43.9

\* Results from the nested case-control analysis by conditional logistic regression.

† From analysis conditioned on age, gender, year of admission, and language.

‡ Adjusted additionally for intravenous (IV) drug use since last visit, number of times IV drugs were used in previous month, borrowed IV equipment since last visit, number of times new IV equipment was used in previous month, and practice of disinfection.

§ Adjusted for variables above and additionally for drug of choice, drug use alone in last 3 months, drug use with regular partners in last 3 months, drug use during occasional encounters in last 3 months, drug use with friends in last 3 months, number of partners from whom IV equipment was borrowed in last month, borrowed IV equipment from an HIV-positive person since last visit, number of acquaintances known to be HIV positive, practiced booting in last 3 months, drug use while in prison, and living status.

ber 1988 through September 1991, 2.73 (95 percent CI 1.6–4.6); January 1991 through December 1993, 3.7 (95 percent CI 1.2–11.1); January 1994 through January 1995, 0.7 (95 percent CI 0.16–2.8).

## DISCUSSION

As shown by the seroprevalence data at entry into the cohort, the Montreal NEP appears to have attracted subpopulations of IDUs with a higher baseline rate of HIV and hepatitis B infections. Consistent NEP attenders also have a higher profile of high risk behaviors than other IDUs.

In spite of these differences among NEP attenders and nonattenders, a positive association between NEP attendance and risk of HIV infection emerged consistently in the three risk assessment scenarios of this study. Recent NEP attendance, a single exposure vari-

able, was a strong predictor of the risk of seroconversion during follow-up among those initially seronegative. In addition, NEP attendance during follow-up was also predictive of seroconversion. Most of the excess risk appeared to be experienced by those reporting consistent and exclusive attendance at NEPs, which was their primary source of new intravenous equipment.

We hypothesized initially that the direction of this association represented simply the net confounding effect by behavioral characteristics biasing the NEP use-risk association toward an effect that would be opposite from the expected protective one. Interviews conducted at entry and on multiple opportunities during follow-up elicited detailed information on numerous potential confounders. These variables were identified empirically by comparing crude and adjusted

**TABLE 5. Odds ratios (ORs) of becoming seropositive to the human immunodeficiency virus during follow-up among injection drug users associated with overall history of participation in a needle exchange program in Montreal, Quebec, Canada, 1988–1995\***

Needle exchange program	No.	OR1†	95% CI	OR2‡	95% CI	OR3§	95% CI
All subjects	408						
Nonusers	129	1.0	Referent	1.0	Referent	1.0	Referent
Users <50% of time	110	1.3	0.5–3.2	0.9	0.3–2.7	0.7	0.7–2.5
Users ≥50% of time	104	3.9	1.7–8.7	2.6	1.0–6.7	2.2	0.6–5.7
Consistent users	65	22.9	8.4–62.3	10.2	3.3–31.5	13.1	2.7–41.0
Males only	367						
Nonusers	116	1.0	Referent	1.0	Referent	1.0	Referent
Users <50% of time	95	1.4	0.5–3.8	0.9	0.3–2.8	0.7	0.2–2.8
Users ≥50% of time	93	4.0	1.7–9.6	2.7	1.0–7.4	2.9	0.6–6.5
Consistent users	63	21.8	7.7–61.5	10.2	3.1–33.1	19.1	2.6–50.1

\* Results from the nested case-control analysis by conditional logistic regression.

† From analysis conditioned on age, gender, year of admission, and language.

‡ Adjusted for intravenous (IV) drug use since last visit, number of times IV drugs were used in previous month, borrowed IV equipment since last visit, number of times new IV equipment was used in previous month, and practice of disinfection.

§ Adjusted for variables above and additionally for drug of choice, drug use alone in last 3 months, drug use with regular partners in last 3 months, drug use during occasional encounters in last 3 months, drug use with friends in last 3 months, number of partners from whom IV equipment was borrowed in last month, borrowed IV equipment from HIV-positive person since last visit, number of acquaintances known to be HIV positive, practiced booting in last 3 months, drug use while in prison, and living status.

estimates of effect for the NEP-risk association. All plausible sociodemographic, behavioral, and drug consumption variables available were examined as potential confounders.

Because of the low threshold for selecting empirical confounders, the regression models included an extensive list of covariates. This may have decreased the precision of the estimates of effect for NEP attendance, further adding an element of conservatism to our strategy. The fact that the association between NEP attendance and HIV infection risk persisted after being scrutinized with such a conservative analytical approach bolsters our conclusion that it is internally valid and merits further attention.

Before we address the possible implications of our study, it is important to consider its limitations. Our study is observational and was not specifically designed to evaluate the efficacy of NEP in preventing HIV infection. We cannot generalize its findings to other IDU populations in Montreal or elsewhere because of the type of recruitment and of the differences between participants and those lost to follow-up. It is also possible that despite the exhaustive data-driven process to identify confounders, some had been left unaccounted for in the analysis because they were absent from the list of variables derived from the interviews. However, this is unlikely, at least for individual variables, because our questionnaires probed repeatedly for detailed information on risk behaviors and other HIV determinants. Any irrelevant variable with respect to HIV risk that could be linked to NEP attendance would be unlikely to confound the associ-

ation because confounding ensues only if a factor is associated with the outcome as well as with the exposure.

Misclassification bias could explain our results if we assume that at least one of the following conditions occurred: 1) HIV-positive attenders falsely reported NEP participation, or 2) HIV-negative NEP attenders underreported participation. These are unlikely to have occurred, however, because subjects were unaware of their serologic status before the follow-up interviews.

Substantial misclassification of confounder variables would also lead to a decreased ability to control for their effects in the regression analysis. The extent of the impact of such a misclassification is difficult to predict.

Apart from the statistical issues described above, what are the possible explanations for our results? In our cohort, subject recruitment has relied mostly on self-selection based on informal word-of-mouth advertisement about the existence of our investigation. One possibility is that this method may have led to oversampling of high risk (HIV infection-prone) individuals among NEP attenders in the cohort, affecting the external validity of our study. Even if subjects lost to follow-up did not differ on NEP attendance, differential attrition might have occurred. However, it is reassuring that an independent study among IDUs recruited at CACTUS-Montreal has found seroprevalence and seroincidence rates comparable with those in our study despite use of a different methodology (23).

Differences in baseline prevalence between groups of IDUs have already been pointed out as a predictor for seroconversion in a study of HIV incidence in different cities of the United States (24). This study may have targeted a subpopulation of IDUs attending NEP who are at particularly high risk for the propagation of HIV.

NEPs are often developed within a global organization of prevention and care for drug users. In Montreal, NEPs have been implemented in an environment where needles and syringes are readily available through pharmacies and where policies encouraging pharmacists to sell intravenous equipment to IDUs were introduced in 1988, a year before the first NEP (25). Among opiate users from Manchester in the United Kingdom, the access to sterile equipment through local pharmacies was thought to have reduced the effects of a NEP on sharing habits (26).

It is also conceivable that through a combination of factors, the dynamics in Montreal might have favored HIV acquisition among NEP attenders. NEPs were developed as multifaceted prevention programs offering additional services such as primary health care, support, and counseling. To achieve these goals, the exchange of needles and syringes in the various programs was deliberately limited in an effort to encourage multiple visits and binding to the program. CACTUS, the largest NEP in Montreal, has a needle and syringe exchange policy based on a ratio of one for one, with a maximum of 15 syringes exchanged per person per night. In view of the high risk population attending NEPs, the number of needles distributed may have been less than the actual number needed. Because of availability of clean equipment through pharmacies, which are often conveniently located in the neighborhood, NEPs might have attracted existing core groups of marginalized, high risk individuals. More importantly, NEP implementation, through new socialization among IDUs, also may have facilitated formation of new sharing networks, with the programs becoming gathering places for isolated IDUs. Nonuniform needle sharing among core group members of NEP attenders also may have contributed to the risk differentials seen in our study. The trends toward a decrease of the association over time in our study might be related to changes in the social dynamics around NEPs as well as to long-term effects of such programs.

In view of the higher baseline prevalence for NEP attenders, the risk of HIV acquisition per sharing episode with another NEP attender may be higher than for nonattenders. With a greater incidence around NEPs, sharing during the seroconversion phase may contribute further to HIV transmissibility because of

the high viral load in the donor blood during that period (27–29). The predominance of closely related and possibly more infectious HIV strains among NEP attenders is also another hypothesis to consider (30).

In summary, Montreal NEP users appear to have higher HIV seroconversion rates than NEP nonusers. This study also indicates that at least in Montreal, HIV infection is associated with NEP attendance. These findings cannot be explained solely on the basis of the concentration around NEPs of a higher risk IDU population with a greater baseline HIV prevalence. Since NEPs have been viewed as a credible preventive intervention for drug users who continue to inject (1, 2), we believe that caution is warranted before accepting NEPs as uniformly beneficial in any setting. Our investigation was not designed to address a possible causal relation between NEP attendance and HIV infection; its conclusions were derived purely from an observational rather than an experimental study design. NEP implementation involves complex dynamics of individual and collective behaviors that may have different and possibly deleterious effects on HIV transmission. The impact of NEPs may be much more context sensitive and locally dependent than previously realized. It is also possible that the apparent impact of a NEP might diminish over time (31). In Amsterdam, a comparison of the injecting behavior of drug users who seroconverted for HIV with a control group that did not seroconvert yielded no evidence overall of a protective effect, except possibly in the early stages of the program (32). It may be possible also that impact of a NEP may have a longer latency period.

Public health authorities have been informed of our findings, and measures have already been implemented at CACTUS since January 1995—notably, removal of the individual quota on syringe distribution. Our work firmly suggests that NEP programs should be fine-tuned to local needs. More studies are needed to elucidate the mechanisms implicated on the transmission of HIV around NEPs in Montreal or elsewhere and to further assess the potential advantages of this intervention. Such expanded studies should include viral load measures, molecular epidemiology analyses of HIV strains, and qualitative investigations of risk behaviors and networking around NEPs.

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