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Short Communication

No association between HIV status and risk of non-fatal overdose among people who inject drugs in Vancouver, Canada

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HIGHLIGHTS

- It is unclear if HIV status is a risk-factor for non-fatal overdose among PWID.
- We examined this longitudinal association among 1760 prospectively-enrolled PWID.
- We found no association between HIV status/viral load and overdose risk.
- These results contrast the predominant findings from earlier research.

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ABSTRACT

Background: The evidence to date on whether HIV infection increases the risk of accidental drug overdose among people who inject drugs (PWID) is equivocal. Thus, we sought to estimate the effect of HIV infection on risk of non-fatal overdose among two parallel cohorts of HIV-positive and –negative PWID.
Methods: Data were collected from a prospective cohort of PWID in Vancouver, Canada between 2006 and 2013. During biannual follow-up assessments, non-fatal overdose within the previous 6 months was assessed. Bivariable and multivariable generalized mixed-effects regression models were used to determine the unadjusted and adjusted associations between HIV status, plasma HIV-1 RNA viral load, and likelihood of non-fatal overdose.
Results: A total of 1760 eligible participants (67% male, median age = 42, and 42% HIV-positive at baseline) were included. Among 15,070 unique observations, 649 (4.3%) included a report of a non-fatal overdose within the previous 6 months (4.4% among seropositive and 4.3% among seronegative individuals). We did not observe a difference in the likelihood of overdose by HIV serostatus in crude (odds ratio [OR]: 1.05, $p = 0.853$) analyses or analyses adjusted for known overdose risk factors (adjusted OR [AOR]: 1.19, $p = 0.474$). In a secondary analysis, among HIV-positive PWID, we did not observe an association between having a detectable viral load and overdose (AOR: 1.03, $p = 0.862$).
Conclusions: Despite the evidence that HIV infection is a risk factor for fatal overdose, we found no evidence for a relationship between HIV disease and non-fatal overdose. However, overdose remains high among PWID, indicating the need for ongoing policy addressing this problem, and research into understanding modifiable risk factors that predict non-fatal overdose.

1. Introduction

There is contradictory evidence as to whether HIV infection confers additional risk for accidental overdose among people who inject drugs (PWID). Although some studies have found no association between HIV status and either fatal or non-fatal overdose (Ferreros, Lumbreras, Hurtado, Perez-Hoyos, & Hernandez-Aguado, 2008; Ochoa et al., 2005), others have suggested HIV infection may be associated with higher risk of either type of overdose among both non-injecting and injecting drug users (Eskild, Magnus, Samuelsen, Sohlberg, & Kittelsen, 1993; Green, McGowan, Yokell, Pouget, & Rich, 2012; Solomon et al., 2009; van Ameijden, Langendam, & Coutinho, 1999; van Haastrecht et al., 1996; Wang et al., 2005; Zaccarelli et al., 1994). Several biological mechanisms have been proposed as potential underlying reasons for

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increased risk, including immunosuppression (Lyles et al., 1997; van Ameijden, Krol, et al., 1999), liver or pulmonary disease (Solomon et al., 2009; Wang et al., 2005), and higher drug use-associated risk behaviors among those with HIV infection (Goedert et al., 1995; van Ameijden, Langendam, et al., 1999). Further explanations for potential causal relationships are summarized in a 2012 systematic review and meta-analysis (Green et al., 2012). Pooling results from 27 studies published between 1988 and 2010, Green et al. estimated that HIV seropositivity was associated with a 74% increase in fatal overdose among samples consisting primarily of PWID. However, it remains uncertain whether HIV status is causally related to increased overdose risk, or if past observational studies have been subject to biases, including unmeasured confounding.

The effect of HIV status on overdose may also differ for fatal versus non-fatal overdose events: specifically, there has been more compelling evidence for an increased risk of fatal overdose among HIV-infected populations (Green et al., 2012). For example, a study of heroin overdose indicated that systemic disease affecting the pulmonary system (i.e., sequelae from immunosuppression caused by HIV disease) may have distinct effects on the risk of non-fatal versus fatal overdoses, although such disease was expected to increase susceptibility to both events (Warner-Smith, Darke, Lynskey, & Hall, 2001). Further work is therefore needed to examine the relationship between HIV status and non-fatal overdose experiences, which until now has not garnered the same attention, and may have been presumed to have the same positive relationship as fatal overdose.

In addition, increased treatment coverage of highly active antiretroviral therapy (HAART) among drug users in some settings warrants a re-examination of the relationship between HIV status and non-fatal overdose, based on more recent data. We are not aware of any currently available evidence that indicates whether those who are virally suppressed are at the same risk of non-fatal overdose as those with detectable levels. With this analysis we hypothesized that, among HIV positive individuals, those with undetectable viral loads would have a reduced risk of non-fatal overdose; thus, the overall relationship between positive HIV status and risk of non-fatal overdose may have diminished in the modern treatment era. To test our hypotheses, we used 8 years of data from two community-recruited cohorts of HIV-positive and –negative PWID in Vancouver, Canada.

2. Material and methods

2.1. Study eligibility and recruitment

We analyzed data from two parallel open prospective cohort studies in Vancouver, Canada: the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS), consisting of HIV-positive PWID, and the Vancouver Injection Drug Users Study (VIDUS), consisting of HIV-negative PWID. The recruitment, assessment, and follow-up procedures for each of these cohorts have been described elsewhere in detail (Strathdee et al., 1998; Tyndall et al., 2003). For both cohorts, community-based recruitment strategies were used, including word-of-mouth, posters, and snowball sampling to recruit PWID in Vancouver's Downtown Eastside neighborhood, an area with high levels of illicit drug use, poverty, and homelessness.

Individuals were eligible for inclusion if they were aged ≥18 years and, in the case of VIDUS, had used illicit drugs via injection in the 30 days prior to the baseline interview. Although ACCESS includes those who do not inject drugs, we restricted this analysis to participants from both cohorts who had injected illicit drugs within the previous 180 days. HIV status for enrollment in VIDUS (HIV-negative) and ACCESS (HIV-positive) is determined by serologic assay at baseline. Participants who seroconvert during follow-up are automatically transitioned from VIDUS to ACCESS. All participants complete interviewer-administered surveys that elicit information on lifetime and recent characteristics, behaviors, and exposures. Participants also undergo examination by a study nurse, including blood sampling for serological analysis. The ACCESS and VIDUS studies have been approved by the University of British Columbia/Providence Healthcare Research Ethics Board. All participants provided written informed consent and received 20 CAD for each study visit.

We included in this analysis all participants ($n = 1760$) who completed at least one baseline or follow-up questionnaire during the study period (2006–2013). During each assessment, participants were asked whether they had experienced a non-fatal overdose (i.e., "a negative reaction from using too much drugs") within the previous 6 months.

2.2. Statistical analyses and models

First, we plotted the proportion of study participants reporting at least one overdose during each assessment, stratified by HIV status. Next, bivariable and multivariable generalized mixed-effects regression models were used to determine the longitudinal unadjusted and adjusted association between HIV status (time-updated to account for participants who seroconverted during follow-up), and non-fatal overdose (Model 1). In a secondary analysis, we examined the relationship between having a detectable viral load (≥50 copies/mL), and non-fatal overdose among HIV-positive individuals (Model 2). For this analysis, we accessed the results of viral load tests held by the Drug Treatment Programme of the BC Centre for Excellence in HIV/AIDS, which dispenses all antiretroviral therapy within British Columbia and maintains a complete clinical monitoring database, including all viral load tests conducted through ACCESS or by each individual's physician. Of note, all HIV/AIDS treatment and care is delivered free of charge in this setting through the universal no-cost medical insurance plan.

In both models, we assessed for inclusion other established risk factors for overdose among PWID, including age; homelessness; heroin injection; cocaine injection; heavy alcohol use (classified here by self-reported binging or no binging); recent incarceration; and methadone treatment (Fischer et al., 2004; Kerr et al., 2007; Sergeev, Karpets, Sarang, & Tikhonov, 2003). We also assessed the following potential risk factors: gender (female vs. male); years of since injection initiation; ethnicity (Caucasian vs. non-Caucasian); education level (≥high school diploma vs. <high school diploma); crack cocaine use; sex work; exposure to violence; hepatitis C virus (HCV) antibody status; the year of study enrollment; and the year of observation. Consistent with previous analyses, all of these variables, with the exception of gender and ethnicity, were time-updated and referred to the 180-day period prior to the study interview. To determine inclusion of covariates for each model, we used a stepwise selection procedure. This backwards selection protocol, as performed previously (Milloy et al., 2011), and suggested by Greenland et al. (Maldonado & Greenland, 1993; Rothman & Greenland, 1998), sequentially removes from the full set of potential confounders any that did not change the estimate of the primary association by >5%. All p-values were two-sided.

3. Results

Between December, 2006 and June, 2013, 1760 participants completed at least one study interview, producing 15,070 unique assessments, or a median of 8 (inter-quartile range [IQR]: 4–12) per participant. In total, 1279 (67%) were male, 1153 (60%) self-reported Caucasian ancestry, and the median age at baseline was 42 (IQR: 36–48) years. Individuals with >1 interview did not differ from those with only one study interview (205, 11%) by gender or self-reported ethnicity (both $p > 0.5$). Individuals who never returned for follow-up were younger (40 vs. 43 years; $p < 0.001$) and more likely to report an overdose in the 6-month period prior to the baseline interview (11% vs. 6%, $p = 0.01$) but not more likely to be HIV-positive (47% vs. 41%, $p = 0.051$).