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A Hazard Analysis of Risk Factors of Mortality in Individuals Who Inject Drugs in Denver CO

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Abstract

Despite multiple risk factors for mortality among People Who Inject Drugs (PWID), more research is warranted that examines sub-populations within PWID. Mortality data from PWID participating in longitudinal HIV prevention research in Denver were obtained from The Colorado Department of Public Health and Environment. Risk factors for both all-cause and acute-toxicity related mortality were analyzed using Cox proportional hazards regression. Two-thousand seven individuals were interviewed at baseline. Eighty-six individuals died during the time frame of the study, 58 of which were due to acutetoxicity. Disabled (HR = 3.3, $p < 0.001$), gay/lesbian-identified (HR = 2.6, $p = 0.03$), white race/ethnicity (HR = 2.4, $p = 0.003$), and use of a shared cooker (HR = 2.1, $p = 0.01$) were important adjusted risk factors. These suggest that drug and HIV interventions should utilize techniques that can address the needs of marginalized populations in addition to HIV drug risk behaviors.

Keywords

PWID; Mortality risk; Disabled; Gay/lesbian identification

Introduction

People Who Inject Drugs (PWID) may be as much as a 20–30 times more likely to experience premature death than their non-drug-using peers [1–4] and acute-toxicity (i.e., drug overdose) is a common cause of death among PWID [2, 4–7]. While acute-toxicity is common, other causes of premature death are prevalent among PWID as well, including but not limited to accidents [5], suicide [8, 9], and HIV-related mortality [10, 11]. Research has also identified important predictors of all-cause and acute-toxicity mortality relevant to PWID, such as sex work [12], unstable housing and/or homelessness [13], polydrug use [14, 15], bisexual orientation [16], and exiting methadone or other drug replacement treatment modalities [17, 18]. PWID also experience increased risk of acute-toxicity mortality after

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Conflict of interest All authors have no conflict of interests to declare.

Compliance with Ethical Standards

Ethical Approval All procedures performed were in accordance with the ethical standards of the Colorado Multiple Institutional Review Board 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.

release from incarceration [19, 20] and male gender is commonly identified as a mortality risk factor [21]. Furthermore, PWID frequently struggle with socioeconomic-related health factors, such as limited access to healthcare and treatment services [22–24] and lack of regular or stable employment, which are all related to premature death in non-drug using populations [25].

Disability, in particular, may be a substantial contributor to mortality burden among PWID, as it is in the general population [26]. PWID suffer from a disproportionately high disability-related disease burden compared to other illicit drug users [27]. Despite the links between PWID and disability, little has been reported on mortality among disabled PWID. With the increase of abuse of prescription drugs following the treatment of injury or chronic pain [28, 29] and the abuse of prescription opiates in young people leading to the injection of illicit drugs [30], research is needed to better understand the relationship between disability and mortality in PWID.

The aforementioned characteristics have social marginalization components which could be related to elevated mortality risk in PWID, as they are in other populations. For example, sexual minorities are at risk for early mortality in the general population, which could be due in part to chronic stress related to social marginalization [31–33]. When considering the well-documented social marginalization experienced by PWID, these components warrant deeper understanding. With the exception of [16] who found an increased risk of acute-toxicity mortality in bisexual PWID [16], sexual orientation as a predictor of mortality has not been reported on extensively in PWID.

Given the elevated mortality risk that subpopulations of PWID may bear, we investigated predictors of mortality among three cohorts of PWID that participated in drug use and HIV prevention research in Denver, Colorado from 1996 to 2011. We present records-based analyses of acutotoxicity and all-cause mortality in PWID.

Materials and Methods

Participants and Mortality Classification

This was records-based research utilizing PWID and was approved by the Colorado Multiple Institutional Review Board protocol 14-1910. Three studies which aimed to reduce HIV risk-related drug behaviors among out-of-treatment injection drug users by facilitating treatment and enhancing treatment retention were conducted between 1996 and 2011. Inclusion criteria for the first two studies were identical and are as follows: injected opiates, cocaine, or methamphetamine within the previous 30 days (verified through visual inspection of recent venipuncture and urinalysis); at least 18 years of age; no drug abuse treatment in the 90-days prior to the interview; not intoxicated or impaired mentally to the extent that they cannot voluntarily consent to participate in the project and/or respond to the interview; live or reside in the geographical areas targeted for participant recruitment; not transient and no known reason (e.g. pending jail time) why they would not be available for follow-up interviews; not involved in research activities in the previous 12 months. The third study recruited opiate users specifically (although they could also use other drugs in combination with opiates) and had the following two additional inclusion criteria: willing to

meet with an Addiction Research and Treatment Services (ARTS) counselor; and did not owe back fees to ARTS of \$500 or greater for previous therapy.

Interviews assessing drug use and HIV-related risk behaviors were conducted with participants at baseline, 6 and 12 month time points. Interviewers were trained to build rapport in order to gain valid reports of behavior. In addition, questions that pertained to a particularly sensitive area (e.g., sex risk behaviors) were asked using Audio Computer-Assisted Self-Interview (ACASI), which gave participants privacy.

Mortality records were obtained from the Colorado Department of Public Health and Environment (CDPHE) and were combined with behavioral information collected during the interviews. CDPHE maintains mortality records for the state of Colorado and returned a list of participants in the three cohorts that died, including causes of death and a corresponding ICD-9/ICD-10 code. The list of deaths received from CDPHE was reviewed and deaths described as drug intoxication, toxicity, or overdose were defined for this study as acute-toxicity. These included: accidental poisoning by and exposure to: antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified (n = 1), narcotics and psychodysleptics, not elsewhere classified (n = 40), other and unspecified drugs, medicaments and biological substances (n = 15), accidental poisoning by drugs, medicinal substances, and biological (n = 1), and toxic effect of ethyl alcohol (n = 1). The analysis utilized acute-toxicity events along with all-cause mortality as primary outcomes. All-cause mortality included individuals with toxic events combined with all other causes. Mortality events were collected to fall between the final interview and the following 24 months and corresponding surviving participants were right censored at this time point for Cox proportional hazard regression models discussed further below. This time period was chosen similarly to another study [13], and to power for infrequent death events. Finally, death information was merged with potential predictor variables collected uniformly across the three projects during interviews. A time varying analysis data set including person-time intervals was created from these data to evaluate interview collected predictors as risk for mortality.

Statistical Analysis

Cox proportional hazards regression was utilized to test associations between potential predictor variables and all-cause mortality and acute-toxicity. Backward elimination was utilized to arrive at parsimonious models. All included regression coefficients also met assumptions for Cox proportional hazards, as assessed through Schoenfeld residual analyses. Additionally, we calculated a crude mortality rate (CMR) by summing events and dividing by person-time contributed in the study and used a Poisson approximation to calculate 95% confidence intervals due to rare events. Significance tests in the Cox regression were conducted via an overall Wald test and z statistics and are shown where appropriate.

Time-varying and time-invariant characteristics examined included: gender, age, years of injecting, sexual orientation, employment status (employed, unemployed and disabled/unable to work), homelessness, race/ethnicity, sex work, methadone or other type of drug treatment within the last 6 months, as well as HIV drug and sex risk behaviors displayed in Table 1. Due to lack of evidence supporting unique risk in narrow classifications, race/

ethnicity was collapsed to compare white to non-white individuals. Disability was defined by self-report if respondents endorsed “unable to work due to disability”. Age was categorized into less than 25, 25–35, 36–45, and greater than 45 for regression analyses to parallel age classification utilized in a similar report [34]. Previous-30 day drug use including heroin, alcohol, marijuana, cocaine and injected cocaine, and speedballs (i.e., injected heroin and cocaine) were also explored. Additionally, cohort effects were examined with the inclusion of a covariate identifying the specific project the individual participated in.

Given the differences in participation criteria and drug use behaviors among the cohorts, interactions by cohort were tested as well. Notably, heroin use in the 2006–2011 cohort 3 was higher where 79.4% reported daily use, while 48.2% reported daily use in cohort 1 and 47.0% in cohort 2. Due to significant interactions and important similarities, cohorts 1 and 2 were combined for stratified analyses on all-cause mortality. Follow-up reduced models were developed for the combined cohorts 1 and 2, and for cohort 3 independently. R version 3.3.0 (<https://cran.r-project.org/>) was used for all analyses.

Results

Table 1 displays the baseline characteristics of the population under study (N = 2007). Participants were 71% male, had a mean age of 38 years, 44% were homeless, and had been injecting a mean of 17 years. Notable differences among the cohorts existed. Specifically, daily heroin injection use in cohort 3 was nearly 80%, in cohort 1 48%, and cohort 2 47% ($p < 0.001$).

Table 2 displays the all-cause mortality of subjects combined into common classes. After collapsing data, there were 58 acute-toxicity events and 86 deaths in total. There were 7 deaths with HIV/AIDS as the primary or secondary cause of death recorded and an additional 3 deaths with hepatitis C (HCV) as a primary or secondary cause. Of the acute-toxicity events, 57% involved more than one substance ($n = 33$). Individuals contributed 5338.6 person years (py) where the crude mortality rate of acute-toxicity was 1.09 (95% CI 0.81, 1.37) per 100 py and crude mortality rate of all-cause mortality was 1.61 (95% CI 1.27, 1.95) per 100 py.

Unadjusted hazard ratios for mortality due to acutetoxicity and due to all causes are presented in Table 3. Notably, unemployed due to disability (HR = 2.99, 95% CI 1.77, 5.10, $z = 4.10$, $p < 0.001$), and gay/lesbian sexual orientation (HR = 2.22, 95% CI 1.02, 4.82, $z = 2.01$, $p = 0.045$) had an unadjusted increased hazard of all-cause mortality. Only white race/ethnicity (HR = 1.76, 95% CI 1.02, 3.04, $z = 2.01$, $p = 0.044$) was an unadjusted predictor of acute-toxicity.

Multivariate hazard regression on all-cause mortality and on acute-toxicity results are presented in Tables 4 A and B. Notably, white race/ethnicity (HR = 1.79, 95% CI 1.14, 2.80, $z = 2.54$, $p = 0.011$) and inability to work due to disability (HR = 3.33, 95% CI 1.96, 5.66, $z = 4.45$, $p < 0.001$) were important adjusted risk factors for all-cause mortality and mortality due to acute-toxicity in all cohorts combined.

Interactions of cohort by ever using a shared cooker in the last 30 days ($p = 0.010$) and age group ($p = 0.003$) were important in the all-cause mortality analysis. Given this and differences highlighted in Table 1, further analyses of all-cause mortality were conducted among cohorts 1 and 2 separately from cohort 3. Tables 4 C and D highlight the stratified differences, where white race, disability, gay/ lesbian identification, and shared cooker use were independent risk factors for all-cause mortality in the combined cohorts 1 and 2. However, age group was the only adjusted mortality risk factor for cohort 3. Younger age had elevated risk, although not significant at an alpha of 0.05 ($HR = 5.31$, 95% CI 1.0, 29.0, $z = 1.93$, $p = 0.054$) over those aged 25–35. Those aged 36–45 ($HR = 5.21$, 95% CI 1.1, 24.6, $z = 2.09$, $p = 0.037$), and those aged more than 45 ($HR = 9.57$, 95% CI 2.2, 41.0, $z = 3.04$, $p = 0.002$) had increased hazard over those aged 25–35.

Discussion

We observed notable risk factors for acute-toxicity and all-cause mortality in 3 cohorts of PWID spanning from 1996 to 2011 in Denver, Colorado. The risk identified in PWID who are disabled, gay/lesbian, non-Hispanic white, and those that used shared a cooker in the last 30 days are novel and may inform new interventions to prevent premature mortality and could be informative regarding HIV prevention among PWID. In a primarily opiate using cohort we noted an age risk profile where those aged 25–35 have the lowest risk of all-cause mortality relative to both younger and older injectors. Additionally, white, disabled, gay/ lesbian-identified, and the use of a shared cooker in the last 30 days may be independent risk factors for mortality in diverse injecting cohorts (cohorts 1 and 2), but not unique risks in a primarily opiate injecting cohort (cohort 3). Interestingly, gender was not a significant adjusted mortality risk in either all-cause or acute-toxicity related deaths. However, we did identify an unadjusted marginally increased ($p = 0.09$) risk for acute toxicity in males over females. Despite the smaller increase, this may support literature commonly identifying male gender as a risk factor for mortality among PWID [21]. On the other hand, this same recent meta-analysis reported substantial heterogeneity where a number of reports found a slight yet non-significant increase in mortality risk among female PWID [21]. The elevated but insignificant risk in this study could be a component of the heterogeneity among various cohorts of PWID and related to cultural effects unique to Denver. More research comparing cultural and behavioral aspects among PWID in different locations could be informative.

CMR of all-cause mortality was 1.61 per 100 py in this population. This was slightly lower than meta-analyses derived average CMR of 2.09 (1.93–2.26) per 100 py in regular opioid users worldwide [17], similar to CMRs reported in Western Europe [35], and similar to CMR for cocaine users that varied from 0.5 to 6.2 per 100 py [36]. These similarities may suggest a level of generalizability of these findings as the CMR is comparable to findings in other locations despite a highly specific geography and recruitment focus. However, additional research is needed to better understand CMR in unique geographic and cultural settings among PWID, given the notable heterogeneity in CMR estimates [17].

Mortality Risk in Disabled PWID

We report unemployment due to disability as a significant risk factor for all-cause mortality and for acute-toxicity. Few reports link disability as a predictor of mortality among PWID despite known effects of disability in other populations. Chronic diseases are the main cause of poor health, disability, and death in the United States [37], and chronic disease is a notable health effect of illicit drug use [27]. In addition, people who are disabled frequently engage in behaviors or have characteristics that increase their health risks, including smoking [38], physical inactivity [39], and obesity [40]. Moreover, disabled adults with mental and/or substance use disorders are at a high risk of dying by non-overdose related events such as suicide or assault [26]. Given these parallels with disabled populations and PWID, further investigations with PWID who are disabled could elucidate specific factors predictive of mortality. Finally, these results suggest that interventions in PWID who are disabled should expand beyond drug cessation and consider challenges frequently faced by disabled individuals, such as access to medical care.

Mortality Risk in Gay/Lesbian-Identified PWID

We present increased risk in gay/lesbian-identified individuals who participated in the first 2 cohorts of diverse polydrug injecting PWID. This supports findings of O'Driscoll et al. who identified bisexual-identified individuals as having a greater risk for an overdose event [16], however, extensive reports on mortality risk in sexual minority PWID are lacking. Gay/lesbian-identified individuals are at higher risk for suicide attempts, smoking, and binge drinking episodes [41, 42]. Further, sexual minorities are at higher risk of early mortality in communities with a high level of social marginalization [32, 33], which could be important when considering the social marginalization already faced by PWID.

It is important to note that gay/lesbian-identified individuals were not at significantly increased risk for death due to acute-toxicity (adjusted and not shown, $p = 0.75$). This suggests that gay/lesbian-identified PWID could benefit from interventions that go beyond addressing drug use behaviors. Further study and careful interventions examining behaviors that may be unique to these populations are warranted.

Mortality Risk of Polydrug Use and HIV Drug Risk Behaviors

Although commonly reported in the literature, we failed to identify self-reported concurrent polydrug use as an independent risk factor for acute-toxicity. Additionally, reported simultaneous polydrug use (e.g., speedballs) was rare and not a risk factor for mortality due to acute-toxicity in these cohorts. However, over half of the toxicity events recorded contained more than one substance. This lack of association could be due to a predominantly concurrent polydrug using cohort and the challenges of self-report. Concurrent and simultaneous polydrug use is a known risk factor for mortality [15, 16, 43] and combinations of heroin and cocaine [43], as well as opiates and benzodiazepines, [44] have been shown to be risk factors for acute-toxicity mortality. Perhaps polydrug users who use heroin predominantly as in cohort 3 (HR 1.75 vs. cohort 1, $p = 0.08$ not shown) or frequently use shared preparation equipment may harbor additional behavioral risks that would be important in all-cause mortality as well.

In the cohorts that were recruited for any injection use (cohorts 1 and 2), the use of a shared cooker at least once in the last 30 days was a significant predictor of all-cause mortality. While this study was not powered to detect HIV-specific mortality the use of shared equipment may mark other risk-taking behaviors that would be predictive of all-cause mortality. Indeed, correlations between unsterile injection practices and major psychiatric conditions such as borderline personality disorder and anti-social personality disorder have been identified within PWID [45, 46]. These conditions may predispose to other risky behaviors through impulsivity and emotional dysregulation that are commonplace in these conditions [47–49].

Finally, we do not show an association between methadone treatment in the last 6 months and mortality, despite extant evidence supporting the effectiveness of treatment in reducing mortality among PWID. However, evidence also suggests that mortality risk around methadone treatment can vary over time and increase with transition periods in and out of treatment [50, 51]. Additionally, different risk profiles have been identified depending on days to weeks from treatment exit [52]. The lack of association in this report could thus be due to less precise time effects available for analysis regarding treatment episodes.

Mortality Risk in Non-minority Populations of PWID

We found increased risk among non-Hispanic white participants. Few studies comment on white race/ethnicity as a predictor of all-cause mortality or acute-toxicity in PWID, where we found an increased risk. On the other hand, minorities had a higher population acute-toxicity rate in the 1990's in New York City, primarily due to cocaine overdoses [43]. An older report showed a higher rate of cocaine acute-toxicity among minorities in Texas [53], and a higher acute-toxicity mortality rate was detected among Hispanic males in New Mexico in the late 1990's and early 2000's [54]. However, the same report from New Mexico identified a higher acute-toxicity mortality rate among white males due to opioids [54]. These differences may be an artifact of the environment in Denver and polydrug behaviors that may change over time and in different locations. Further research with large populations and individual level socioeconomic and simultaneous polydrug use data may be useful in describing race/ethnicity as a predictor of mortality in PWID populations.

Age Risk in a Primarily Opiate Using Cohort

We identified an age profile of risk in a primarily opiate injecting cohort suggesting that those aged 25–35 were at the lowest risk of all-cause mortality relative to other ages. Younger and older age groups were at increased risk. This supports findings from Glasgow, where a large increase in standardized mortality ratio was identified among younger PWID [34]. Additionally, younger PWID have been shown to engage in more high-risk behaviors than their older counterparts [55]. However, we only identified this age effect in the primarily opiate-using cohort. This may suggest an increased danger in opiate injectors over other injectors as noted in San Diego [56], and age-related risk behaviors could be more important among heroin users. Additional research is needed to better understand the age-specific effects on risk of mortality among opiate injectors in Denver.

Limitations and Conclusions

As in most survey research, these results are based on self-report data and recall of past behaviors, thus caution is recommended in the interpretation of results. However, self-report data has been validated in these populations and this study incorporated substantial and important techniques to minimize biases that may exist due to stigmatization and other barriers to accurate self-report [57, 58]. Further, previous 30 day windows were used to minimize recall errors. Additional limitations exist due to the recruiting environment, technique, and sample. Participants were recruited by street outreach in Denver to encourage treatment entry and other facets of HIV risk behavior reduction. This limits broad generalizability as Denver will have cultural differences relevant to PWID versus other developed cities. However, similar CMRs were identified suggesting a level of comparability. In conclusion, we identify important all-cause mortality risk in gay and disabled PWID that suggests additional research and interventions are needed to address the unique characteristics within these subpopulations. Interestingly, we identify a drug HIV risk factor as a risk for all-cause mortality. This may suggest a level of applicability to HIV prevention techniques as a subpopulation may exist that is uniquely tolerant to risk behaviors relative to other PWID. Substantial underlying mental health conditions that affect impulsivity and emotional regulation could predispose to both, early all-cause mortality and increased HIV drug risk behaviors.

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Table 1

Baseline characteristics of study population

Characteristic	% (n)	Cohort 1 (1996–2000) % (n)	Cohort 2 (2000–2005) % (n)	Cohort 3 (2006–2011) % (n)	Test statistic	p value
Gender					$\chi^2 = 6.49$, df = 2	0.039
Male	71.3 (1431)	67.4 (385)	72.0 (584)	73.9 (462)		
Female	28.7 (576)	32.6 (186)	28.0 (227)	26.1 (163)		
Age, mean (SD)	38.3 (11.0)	37.7 (10.9)	38.8 (10.8)	38.2 (11.5)	F = 1.52, df = 2	0.219
Race/ethnicity					$\chi^2 = 152.90$, df = 6	<0.001
White, non-Hispanic	54.5 (1093)	43.4 (248)	49.3 (400)	71.2 (445)		
Black, non-Hispanic	14.5 (292)	12.3 (70)	21.3 (173)	7.8 (49)		
Hispanic	22.6 (453)	32.6 (186)	20.2 (164)	16.5 (103)		
Other ^a	8.4 (169)	11.7 (67)	9.1 (74)	4.5 (28)		
Employment					$\chi^2 = 25.28$, df = 4	<0.001
Employment-disabled	19.6 (393)	24.0 (137)	17.8 (144)	17.9 (112)		
Employment-unemployed	43.3 (870)	36.1 (206)	43.8 (355)	49.4 (309)		
Sexual orientation					$\chi^2 = 6.74$, df = 6	0.345
Gay	2.6 (51)	2.5 (14)	3.2 (26)	1.8 (11)		
Lesbian	1.4 (27)	1.2 (7)	1.9 (15)	0.8 (5)		
Bisexual	8.9 (177)	9.3 (52)	9.1 (74)	8.2 (51)		
Drinks in last 30 days					$\chi^2 = 168.80$, df = 6	<0.001
Less than or equal to 10	55.7 (1116)	40.2 (228)	52.3 (424)	74.2 (464)		
11–20	6.7 (135)	7.2 (41)	6.5 (53)	6.6 (41)		
21–30	5.2 (105)	6.9 (39)	4.3 (35)	5.0 (31)		
31+	32.3 (646)	45.7 (259)	36.8 (298)	14.2 (89)		
Years of Injecting, mean (SD)	17.0 (12.0)	17.2 (11.7)	17.6 (12.0)	16.0 (12.3)	F = 3.32, df = 2	0.037
Heroin injection ^c	57.4 (1152)	48.2 (275)	47.0 (381)	79.4 (496)	$\chi^2 = 179.21$, df = 2	<0.001
Speedball injection ^c	4.7 (94)	1.2 (7)	5.3 (43)	7.0 (44)	$\chi^2 = 23.76$, df = 2	<0.001
Cocaine injection ^c	6.1 (122)	5.6 (32)	8.0 (65)	4.0 (25)	$\chi^2 = 10.28$, df = 2	0.006
Used marijuana ^c	10.1 (202)	11.7 (67)	9.5 (77)	9.3 (58)	$\chi^2 = 2.47$, df = 2	0.290

Characteristic	% (n)	Cohort 1 (1996–2000) % (n)	Cohort 2 (2000–2005) % (n)	Cohort 3 (2006–2011) % (n)	Test statistic	p value
Used shared cooker in last 30 days ^d	55.2 (1079)	59.8 (339)	55.5 (437)	49.8 (303)	$\chi^2 = 12.16$, df = 2	0.002
Used shared cotton in last 30 days ^d	45.1 (884)	46.7 (264)	46.9 (367)	41.3 (253)	$\chi^2 = 5.30$, df = 2	0.071
Used shared rinse water in last 30 days ^d	40.6 (795)	41.5 (236)	42.9 (336)	36.9 (223)	$\chi^2 = 5.45$, df = 2	0.065
Split drug solution in last 30 days ^d	62.0 (1215)	69.4 (392)	61.6 (484)	55.7 (339)	$\chi^2 = 23.49$, df = 2	<0.001
Number of sex partners in last 30 days					$\chi^2 = 14.50$, df = 2	0.001
0–1 partners	83.9 (1665)	83.0 (474)	81.1 (647)	88.5 (544)		
2 or more partners	16.1 (319)	17.0 (97)	18.9 (151)	11.5 (71)		
Exchanged sex for drugs/money- ever in last 30 days	7.0 (140)	4.9 (28)	9.2 (75)	5.9 (37)	$\chi^2 = 11.30$, df = 2	0.004
Homeless	44.3 (888)	34.7 (198)	47.0 (381)	49.4 (309)	$\chi^2 = 29.57$, df = 2	<0.001

^a Includes, Asian, Native American and Other

^b N does not equal 2007 due to missing data

^c 1 times per day in the past 30 days

^d 1 times in the past 30 days

Table 2

Causes of deaths

		Cohort 1 (1996–2000)	Cohort 2 (2000–2005)	Cohort 3 (2006–2011)
Cause of death	N = 86	n = 18	n = 34	n = 34
Toxicity	67.4% (58)	66.7% (12)	67.6% (23)	67.6% (23)
Accident	3.5% (3)	5.6% (1)	2.9% (1)	2.9% (1)
Cancer	2.3% (2)			5.9% (2)
Cardiac	2.3% (2)		2.9% (1)	2.9% (1)
Cerebral	1.2% (1)			2.9% (1)
Cirrhosis	2.3% (2)		2.9% (1)	2.9% (1)
Complications of diabetes	1.2% (1)			2.9% (1)
HIV-related	8.1% (7)		17.6% (6)	2.9% (1)
Infection	1.2% (1)			2.9% (1)
Other alcohol-related	3.5% (3)	11.1% (2)		2.9% (1)
Other drug-related	3.5% (3)	5.6% (1)	5.9% (2)	
Pulmonary	1.2% (1)			2.9% (1)
Unknown	2.3% (2)	11.1% (2)		

Table 3

Unadjusted hazard ratios

Characteristic	HR		Death all cause all cohorts		HR		Acute-toxicity all cohorts	
	95% CI	z score	p value	95% CI	z score	p value	95% CI	z score
Gender male versus female	1.47	0.88, 2.44	1.47	0.142	1.78	0.92, 3.43	1.72	0.085
Age category								
Less than 25	1.91	0.90, 4.07	1.69	0.092	1.94	0.86, 4.40	1.59	0.112
25–35 (ref)	–	–	–	–	–	–	–	–
36–45	1.72	0.89, 3.31	1.63	0.104	1.33	0.63, 2.80	0.75	0.451
>45	1.80	0.94, 3.44	1.76	0.078	1.13	0.52, 2.43	0.31	0.760
Non-Hispanic white race/ethnicity ^b	1.52	0.98, 2.40	1.86	0.063	1.76	1.02, 3.04	2.01	0.044
Employment disabled ^a	2.99	1.77, 5.10	4.10	<0.001	1.79	0.93, 3.43	1.75	0.081
Employment unemployed ^a	1.35	0.79, 2.32	1.11	0.268	1.18	0.64, 2.16	0.52	0.602
Sexual orientation Gay/Lesbian	2.22	1.02, 4.82	2.01	0.045	0.89	0.22, 3.65	–0.17	0.869
Sexual orientation bisexual	1.12	0.54, 2.34	0.31	0.765	1.00	0.39, 2.48	–0.02	0.981
More than 30 alcoholic drinks in last 30 days	0.79	0.46, 1.36	–0.81	0.395	1.04	0.57, 1.91	0.12	0.902
Years of Injecting (per additional year)	1.01	0.99, 1.03	0.91	0.362	0.99	0.97, 1.02	–0.57	0.572
Heroin injections (per day in last 30)	1.01	1.00, 1.03	1.47	0.141	1.02	1.00, 1.04	1.53	0.127
Speedballs	0.99	0.96, 1.02	–0.75	0.452	0.99	0.96, 1.03	–0.35	0.729
Cocaine injections	0.98	0.95, 1.02	–0.96	0.336	1.00	0.97, 1.03	–0.02	0.983
Cocaine other than injection	0.14	0.02, 1.00	–1.96	0.050	0.21	0.03, 1.52	–1.55	0.122
Marijuana	1.01	0.98, 1.03	0.51	0.607	1.02	0.99, 1.04	1.17	0.243
Used shared cooker ever in last 30 days	1.50	0.97, 2.30	1.82	0.070	1.29	0.77, 2.20	0.93	0.352
Used shared cotton ever in last 30 days	1.24	0.79, 1.94	0.92	0.358	1.14	0.65, 1.98	0.46	0.649
Used shared rinse water ever in last 30 days	1.08	0.67, 1.73	0.32	0.748	0.84	0.46, 1.55	–0.54	0.590
Split drug solution in last 30 days	1.30	0.84, 2.01	1.19	0.234	1.46	0.86, 2.46	1.41	0.157
Number of sex partners in last 30 days								
0–1 partners (ref)								
2 or more partners	0.88	0.46, 1.71	–0.37	0.710	0.93	0.42, 2.05	–0.18	0.860
Sex in exchange for drugs or money	0.91	0.33, 2.48	–0.19	0.847	0.33	0.05, 2.37	–1.10	0.270
Homeless	0.97	0.63, 1.49	–0.13	0.891	1.12	0.67, 1.88	0.43	0.665

Characteristic	HR	Death all cause all cohorts		Acute-toxicity all cohorts	
		95% CI	p value	95% CI	p value
Treatment ever in last 6 months	1.00	0.58, 1.73	-0.00	0.67, 2.33	0.69
			0.996		0.488

^aVersus employed

^bVersus non-white race/ethnicity

Table 4

A, B, C, D. Adjusted hazard ratios of all-cause mortality and acute toxicology events

Characteristic	HR	95% CI	z-score	p value
(A) Death all cause all cohorts				
White ^b	1.79	1.14, 2.80	2.54	0.011
Disabled ^a	3.33	1.96, 5.66	4.45	<0.001
Unemployed ^a	1.33	0.78, 2.29	1.06	0.288
Wald = 25.30 on 3 df, p < 0.001				
(B) Acute-toxicity all cohorts				
White ^b	1.92	1.10, 3.35	2.29	0.022
Disabled ^a	2.02	1.04, 3.90	2.09	0.037
Unemployed ^a	1.16	0.63, 2.12	0.47	0.635
Wald = 8.49 on 3 df, p = 0.034				
(C) Death all cause cohorts 1 and 2				
White ^b	2.38	1.33, 4.29	2.88	0.003
Disabled ^a	3.47	1.71, 6.79	3.49	<0.001
Unemployed ^a	1.38	0.68, 2.80	0.88	0.380
Bisexual	0.83	0.30, 2.34	-0.34	0.876
Gay/lesbian	2.55	1.07, 6.10	2.11	0.034
Dirty Cocker in last 30 days	2.06	1.16, 3.66	2.47	0.014
Wald = 31.45 on 9 df, p < 0.001				
(D) Death all cause cohort 3				
Less than 25	5.31	0.97, 29.0	1.93	0.054
25–35 (ref)	–	–		–
36–45	5.21	1.11, 24.6	2.09	0.037
45	9.57	2.24, 41.0	3.04	0.002
Wald = 10.47 on 3 df, p = 0.015				

^aVersus employed^bVersus non-white race/ethnicity