Addiction
RESEARCH REPORT
doi:10.1111/add.12736

Ongoing impact of HIV infection on mortality among people who inject drugs despite free antiretroviral therapy

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ABSTRACT

Aims To determine the impact of HIV infection on mortality over time among people who inject drugs (PWID) in settings with free HIV/AIDS care. **Design and Setting** Prospective cohort study of PWID in Vancouver, Canada, recruited between May 1996 and December 2011. We ascertained morality rates and causes of death through a confidential linkage with the provincial vital statistics registry. **Participants** A total of 2283 individuals were followed for a median of 60.9 months (interquartile range: 34.4–113.1), among whom 622 (27.2%) individuals were HIV-positive at baseline, and 179 (7.8%) seroconverted during follow-up. **Measurements** The primary and secondary outcomes of interests were all-cause mortality and cause of death, respectively. The main independent variable of interest was HIV serostatus (positive versus negative). We used Cox proportional hazards regression to determine factors associated with mortality, including socio-demographic variables, drug use behaviors and other risk behaviors. **Findings** During the study period, 491 (21.5%) individuals died. In multivariate analyses, HIV infection remained associated independently with all-cause mortality (adjusted hazard ratio = 3.15; 95% CI: 2.59–3.82). While all-cause mortality rates declined markedly during the study period ($P < 0.001$), the independent effect of HIV infection on mortality remained unchanged over time ($P = 0.640$). Among HIV-positive individuals, significant changes in causes of death from infectious and AIDS-related causes to non-AIDS-related etiologies were observed. **Conclusions** HIV infection continues to have a persistent impact on mortality rates among people who inject drugs in settings with free HIV/AIDS care, although causes of death have shifted markedly from infectious and AIDS-related causes to non-AIDS-related etiologies.

Keywords free HIV/AIDS care, HIV/AIDS, illicit drug use, injection drug use, mortality, people who inject drugs (PWID), Vancouver.

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Submitted 1 June 2014; initial review completed 1 August 2014; final version accepted 27 August 2014

INTRODUCTION

Injection drug use is a well-established risk factor for morbidity and premature mortality due to various causes, including HIV infection [1–3]. A recent systematic review and meta-analysis that included more than 60 cohorts of people who inject drugs (PWID) demonstrated a pooled crude mortality rate of 2.4 per 100 person-years among this population, and found a pooled standardized mortality ratio to be almost 15 times higher among those who inject drugs compared to the general population [1]. Premature mortality among this population results primarily from potentially preventable causes such as accidental overdose, infectious diseases including HIV infection, suicide and injuries [1–5].

Globally, it is estimated that one in three new HIV infections outside sub-Saharan Africa occur among PWID [6,7], and HIV infection has consistently been a risk factor for premature mortality among this population [8]. However, with the advancements in and increased availability of combination antiretroviral therapy (ART), the natural history of HIV disease has

changed, such that people infected with HIV have enjoyed substantial reductions in HIV/AIDS-associated morbidity and mortality [9–11].

Previous studies have shown that PWID with optimal access and adherence to highly active antiretroviral therapy (HAART) can benefit from HIV treatment to the same degree as other HIV-infected populations [12,13]. It is important to note, however, that PWID are often less likely to be prescribed ART, frequently because of clinicians' fears of non-compliance and the subsequent development of antiretroviral resistance [14–16]. Furthermore, in many settings PWID face numerous structural barriers to optimal HIV/AIDS care, not the least of which are financial barriers to HIV/AIDS treatment [14,17,18]. As a result of these barriers, the improved survival rates seen in HIV populations overall have been less pronounced among HIV-positive PWID [1,19–22].

Although there have been various past assessments of mortality among PWID [1,22], there are few recent studies to examine the long-term impacts of ART use and HIV infection on mortality, especially in settings with universal no-cost HIV/AIDS care and treatment. We therefore conducted the present study to determine the impact of HIV infection on mortality among PWID in a Canadian setting, where access to all HIV/AIDS care and treatment is offered free of charge through a universal health-care system.

METHODS

Study sample

The Vancouver Injection Drug Users Study (VIDUS) and AIDS Care Cohort to Evaluate Access to Survival Services (ACCESS) are open prospective cohorts of people who use drugs in Vancouver, Canada. To allow for combined analyses, the recruitment and follow-up procedures for the two studies are identical, the only substantive difference being that HIV-positive individuals who use illicit drugs other than cannabis are followed in ACCESS, whereas HIV-negative individuals who injected drugs in the month prior to the enrollment are followed in VIDUS. In both studies the primary modes of enrollment were self-referral, word of mouth and street outreach. The shared sampling and recruitment procedures for these two cohorts have been described previously [23,24].

Participants who were 18 years of age or older and resided in the greater Vancouver region were eligible to be enrolled into the two cohorts. All participants provided written informed consent. Participants were given a stipend ($20 CDN) at each study visit for their time and transportation. The study was approved by the University of British Columbia/Providence Healthcare Research Ethics Board.

Outcome measures

At baseline and at semi-annual follow-up visits, participants completed an interviewer-administered questionnaire that elicited a range of data, including demographic characteristics, information regarding injection and non-injection drug use and sexual risk behaviors. In addition, venous blood samples were drawn to test for HIV and hepatitis C virus (HCV) at baseline and at each follow-up visit for individuals whose test results were negative at the previous assessment. All participants had private interviews and were offered both pre- and post-test counseling with trained nurses. Referral for free health care was provided to those who tested positive for HIV, and these individuals were subsequently followed in the ACCESS cohort, rather than VIDUS.

We ascertained all-cause mortality rates and underlying causes of death among participants through a confidential record linkage with the British Columbia Vital Statistics Agency, the centralized mortality registry for the province of British Columbia. The provincial Vital Statistics database recorded causes of death according to the International Classification of Diseases, 10th edition (ICD-10).

The present study included individuals who reported injection drug use in the previous 6 months at baseline and completed at least one follow-up visit between May 1996 and December 2011. To avoid potential bias relating to long durations between the last study visit, where HIV status and behavioral information were assessed, and the date of death (i.e. loss to regular follow-up), individuals who were identified as deceased more than 24 months after the last follow-up visit were treated as censored on the date of the last follow-up and only considered in subanalyses.

The primary end-point in this analysis was all-cause mortality. The primary explanatory variable of interest was HIV serostatus (positive versus negative), and this was treated as a time-updated covariate based on semi-annual HIV testing. Potential confounders that were considered included: gender (male versus female), age (per 10 years older), ethnicity (Caucasian versus other), homelessness (yes versus no), daily heroin injection (yes versus no), daily cocaine injection (yes versus no), daily non-injection cocaine use (yes versus no), years since first injection (per year longer), HCV serostatus (positive versus negative), sex work involvement (yes versus no), enrollment in methadone maintenance therapy (yes versus no) and calendar year (4-year intervals). With the exception of gender and ethnicity, all other variables were measured at each semi-annual follow-up visit and were treated as time-updated. All behavioral variables referred to the participant's behavior in the 6 months prior to the interview. Sex work involvement was defined as

exchanging sex for money, gifts, food, shelter, clothes, etc., as in a previous study [25].

Statistical analyses

First, we compared the baseline characteristics of participants using the χ^2 test (for binary measures) and the *t*-test (for continuous measures). All-cause mortality rate and 95% confidence intervals (CI) were then calculated using the Poisson distribution. Survival probabilities for baseline HIV-negative and -positive participants were estimated using the Kaplan–Meier product–limit method, and compared using the two-sample log-rank test.

We then used Cox proportional hazards regression to examine bivariate associations between each explanatory variable and the time to all-cause mortality. We subsequently used Cox proportional hazards regression to develop a fixed multivariate model, which included HIV serostatus and all the covariates to account for potential confounding.

To determine if the independent effect of HIV serostatus on all-cause mortality has changed over time, we subsequently tested for significant interactions between HIV serostatus and calender year. The adjusted hazard ratios and 95% CIs for HIV serostatus over time were presented graphically, with the follow-up period divided into 4-year intervals.

ART adherence

In order to determine the potential effect of ART adherence on mortality among those who were HIV-positive, we calculated mortality rates for those who were HIV-positive and had ≥95% ART adherence and compared them with the mortality rates of the persistently HIV-negative participants. We selected ≥ 95% adherence as previous studies have shown that ART adherence rates of ≥95% are an important predictor of survival [9] and slower progression of disease [26], and are also associated with improved virological and immunological outcomes [27–29]. Data on HIV treatment were obtained from the British Columbia Centre for Excellence in HIV/AIDS Drug Treatment program, as described elsewhere [13]. In brief, information from a province-wide centralized ART pharmacy provides complete information on all antiretroviral medications dispensed to all participants during the study period. We measured adherence to therapy using pharmacy refill data. We have previously demonstrated the clinical validity of these pharmacy refill data and have shown that they predict virological suppression [27,30] and survival reliably [9,13].

Causes of death

A subanalysis was conducted where we examined the cause of death according to ICD-10 classification among those patients who were HIV-positive in order to examine specifically trends in mortality over time. Causes of death were classified into three groups: HIV-related causes of death (ICD-10 codes: B20–24 and R99 with descriptions 'HIV' or 'HIV related' in the community follow-up record), accidental causes of death (including overdoses, suicides and homicides) and non-AIDS-related causes. In order to examine if there has been a change in the number of deaths related to infectious etiologies compared to non-infectious causes over time, we also classified deaths in the non-AIDS-related group as either infectious or non-infectious and examined trends over time.

All statistical analyses were performed using SAS software version 9.3 (SAS Institute, Cary, NC, USA). All *P*-values were two-sided.

RESULTS

Study sample

A total of 2597 eligible individuals were recruited between May 1996 and December 2011, among whom 314 (12.1%) were ineligible due to the lack of follow-up visit information to ascertain behavioral or biological information. In comparing the study sample to those that were excluded for this reason, the excluded sample was younger and was more likely to be homeless, to be HCV-positive and had shorter time since first injection (all $P < 0.05$), but there was no difference by HIV status ($P = 0.28$). The mortality rate for the excluded sample was 0.44 (95% CI = 0.25–0.77) deaths per 100 person-years.

In total, 2283 individuals were included in the present analyses and were followed for a median of 60.9 months [interquartile range (IQR) = 34.4–113.1]. Table 1 shows the characteristics of the cohort stratified by HIV serostatus at baseline. At baseline, 622 (27.2%) were HIV-positive, and 1925 (84.3%) were HCV-positive. Compared to HIV-negative individuals, those who were HIV-positive at baseline were more likely to be older, to participate in a methadone program, to have a longer time since first injection and to be coinfected with HCV. They were less likely to be Caucasian and to inject heroin daily.

Mortality rates

During the study period, 179 (7.8%) individuals seroconverted to HIV and 491 (21.5%) individuals died, for an incidence density of mortality of 3.23 (95% CI = 2.96–3.52) deaths per 100 person-years. Figure 1 shows the results of the Kaplan–Meier analysis of time to all-cause mortality stratified by HIV serostatus at baseline. As shown, HIV-positive individuals were significantly more likely to die during follow-up than HIV-negative individuals ($P < 0.001$).

Table 1 Baseline characteristics of the study sample stratified by HIV serostatus at baseline ($n = 2283$).

		HIV serostatus			
Characteristic	*Total n (%)*	*HIV-positive 622 (27.2)*	*HIV-negative 1661 (72.8)*	*Odds ratio[d] (95% CI)*	*P-value*
Gender					
Male	1522 (66.7)	402 (64.6)	1120 (67.4)	0.88 (0.73–1.07)	0.213
Female	761 (33.3)	220 (35.4)	541 (32.6)		
Age, in years (mean, SD[c])	36.9 (9.7)	38.9 (9.1)	36.2 (9.8)	2.7 (1.9–3.6)[b]	<0.001
Ethnicity					
Caucasian	1395 (61.1)	359 (57.7)	1036 (62.4)	0.82 (0.68–0.99)	0.043
Other	888 (38.9)	263 (42.3)	625 (37.6)		
Homelessness[a]					
Yes	510 (22.3)	137 (22.0)	373 (22.5)	0.98 (0.79–1.23)	0.910
No	1769 (77.5)	481 (77.3)	1288 (77.5)		
Sex work involvement[a]					
Yes	538 (23.6)	164 (26.4)	374 (22.5)	1.23 (1.00–1.52)	0.059
No	1737 (76.1)	456 (73.3)	1281 (77.1)		
Daily heroin injection[a]					
Yes	882 (38.6)	164 (26.4)	718 (43.2)	0.47 (0.38–0.57)	<0.001
No	1396 (61.2)	458 (73.6)	938 (56.5)		
Daily cocaine injection[a]					
Yes	711 (31.1)	204 (32.8)	507 (30.5)	1.11 (0.91–1.35)	0.335
No	1558 (68.2)	416 (66.9)	1142 (68.8)		
Daily non-injection cocaine use[a]					
Yes	546 (23.9)	161 (25.8)	385 (23.2)	1.16 (0.94–1.43)	0.186
No	1734 (76.0)	460 (74.0)	1274 (76.7)		
Enrollment in a methadone program[a]					
Yes	514 (22.5)	189 (30.4)	325 (19.6)	1.80 (1.46–2.22)	<0.001
No	1759 (77.1)	430 (69.1)	1329 (80.0)		
Years since first injection, in years (mean, SD[c])	15.6 (10.7)	17.2 (10.3)	15.0 (10.8)	2.2 (1.2–3.2)[b]	<0.001
HCV serostatus					
Positive	1925 (84.3)	591 (95.0)	1334 (80.3)	4.67 (3.19–6.84)	<0.001
Negative	358 (15.7)	31 (5.0)	327 (19.7)		

[a]Behaviors in the last 6 months. [b]Difference between means. [c]SD = standard deviation. [d]Comparisons were made as HIV-positive versus HIV-negative. CI = confidence interval; HCV= hepatitis C virus.

Table 2 shows the results of the bivariate and multivariate Cox regression analyses of all-cause mortality. In the multivariate analysis, after adjustment for potential confounders, HIV seropositivity remained associated independently and positively with time to all-cause death [adjusted hazard ratio (AHR) = 3.15, 95% CI = 2.59–3.82]. Other variables that were associated independently and positively with time to all-cause mortality included age (AHR = 1.43, 95% CI = 1.23–1.66, per 10 years older), longer time since first injection (AHR = 1.01, 95% CI = 1.00–1.03, per year longer) and homelessness (AHR = 1.16, 95% CI = 0.90–1.50), while participation in a methadone maintenance program (AHR = 0.78, 95% CI = 0.65–0.95) was associated negatively with time to all-cause mortality.

Mortality over time

In a multivariate analysis, calendar year was associated independently and negatively with time to all-cause death. Using the calendar year interval of 1996–99 as a reference group, statistically significant reductions in all-cause mortality were seen in the year intervals of 2000–03, 2004–07 and 2008–11. However, no statistically significant interaction was found with HIV serostatus and calendar year ($P = 0.640$). As shown in Fig. 2, the independent effect of HIV serostatus on mortality did not change significantly when the adjusted hazard ratios were examined graphically over time. In subanalyses (data available from the corresponding author), we found that adjusting for cohort of recruitment did not confound the effect of other covariates.

ART adherence

The overall mortality rate for all HIV negative participants was 2.11 (95% CI = 1.85–2.40) deaths per 100 person-years, while the mortality rates for HIV-positive participants with ≥95% adherence to ART was 4.60 (95% CI = 3.65–5.79) deaths per 100 person-years.

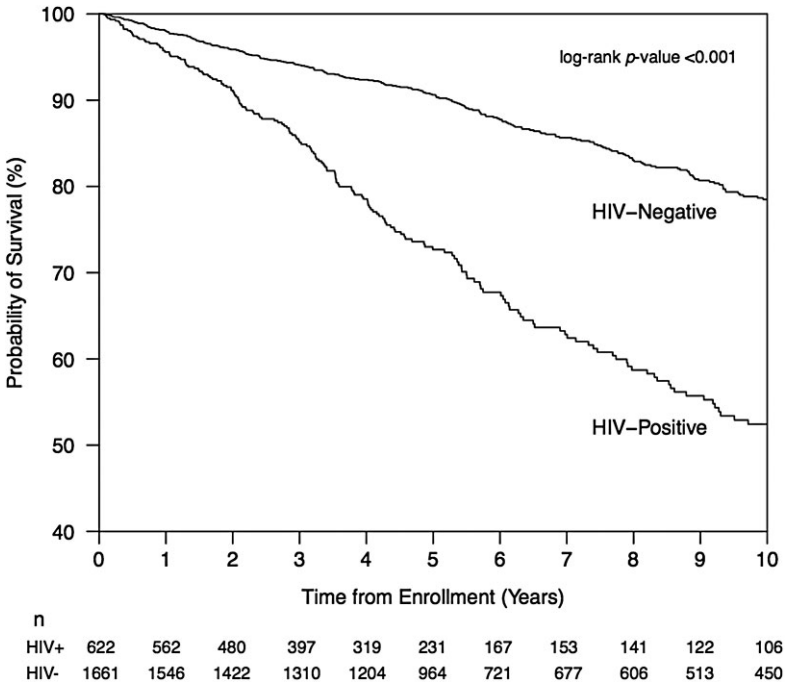

Figure 1 Kaplan–Meier survival curve showing cumulative survival probability from all-cause mortality, stratified by baseline HIV seropositivity

Table 2 Bivariate and multivariate Cox proportional hazard regression analyses of the time to all-cause mortality among people who inject drugs in Vancouver, Canada ($n = 2283$).

	Unadjusted hazard ratio (HR)			*Adjusted hazard ratio (AHR)*[b]		
Variable	*HR*	*95% CI*	*P-value*	*AHR*	*95% CI*	*P-value*
HIV serostatus[a] (positive versus negative)	2.88	2.41–3.45	<0.001	3.15	2.59–3.82	<0.001
Gender (male versus female)	1.10	0.91–1.32	0.339	0.96	0.78–1.18	0.683
Ethnicity (Caucasian versus other)	1.06	0.89–1.27	0.499	1.10	0.91–1.34	0.330
Sex work involvement[a] (yes versus no)	0.77	0.57–1.04	0.091	0.94	0.67–1.31	0.699
Daily heroin injection[a] (yes versus no)	0.80	0.64–1.01	0.057	0.91	0.72–1.15	0.420
Daily cocaine injection[a] (yes versus no)	1.43	1.14–1.79	0.002	1.21	0.96–1.53	0.104
Daily non-injection cocaine use[a] (yes versus no)	0.89	0.73–1.08	0.235	1.05	0.84–1.30	0.690
Years since first injection (per year longer)	1.02	1.01–1.03	<0.001	1.01	1.00–1.03	0.050
HCV serostatus[a] (positive versus negative)	1.94	1.26–3.00	0.003	0.92	0.57–1.46	0.711
Calendar year						
1996–99	1.00			1.00		
2000–03	0.54	0.38–0.79	0.001	0.56	0.38–0.82	0.003
2004–07	0.58	0.39–0.85	0.006	0.61	0.40–0.94	0.023
2008–11	0.33	0.22–0.48	<0.001	0.28	0.19–0.40	<0.001

[a]Behaviors in the last 6 months; [b]also adjusted for age, homelessness and enrollment in methadone. CI = confidence interval; HCV= hepatitis C virus.

Despite having ≥95% adherence to ART, the HIV-positive participants in this group continued to have an increased risk of death [hazard ratio (HR) = 2.17, 95% CI = 1.65–2.85], compared to those who were HIV-negative.

Causes of death

We then grouped causes of death among HIV-positive individuals as defined a priori into three mutually exclusive groups: HIV-related, accidental (including overdoses) and non-AIDS-related causes. As shown in Fig. 3, HIV-related mortality rates fell from a high of 27.29 deaths (95% CI = 19.32–38.53) per 1000 person-years in the 1996–99 period to 16.46 deaths (95% CI = 11.10–24.39) per 1000 person-years in the 2008–11 period. Rates of accidental death fell from 12.79 deaths (95% CI = 7.71–21.22) per 1000 person-years in the 1996–99 period to 8.56 deaths (95% CI = 4.97–14.74) per 1000 person-years in the 2008–11 period. Finally, non-AIDS-related mortality rates rose from 8.53 deaths (95%

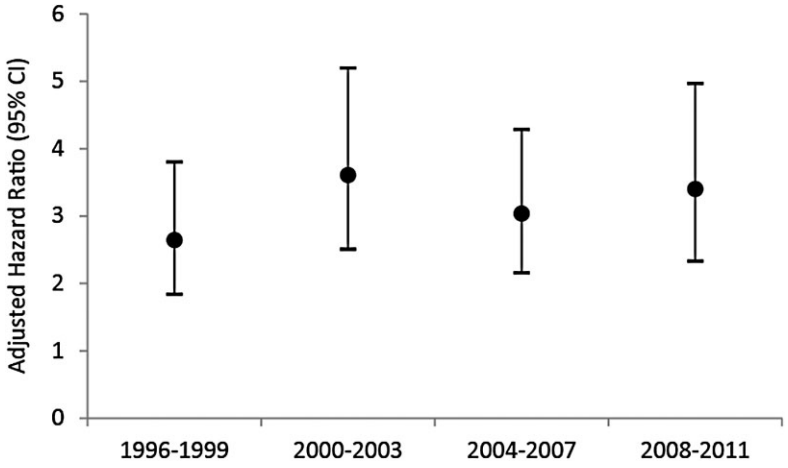

Figure 2 Adjusted hazard ratios for HIV seropositivity to all-cause mortality by 4-year intervals. Adjusted for age, homelessness, sex work involvement, daily heroin injection, daily cocaine injection, time since first injection, hepatitis C virus infection and participation in a methadone maintenance program

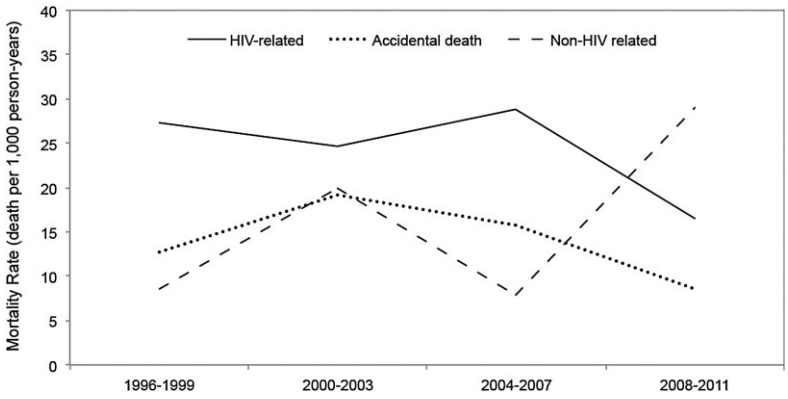

Figure 3 Causes of death among HIV-positive participants between 1996 and 2011

CI = 4.59–15.85) per 1000 person-years in the 1996–99 period to 28.96 deaths (95% CI = 21.67–38.71) per 1000 person-years in the 2008–11 period. Although there was a high prevalence of HCV infection among the total cohort (84.3%), we observed only three deaths among the HIV-negative group and five deaths among the HIV-positive group that were attributable to HCV infection throughout the study period.

Of those classified as non-AIDS-related causes, the primary underlying causes of death included infections (24.7%), non-AIDS-defining neoplasms (15.1%), respiratory disease (11.0%), cerebrovascular disease (8.2%) and cardiovascular disease (5.5%). Nineteen of the deaths in this category (26.0%) were specified as 'other ill-defined and unspecific cause mortality'. The remaining causes of death contributed individually to less than 5% of mortality in this category. Among those classified in the non-AIDS-related group, we saw a decline in the number of deaths from infectious etiologies during the study period, with 5.99 deaths (95% CI = 2.86–12.58) per 1000 person-years in the 1996–99 calendar year interval to 2.63 (95% CI = 0.99–7.03) deaths per 1000 person-years in the 2008–11 calendar year interval. There was a steady increase in deaths from non-infectious causes during the study period, from 2.57 deaths (95% CI = 0.83–7.96) per 1000 person-years in 1996–99 calendar year interval to 26.33 deaths (95% CI = 19.43–35.67) per 1000 person-years in the 2008–11 calendar year interval.

DISCUSSION

The present study demonstrated that, among a long-standing sample of PWID, HIV-positive individuals were at a significantly increased risk of death compared to those who were HIV-negative, even after consideration of age, ART adherence and other important risk factors for mortality. Our study also demonstrated that although all-cause mortality rates have declined substantially during the study period, the effect of HIV infection on mortality has been persistent and largely unchanged. This has occurred despite free health-care services and free ART through universal coverage for all HIV/AIDS care. Among HIV-positive individuals who died during the study period, we observed a marked shift away from deaths from AIDS-related etiologies (i.e. AIDS-defining illnesses) and accidental deaths (including overdoses) to deaths from other causes (i.e. non-AIDS-defining malignancies, respiratory disease, cerebrovascular disease as well as cardiac disease). While the proportion of deaths

related to chronic etiologies appears to be rising among people with HIV, close to one-quarter of the non-AIDS-related deaths in our study were related to infectious causes, which may be a reflection of HIV-positive PWID being at elevated risk of non-AIDS-associated infectious diseases [31].

Our findings showing changing patterns in causes of death among HIV-positive PWID are congruent with the previous literature that has focused primarily on groups other than PWID [32]. Specifically, recent evidence suggests that HIV-positive individuals who have demonstrated viral suppression on ART continue to have a higher than expected risk for comorbidities that are seen commonly in an aging HIV-negative population, including cardiovascular disease, renal disease, liver disease and non-AIDS-related cancers [32–35]. This suggests that HIV infection, even when well managed with ART, probably produces chronic inflammation which contributes to increased atherosclerotic risk [34,36]. Furthermore, cumulative exposure to ART over decades can be associated with metabolic changes that may increase the risk of cerebrovascular disease, including body fat redistribution (central lipoaccumulation and peripheral lipoatrophy), as well as insulin resistance, diabetes and hyperlipidemia [37]. An important consideration for people living with HIV with a history of injection drug use is related to other life-style issues such as tobacco use [38,39]. While past studies have shown that individuals with a history of illicit drug addiction (e.g. heroin) are amenable to smoking cessation strategies [40], this intervention is commonly overlooked in this population [41].

Our findings of declining overdose deaths over the study period may be related to improved harm-reduction strategies in the Vancouver area. Previous literature has shown that the opening of Insite, a supervised injection facility in Vancouver's Downtown Eastside, was associated with a significant decline in the number of fatal overdose deaths in the surrounding neighborhood [42]. Additionally, interaction with the staff and nurses at harm reduction services provides people who inject drugs with an opportunity to seek medical attention, for example for acute infections before they become life-threatening, [43]. Additionally, previous studies among this cohort have observed a pattern in reduced injection drug use [44] in favor of increased crack smoking [45], which may also contribute to the decreased overdose deaths observed in this study. Finally, the number of patients enrolled in methadone maintenance therapy has increased in British Columbia, Canada over time [46], an intervention which has been shown previously to decrease mortality rates [47,48].

Our study has several limitations. First, as the study was not recruited at random, our findings may not be generalizable to all PWID. Secondly, the self-reported data may be affected by reporting biases, including recall bias and socially desirable responding. However, we note that our end-points were based on laboratory (i.e. HIV infection) and mortality data, and self-reported data have been commonly used to control for potential confounding in observational studies involving PWID and found to be valid [49]. Thirdly, as with all observational studies, the relationships between the explanatory variables and outcome assessed may be under the influence of unmeasured confounding. While we sought to address this bias with multivariate adjustment of the key demographic and behavioral predictors of survival, there may be residual confounding. For example, we were unable to control for tobacco use in this study which, as mentioned earlier, contributes to increased morbidity and mortality among PWID who are HIV-positive [39]. Fourthly, mortality rates may have been underestimated, as participants who died outside the province were not included in the provincial registry and were thus not accounted for. However, previous studies have shown that migration rates among drug users are relatively low in this setting [50]. Finally, when examining the causes of death, more than one-quarter of patients were specified as dying from 'other ill-defined and unspecific cause mortality', making it difficult to assess true trends in all causes of death.

Despite advances in the availability and tolerability of ART, HIV infection continues to play a significant and ongoing role on mortality rates among PWID in this setting. These findings highlight the necessity to continue to promote and implement HIV prevention services among this population. Of those who are HIV-positive, an increasing proportion of deaths was attributable to infections as well as chronic disease. This underscores the importance of encouraging safe injection practices to prevent infections, as well as engaging in chronic disease management and other health promotion (e.g. smoking cessation) activities in these patients. Once patients are established on ART, treatment priorities must shift to a preventative approach for chronic disease while remaining closely attuned to infections and illnesses associated with HIV infection.

Declaration of interests

None.

Acknowledgements

The authors thank the study participants for their contribution to the research, as well as current and past researchers and staff. The study was supported by the US National Institutes of Health (VIDUS: R01DA011591). This research was undertaken, in part, thanks to funding for a Tier 1 Canada Research Chair in Inner City Medicine, which supports Dr Evan Wood. Dr Milloy is

supported by the Canadian Institutes of Health Research and the Michael Smith Foundation for Health Research. Dr Hayashi is supported by the Canadian Institutes of Health Research.

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