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ORIGINAL PAPER

Association of History of Injection Drug Use with External Cause-Related Mortality Among Persons Linked to HIV Care in an Urban Clinic, 2001–2015

Kanal Singh[1] · Geetanjali Chander[2] · Bryan Lau[1] · Jessie K. Edwards[3] · Richard D. Moore[1,2] · Catherine R. Lesko[1]

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Abstract
High mortality rates among persons with HIV with a history of injection drug use (PWID) are thought to be driven in part by higher rates of external cause-related mortality. We followed 4796 persons aged 18–70 engaged in continuity HIV care from 2001 to 2015 until death or administrative censoring. We compared cause-specific (csHR) and subdistribution hazards (sdHR) of death due to external causes among PWID and persons who acquired their HIV infection through other routes (non-IDU). We standardized estimates on age, sex, race, and HIV-related health status. The standardized csHR for external cause-related death was 3.57 (95% CI 2.39, 5.33), and the sdHR was 3.14 (95% CI 2.16, 4.55). The majority of external cause-related deaths were overdose-related and standardized sdHR was 4.02 (95% CI 2.40, 6.72). Absolute rate of suicide was low but the csHR for PWID compared to non-IDU was most elevated for suicide (6.50, 95% CI 1.51, 28.03). HIV-infected PWID are at a disproportionately increased risk of death due to external causes, particularly overdose and suicide.

Keywords Cause-specific mortality · Competing risks · Injection drug use · Injury-related mortality · Survival

Introduction

The advent and refinement of antiretroviral therapy (ART) for HIV over the past several decades along with increased efforts to identify newly infected individuals and link them with care have significantly reduced mortality among many persons with HIV (PWH) [1–3]. However, persons with a history of injection drug use as a risk factor for HIV acquisition (PWID) continue to have disproportionally higher mortality risk than persons infected with HIV through other routes (non-injection drug use; non-IDU) [4, 5]. The reasons for this are likely multifactorial and not entirely clear, but may be related to lifestyle behaviors more common in this population that are generally detrimental to overall heath (e.g. alcohol and illicit substance abuse, tobacco smoking) [6–9] and increased rates of non-AIDS related medical comorbidities (e.g. hepatitis C virus infection, cirrhosis, malnutrition, cardiovascular disease) [10–12]. PWID are also generally presumed to have higher risk of death than non-IDU due to external causes, including drug overdose, violence, and trauma [13, 14], as a result of higher prevalence of psychiatric comorbidities [15, 16] and greater exposure to sexual and physical violence [17, 18]. To our knowledge, this hypothesis has not been formally evaluated.

Herein, we describe the cumulative incidence (risk) and hazard of mortality due to external causes associated with a history of injection drug use among PWH who enrolled in continuity care in an HIV clinic in Baltimore, Maryland.

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✉ Catherine R. Lesko
clesko2@jhu.edu

1 Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 N Wolfe St, Baltimore, MD 21205, USA

2 Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD, USA

3 Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Methods

Study Sample

The Johns Hopkins HIV Clinical Cohort (the Cohort) is an open, longitudinal cohort of PWH aged 18 and older who established care at the Johns Hopkins HIV clinic and who consented to share their data (> 90% of all patients). PWID are notably well-represented in this cohort because Baltimore City has historically had a high rate of injection drug use and a high proportion of PWID among PWH. Collection of data on these patients and their analysis was approved by the Johns Hopkins University School of Medicine Institutional Review Board. A complete description of the cohort is available elsewhere [19].

For this analysis, we included all persons enrolled in the Cohort who were in care (defined as having had at least one clinic visit or laboratory measurement) between January 1, 2001 and August 31, 2015. Patient characteristics measured at enrollment into the Cohort include: age; sex; race, defined as black, white, or other; prior AIDS diagnoses; history of antiretroviral use; and most likely route of HIV acquisition, including male-to-male sexual contact (MSM) and history of injection drug use (IDU). Routes of HIV acquisition are self-reported by patients in a structured interview and are not mutually exclusive. Our primary exposure of interest was reporting a history of IDU as a likely route of HIV acquisition; we designate this subset of the sample "PWID", in contrast to patients who did not report IDU as a likely route of HIV acquisition whom we designate "non-IDU". We classified patients as ART experienced if they had ever initiated ≥ 3 antiretroviral medications on the same day. CD4 cell count (cells/μL) and HIV viral load (copies/mL) were the measurements most proximal to Cohort enrollment that were obtained within a window of 6 months prior to 1 month following start of follow-up.

Outcome

Our primary outcome of interest was external cause-related mortality. Deaths are routinely ascertained through regular matches against the Social Security Death Index or National Death Index Plus (NDI Plus). Historically, deaths among cohort members were reviewed by clinic physicians and assigned an underlying cause using ICD-9 coding. Starting in 2000, underlying causes of death based on ICD-10 codes have been available from death certificate on file with NDI Plus. ICD-10 codes were available for most deaths (98%). However, when both ICD-9 and ICD-10 codes were available for a particular death (37% of deaths), we assigned cause of death based on the ICD-9 code because ICD-9 codes were assigned locally and with access to the patients' complete medical history while they were in care within the Johns Hopkins Medical system. In contrast, ICD-10 codes came from the death certificate and may have been assigned with varying degrees of access to patients' medical history. Causes of death were classified as "external" in accordance with classifications by the National Center for Health Statistics [20] and included deaths due to accident, suicide, assault, and "other external causes." The majority of deaths classified as due to "other external causes" were overdose-related deaths. Twenty-five individuals who died during the study period (< 2% of all deaths) were missing cause of death. We multiply imputed cause of death for these individuals along with missing covariates, based on the analysis described below [21, 22].

Statistical Analyses

Study participants contributed follow-up time from Cohort enrollment or first follow-up clinical encounter after January 1, 2001 (for persons who enrolled prior to 2001, to ensure they were engaged in care at least once during the study period) until death or administrative censoring at age 70 or end of administrative follow-up on August 31, 2015. For analyses, the time origin was age 18 and the time metric was age in years. Patients who enrolled in the Cohort after age 18 were included as late entries. This analysis allowed us to describe the risk of external cause-related death as a function of age and to tightly control for age as a confounder of the association between history of IDU and external cause-related death [13, 23].

We fit Cox proportional hazard models [24] to estimate cause-specific hazard ratios (csHR) and Fine and Gray subdistribution proportional hazard models to estimate subdistribution hazard ratios (sdHR) for cause-specific mortality [25]. Cause-specific hazard ratios compare the instantaneous rates of an event for two groups among those who remain alive and under follow-up. The subdistribution hazard ratios correlate directly with cumulative incidence (risk) of external cause-related mortality when the risk of other causes of death (i.e., natural causes of death) is high and may differ between the two groups (as is the case for this study). We also generated Aalen-Johansen risk functions [26, 27]. We summarize differences between the risk functions by estimating risk differences (RD) and risk ratios (RR) comparing persons with and without a history of IDU at 35, 45, 55 and 65 years.

To control for possible confounders of the association between history of IDU and external cause-related mortality, we also report csHRs, sdHRs, RDs and RRs standardized to the distribution of baseline patient characteristics in the entire sample. We standardized using inverse probability weights [5, 28, 29]. We estimated the weights using predicted probabilities from a logistic regression for probability of reporting a history of IDU conditional on sex, age, race, MSM, history of ART or AIDS upon enrollment into the Cohort, and baseline CD4 cell count and viral load. We modeled age and CD4 cell count with restricted quadratic splines with knots at the 5th, 35th, 65th and 95th percentiles [30]. We dichotomized viral load into detectable (> 400 copies/mL) or undetectable (≤ 400 copies/mL). We standardized weights by the marginal probability of reporting the history of IDU that was reported.

Missing baseline covariate data were presumed to be missing at random (MAR). We dealt with missing data by multiply imputing missing values based on all patient demographics and HIV-related clinical variables (Table 1), auxiliary variables measured at cohort entry (current smoking, alcohol use, cocaine use, heroin use, BMI, hepatitis C virus infection), age at Cohort entry, age at the end of follow up, status at end of follow up (i.e. death due to external cause, death to competing cause, or administrative censoring) and the estimated cumulative hazards of external cause-related mortality and mortality due to a competing cause at the time the individual exited follow-up [31, 32]. We generated 40 imputed data sets using multiple imputation by chained equations (analysis conducted with IVEware Version 0.3 with SAS [33]), conducted the analyses outlined above in each of those data sets, and then combined the estimates using Rubin's method [34].

All analyses were conducted using SAS version 9.4 (Cary, NC).

Table 1 Baseline characteristics of 4796 persons with HIV enrolled in continuity care the Johns Hopkins HIV Clinical Cohort, 2001–2015, stratified by history of injection-drug use as an HIV acquisition risk factor

	PWID	Non-IDU	Total
N	1665	3131	4796
Male sex	1105 (66)	2056 (66)	3161 (66)
Age[a]	43 (38, 49)	39 (32, 46)	41 (35, 47)
Race			
Black	1365 (82)	2245 (72)	3610 (75)
White	279 (17)	733 (23)	1012 (21)
Other	21 (1)	153 (5)	174 (4)
MSM	141 (8)	1172 (37)	1313 (27)
History of ART[b]	1079 (65)	1939 (62)	3018 (63)
History of AIDS	548 (33)	901 (29)	1449 (30)
CD4 cell count[a]	289 (120, 485)	309 (131, 506)	300 (127, 501)
< 50	195 (14)	422 (15)	617 (14)
50–199	329 (23)	556 (19)	885 (21)
200–349	334 (23)	627 (22)	961 (22)
≥ 350	570 (40)	1280 (44)	1850 (43)
Missing	237	246	483
HIV Viral Load ($\log_{10}$ copies/mL)[a]	3.88 (2.60, 4.82)	3.92 (2.60, 4.88)	3.91 (2.60, 4.87)
≤ 400 copies/mL	930 (68)	1914 (68)	2844 (68)
Missing	288	334	622

ART antiretroviral therapy, *HIV* human immunodeficiency virus, *MSM* men who have sex with men, *PWID* persons who inject drugs (as a risk factor for HIV acquisition)

[a]Median (IQR)

[b]History of ART use defined as having initiated ≥ 3 antiretroviral medications on the same day

Secondary Analyses

To investigate the potential impact that misclassification of cause of death may have had on our results, we present RDs at 35, 45, 55 and 65 years comparing PWID and non-IDU, corrected for measurement error [35]. To do this, we used estimates from a prior study of the sensitivity of the death certificate for classifying deaths as injury-related or natural: 96.3 and 89.1%, respectively. The gold-standard in this study was independent review by a panel of physicians with access to all pertinent medical and legal documentation [36].

Results

The majority of the 4796 study participants were male (66%) and black (75%). Median age was 41 years (interquartile range [IQR] 35, 47). Compared with non-IDU, upon entry to care, PWID were slightly younger (median age: 39 years vs. 43 years) and a higher proportion of PWID were black (82% vs. 72%), but baseline CD4 cell count, HIV viral load, history of AIDS-defining illnesses and use of antiretroviral medications at time of study entry were comparable between the two groups (Table 1). PWID and non-IDU contributed 13,505.3 person-years and 26,659.4 person-years of follow-up to the analysis, respectively. PWID and non-IDU were followed for a median of 8.1 years (IQR 4.4, 13.8) and 7.5 (IQR 3.9, 13.6) years, respectively.

Compared to non-IDU, PWID had a higher all-cause mortality rate (50.5 vs. 22.5 per 1000 person years); the standardized HR for all-cause mortality comparing PWID and non-IDU was 2.91 (95% CI 1.92, 2.44).

PWID also had a higher external cause-related mortality rate compared to non-IDU (7.0 vs. 1.5 per 1000 person-years). The crude csHR for death from external causes comparing PWID to non-IDU was 4.71 (95% CI 3.21, 6.90). Standardization attenuated the csHR slightly, but PWID still had over three times the hazard of external cause-related mortality compared with non-IDU (standardized csHR = 3.57, 95% CI 2.39, 5.33). This higher rate of external cause-related mortality translated into an elevated risk of external cause-related mortality (despite a correspondingly high rate of mortality due to competing causes). While prior to age 30 years, there were few persons under follow-up and thus estimates of risk are unstable, from age 30 through age 70, the risk of external cause-related mortality was higher for PWID compared to non-IDU (Fig. 1). RDs and RRs summarizing the risk curves appear in Supplemental Table 1. The crude sdHR for death from external causes comparing PWID to non-IDU was 4.31 (95% CI 2.93, 6.33).

Standardization attenuated the risk of death from external causes among PWID, but PWID still had a meaningfully higher risk of external cause-related mortality than did non-IDU at all ages (Fig. 1). The standardized sdHR (which provides a summary measure of the differences between these risk curves across all of follow-up) was 3.14 (95% CI 2.16, 4.55). PWID had higher mortality rates and hazards of death of all NCHS subcategories of external cause-related mortality compared to non-IDU (Table 2). Overdose was responsible for the largest contribution to the rate of external cause-related mortality; the rate of overdose among PWID was 4.7 per 1000 person-years compared to only 0.8 overdose

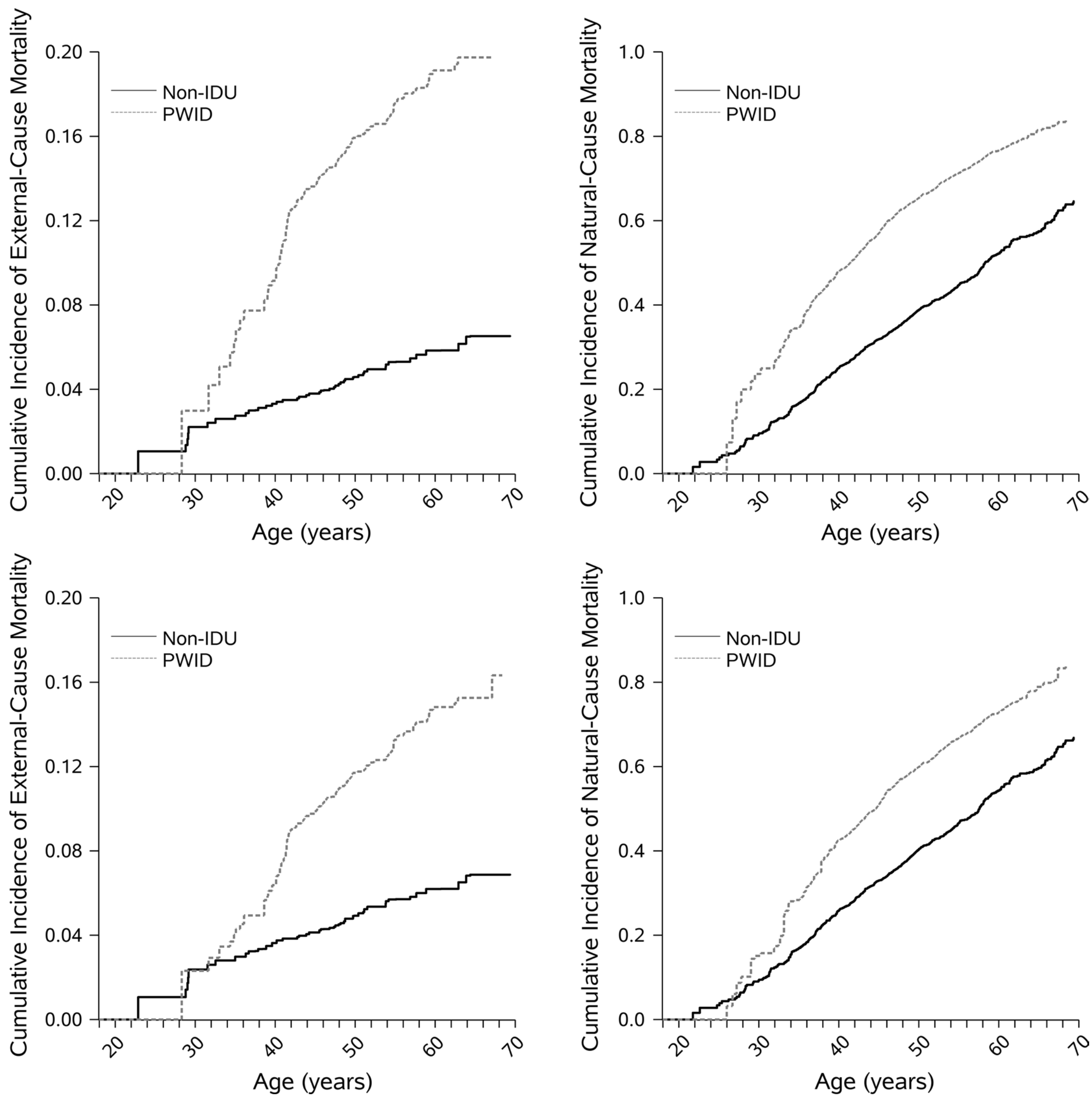

Fig. 1 Crude (top row) and standardized (bottom row) cumulative incidence curves for external cause-related mortality (left column) and natural cause-related mortality (right column) among PWID (dashed line) and non-IDU (solid line) who enrolled in the Johns Hopkins HIV Clinical Cohort, 2001–2015. Standardized on: sex, race, baseline HIV sexual transmission risk, and age, CD4 cell count, HIV viral load, prior diagnosis of AIDS, and history of ART use upon entry into the cohort

Table 2 Overall and cause specific mortality rates and cause-specific (csHR) and subdistribution hazard ratios (sdHR) among 4796 HIV-infected persons in the Johns Hopkins HIV Clinical Cohort from 2001 to 2015, stratified by history of injection drug use as HIV acquisition risk

	PWID		Non-IDU		Crude csHR	Standardized[b] csHR	Crude sdHR	Standardized[b] sdHR
	Events	Rate[a]	Events	Rate[a]				
All-cause mortality	682	50.5	601	22.5	2.16 (1.92, 2.44)	2.91 (1.65, 2.21)	N/A	N/A
External cause-related mortality	94	7.0	41	1.5	4.71 (3.21, 6.90)	3.57 (2.39, 5.33)	4.31 (2.93, 6.33)	3.14 (2.16, 4.55)
Accident	11	0.8	11	0.4	1.81 (0.76, 4.31)	1.36 (0.56, 3.31)	1.51 (0.64, 3.61)	1.12 (0.45, 2.83)
Suicide	6	0.4	3	0.1	3.38 (0.81, 14.00)	6.50 (1.51, 28.03)	3.08 (0.73, 12.92)	5.54 (1.34, 23.01)
Assault	10	0.7	5	0.2	4.64 (1.47, 14.63)	2.65 (0.86, 8.21)	4.27 (1.34, 13.65)	2.30 (0.79, 6.67)
Overdose	63	4.7	20	0.8	6.75 (4.08, 11.18)	4.60 (2.67, 7.95)	6.31 (3.80, 10.48)	4.02 (2.40, 6.72)

Hazard ratio estimates provided with 95% confidence intervals; confidence intervals for standardized hazard ratios based on robust variance estimator

csHR cause-specific hazard ratio, *IDU* injection drug use, *PWID* persons who inject drugs (as a risk factor for HIV acquisition), *sdHR* subdistribution hazard ratio

[a]Rate per 1000 person-years; total person years was 13,505.3 among PWID, and 26,659.4 among non-IDU

[b]Standardized to marginal distribution of age, sex, race, baseline HIV sexual transmission risk, CD4 cell count, HIV viral load, prior diagnosis of AIDS and history of ART use using inverse probability of exposure weighting

deaths per 1000 person-years among non-IDU (standardized sdHR = 4.02, 95% CI 2.40, 6.72). The highest relative contribution to external cause-related mortality comparing PWID to non-IDU was for suicides (standardized sdHR = 5.54, 95% CI 1.34, 23.01), although the absolute rate of suicides was low (0.4 per 1000 person-years for PWID and 0.1 per 1000 person-years for non-IDU).

Secondary Analyses

Accounting for imperfect classification of causes of death as due to external cause or not [36] lowered estimates of the risk of external cause-related mortality in both PWID and non-IDU and generally attenuated differences in risk associated with history of IDU as an HIV acquisition risk factor, but increased relative risk (because the referent risk was smaller) (Supplementary Table 2). Overall, even if underlying causes of death were recorded incorrectly on the death certificate (assuming rates of misclassification were non-differential with respect to history of IDU), our conclusions about the higher risk and rate of external cause-related mortality among PWID were not altered.

Discussion

In this cohort of persons in continuity care for HIV, history of IDU was strongly associated with both a higher rate and a higher risk of external cause-related mortality. This association persisted even after adjustment for key confounders of sex and race and age, CD4 cell count, HIV viral load, history of clinical AIDS, and ART use upon entry into HIV care. Our results are comparable to prior studies that examined mortality among PWID [13, 37–39] and HIV-infected PWID in particular [40–42]. Risk of death due to external causes increases at a relatively early age (around 30 years old) and remains elevated throughout an individual's lifetime. To understand specific drivers of high rates of external cause-related mortality, we calculated mortality rates and hazard ratios for four distinct subcategories of external causes of death commonly used by the NCHS [20]. Unsurprisingly, the majority of deaths were due to overdose, a finding that has been previously described among both HIV-infected and uninfected persons who inject drugs [13, 38, 39, 43, 44]. We also observed elevated mortality rates and hazards among PWID due to assault and suicide, similar to prior published results data [45, 46]; our estimated HRs are fairly imprecise because there were small numbers for specific causes of death in our cohort, but the data are still consistent with an elevated risk of mortality among PWID from any of the subcategories of external causes of death when compared to non-IDU.

One notable limitation of our study is the potential for misclassification of cause of death, an inherent challenge when using cause-of-death coding data because the consistency and completeness of coding of death may from vary from site and by individual examiner [47–50]. We made several efforts to minimize these risks of bias; first, by using an accredited and universal categorization system (i.e. NCHS) we kept classifications of death consistent and comparable with prior, similar studies which generally use the same classification scheme [20]. Second, by limiting our outcome of interest specifically to externally-caused deaths we minimized the risk of misclassification as these types of deaths are plausibly less prone to adjudicator subjectivity than more complex medically-related diagnoses (where often more knowledge and/or auxiliary testing is required for an accurate death diagnosis) [51, 52]. It is possible that under the heading of externally-caused deaths, specific cause of death was misclassified, however (for example, suicides and assaults or suicides and overdoses may be difficult to distinguish without information about intent); thus results related to rates and relative hazards of specific causes of external cause-related deaths should be interpreted cautiously. Finally, our sensitivity analysis that corrected risk estimates using previously reported estimates for the sensitivity of the death certificate for identifying injury-related deaths failed to nullify our findings of increased risk of external cause-related mortality associated with history of IDU.

There are additional limitations to our analyses. Although a history of IDU was associated with an increased risk of death due to external causes in our study, this association does not reflect a causal effect of IDU. Because participants who reported a history of IDU could have ceased injecting, and those with no history of IDU at enrollment could have initiated injecting (likely a smaller number) or could be using illicit drugs through other routes of administration, our estimates likely underestimate the effect of illicit drug use on external cause-related mortality. We also did not necessarily have information on additional key confounders which would be been important to adjust for, such as a patient's history of prior medical and/or mental health comorbidities [10, 53], or other influential confounders such as socioeconomic status and income [54, 55]. However, our purpose was not necessarily to estimate a causal effect of drug use on external cause-related mortality but rather to illustrate or explain part of the disparity in all-cause mortality rates observed for persons with a history of IDU in prior studies.

Additionally, our study was restricted to PWH who were diagnosed and who engaged in continuity care in the Johns Hopkins HIV Clinic. PWID who are infected with HIV are less likely to be undiagnosed than persons infected through other routes [56], but more likely to present to care for the first time with a low CD4 cell count ("delayed" or "late presentation to care") [57]. If PWID who are infected with HIV have a higher mortality rate prior to diagnosis and entry to care than non-IDU (as seems plausible based on the literature), our estimates of association may be closer to the null than they would have been had we been able to follow persons from the point of HIV infection. This is because the PWID in our sample would be "heartier" by nature of having been those who survived long enough to enter HIV care.

Our analyses have several key strengths. First, we believe ours to be the first analysis to describe risks and hazards of external-cause death for this population accounting for other causes of death as competing events. The inclusion of cumulative incidence curves in our report increases the interpretability of our results. Second, our cohort was well-constructed to investigate the impact of external-cause related death among PWID due to the prevalence of this exposure and outcome in our study population. Third, ascertainment of death was complete within this cohort, and we were able to allow for late entries by our study design. Fourth, by using multiple imputation methods to handle missing data in lieu of a complete-case analysis, we increased our precision and made fewer assumptions about the missing data mechanisms. Our multiple sensitivity analyses also provided bounds on the assumption we made regarding cause of death.

Our study highlights the pervasive problem of external cause-related mortality among HIV-infected PWID, a population that faces a complex array of challenges likely related to their higher incidence of medical and psychiatric comorbidities, adverse health-related behaviors, and lower retention in healthcare programs, all of which may be compounded due to societal stigma [58]. Recent efforts have been made to improve health-related outcomes in this population, such as wide scaled campaigns to train healthcare workers and laypersons in the use of Naloxone as a means reverse potentially fatal cases of opioid intoxication [59, 60]. Our clinic did institute a buprenorphine program during the study period, although enrollment has not reached all patients who could potentially benefit. Additional efforts to diagnose and treat psychiatric comorbidities could be targeted towards PWID. Finally, system-wide interventions to reduce exposure to violence are needed [61]. Baltimore, Maryland has historically had high rates of violence, and in recent years, violent crime has been increasing [62]. Without other complementary interventions that address the multidimensional problems faced by PWID, solitary efforts will likely be incapable of having the impact needed to truly reduce the risk of death from external causes in this population. It is imperative that healthcare providers remain vigilant about the health risks faced by PWID and continue to educate them on ways to reduce risk of external cause-related death. Additionally, public health officials and policy makers need to help create regulations that would foster environments with improved access and availability of necessary resources for PWID such as drug rehabilitation and mental health services.

In summary, we found that HIV-infected PWID in Baltimore are at a disproportionately increased risk of death due to external causes, particularly death from overdose. This risk persisted even after adjustment for common confounders.

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Compliance with Ethical Standards

Conflict of interest The authors declare no conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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