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Death after diagnosis of non-communicable disease comorbid conditions, stratified by injection drug use

Catherine R. LESKO^a, Bryan LAU^{a,b}, Geetanjali CHANDER^{a,b}, and Richard D. MOORE^{a,b}

^aDepartment of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

^bDepartment of Medicine, Johns Hopkins School of Medicine, Baltimore, MD, USA

Abstract

Objective: Describe all-cause mortality associated with history of injection drug use (IDU) after a validated diagnosis of four non-communicable disease (NCD) diagnoses: 1) end-stage liver disease (ESLD); 2) end-stage renal disease (ESRD); 3) cancer; or 4) myocardial infarction (MI) or stroke.

Design: We followed 4 cohorts of persons in continuity HIV care in the Johns Hopkins HIV Clinic with a validated diagnosis of ESLD (n=67), ESRD (n=187), cancer (n=424), and MI or stroke (n=213) from 1996 through approximately 2014.

Methods: Crude and adjusted Cox proportional hazards models to estimate hazard ratios [HR] for death after a validated diagnosis of one of four NCD diagnoses associated with history of IDU as an HIV acquisition risk factor.

Results: History of IDU was not associated with death after ESRD (standardized HR=0.98, 95% Confidence Interval [CI]: 0.57, 1.68). Associations between history of IDU and death after ESLD and MI or stroke were weak, imprecise and not statistically significant (HR=1.17, 95% CI: 0.63, 2.19; HR=1.21, 95% CI: 0.80, 1.83). History of IDU was not associated with death after cancer in the first 6 months, but subsequently, the adjusted HR was 2.03 (95% CI: 1.26, 3.27).

Conclusion: PWID and non-IDU had strikingly similar risk and hazard of mortality after several major NCD diagnoses. Mortality after cancer diagnosis in this cohort was higher for persons with a history of IDU than those without; this may be due to being diagnosed with a different mix of specific sites and stages of cancers.

With improved survival among persons with HIV (PWH) in the modern antiretroviral therapy (ART) era (1), the incidence of non-AIDS-related morbidity and non-communicable diseases (NCD) has increased. Non-AIDS-related causes of death including liver disease, cardiovascular disease, and cancer now represent a majority of all deaths among PWH (2–4). It is increasingly necessary to understand contributors to the risk of NCD morbidity and mortality.

Correspondence: Catherine R. Lesko, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe St, E7139, Baltimore, MD 21205, Phone: 410-614-6517 (office), Fax: 410-955-0863, clesko2@jhu.edu.

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Persons with a history of injection drug use (PWID) have higher rates of NCD morbidity and mortality than do other PWH (non-IDU) (5, 6). This may be due to illicit drugs, exposure to other agents introduced parenterally (e.g., hepatitis C virus [HCV]), or because IDU is associated with other risk behaviors known to increase the risk of NCDs (e.g., cigarette smoking or hazardous alcohol use) (7, 8). However, PWID may experience lower absolute risk of NCDs because they have higher rates of death from other causes, which would preclude development of a comorbidity (9). In a recent study from our group (9), age-specific risk of end-stage liver disease (ESLD) and end-stage renal disease (ESRD) was markedly elevated among PWID compared to non-IDU. PWID had a higher rate of stroke, however because they were more likely to die from other causes first, the overall risk of stroke was similar among PWID and non-IDU. PWID and non-IDU had similar age-specific risk and rate of myocardial infarction (MI) and non-AIDS-defining cancer.

Survival after a NCD diagnosis may be worse for PWID for the same reasons that incidence of NCDs or cause-specific mortality is higher among non-IDU; mechanisms that led to development of disease in PWID and non-IDU may differ, leading to different prognosis. Alternately, survival may be similar for PWID and non-IDU because the NCDs of interest impose such a threat to health that there is little room for a gradient in the survival probabilities. Disparities in survival after a major NCD diagnosis among PWID and non-IDU are as-yet undescribed. The purpose of this analysis was to describe survival after several major NCD diagnoses: ESLD; ESRD; cancer; and MI or stroke (CVD events). We compare survival probabilities and hazards according to history of IDU as an HIV acquisition risk factor.

METHODS

Study samples

The Johns Hopkins HIV Clinical Cohort (JHHCC) is an open, clinical cohort enrolling patients engaged in continuity care in the Johns Hopkins HIV Clinic who consent to share their medical record data (>90% of patients). A full description of the cohort is available elsewhere (10). Briefly, patient demographics, most likely route of HIV acquisition by patient self-report and medical history are collected upon enrollment into clinical care. Diagnoses, laboratory test results, prescriptions and visit data are abstracted from the electronic medical record. Laboratory test results are available from the Johns Hopkins Medical system or either of two major commercial laboratories. Evidence of alcohol use or cigarette smoking is abstracted from the medical record every 6 months. Alcohol use was coded as social or hazardous; hazardous use was not strictly defined but was generally classified as daily or binge drinking (8). Cigarette and alcohol use in the prior 6 months was also self-reported by a subset of patients approximately every 6 months on a Computer-Assisted Self-Interview. Self-reported alcohol use is ascertained using the Alcohol Use Disorders Identification Test alcohol consumption questions (AUDIT-C), and hazardous use was defined as a score >3 for women and >4 for men (11).

Diagnoses of five major NCDs are validated in the JHHCC according to standardized protocol. We included diagnoses of the following NCDs that occurred in the noted time frames: ESLD, March 1996-May 2013 (12, 13); ESRD, August 1996-September 2014 (12,

13); cancers, April 1996-September 2014 (14, 15); and MI or stroke, August 1996-September 2012 (16, 17). Deaths are ascertained by clinical record review and matches against the Social Security Death Index and National Death Index Plus.

We created 4 study samples that included persons in the cohort with validated: 1) ESLD; 2) ESRD; 3) cancer; or 4) MI or stroke. Patients diagnosed with more than one NCD appeared in more than one study sample. We defined baseline as the date of diagnosis and assigned covariates as those values measured closest to, within one year prior to 30 days after, baseline. We calculated FIB-4 based on patients' age, aspartate aminotransferase (AST) level, alanine aminotransferase (ALT) level and platelet count (18, 19). We classified patients as using cigarettes or drinking hazardously if indicated on either the medical record review or self-report interview.

Statistical analyses

Patients were followed from the date of NCD diagnosis until death or administrative censoring at 5 years. Because deaths are ascertained through linkage to a death registry, there is no loss to follow-up for this set of analyses. We estimated crude and adjusted hazard ratios (HR) and generated crude and adjusted cumulative incidence functions comparing PWID and non-IDU. HRs were estimated using Cox proportional hazards models. The proportional hazards assumption was checked by interacting history of IDU with time in the model; product terms that were statistically significant at $\alpha=0.05$ were taken as an indication of a violation of the proportional hazards assumption and we then stratified follow-up time based on visual inspection of risk curves and report stratified HRs.

Adjustment

We adjusted estimates using inverse probability (IP) weighting (20, 21). Inverse probability weighting is a method of adjustment akin to direct standardization, in that it creates a pseudo-population that has the same distribution of covariates as the study sample but in which the exposure and the covariates are not associated (and thus covariates cannot bias the association between the exposure and the outcome). The denominators of the IP weights were estimated using predicted probabilities from logistic models with the outcome of history of IDU. Because there was sparse data, particularly for death after ESLD, we penalized odds ratios for the association with patient covariates and exposure using weak prior data augmentation for dichotomous variables (22). Without this penalization, within some bootstrap resamples of the data, predicted probabilities of exposure were 0 or 1 and weights were undefined.

Covariates adjustment sets varied by diagnosis. Covariates were chosen based on the literature as those hypothesized to be associated with IDU and predictive of death after an NCD diagnosis (i.e., associated with prognosis) (23). Estimates for risk of death after ESLD were adjusted for: black race; HBV infection; FIB-4; hazardous alcohol use; and calendar year. Estimates for risk of death after ESRD were adjusted for: age; body-mass index (BMI); hypertension; diabetes; hemoglobin A1C; LDL cholesterol; FIB-4; CD4 cell count; hazardous alcohol use; and calendar year. Estimates for risk of death after cancer were adjusted for: black race; age; BMI; hypertension; diabetes; FIB-4; CD4 cell count; $\log_{10}$

HIV viral load; hazardous alcohol use; cigarette smoking; and calendar year. Estimates for risk of death after MI or stroke were adjusted for: sex; black race; age; BMI; hypertension; diabetes; LDL cholesterol; CD4 cell count; cigarette smoking; ART use; and calendar year.

Missing data

To account for missing covariate data, we created 40 copies of each dataset and imputed missing values using multiple imputation by chained equations (24–27). Missing covariates were imputed conditional on all covariates in table 1 (all covariates used for standardization for any outcome, plus auxiliary variables to improve prediction); plus time in care in the JHHCC prior to NCD diagnosis; time to death or censoring after diagnosis; an indicator for death or censoring; and the cumulative hazard of death at the time of study exit. We ran all analyses in each of the 40 imputed datasets and combined estimates using Rubin's equations (25). We used the sandwich estimator of the variance for standardized HRs. We estimated the standard error of standardized RDs and RRs by using the standard deviation of 1000 estimates from unrestricted random bootstrap samples from each imputed dataset (28). All analyses were conducted using SAS version 9.4 (Cary, NC).

RESULTS

We followed 67 patients after ESLD (70% PWID), 187 patients after ESRD (50% PWID), 424 patients after cancer diagnosis (33% PWID), and 213 patients after MI or stroke diagnosis (53% PWID) (Table 1).

Mortality rates were high in the first 5 years after all diagnoses: 37.4 per 100 person-years after ESLD; 24.8 per 100 person-years after ESRD; 21.2 per 100 person-years after cancer; and 16.3 per 100 person-years after MI or stroke. The crude hazard of mortality was higher for PWID than for non-IDU for each of the NCDs (Table 2). Correspondingly, crude risks of mortality were higher for PWID than for non-IDU over 5 years after diagnosis (Figure 1).

ESLD:

The crude HR for death after ESLD diagnosis associated with history of IDU was 1.64 (95% confidence interval [CI]: 0.85, 3.17, Table 2). After adjustment, the association between history of IDU and mortality after ESLD diagnosis was attenuated (HR=1.17, 95% CI: 0.63, 2.19). Visual inspection of the adjusted cumulative incidence curves (Figure 2) support the conclusion that mortality in PWID and non-IDU is similar in the 5 years after ESLD diagnosis. Both curves rise quickly after diagnosis with median survival time just over 1 year and 5-year mortality exceeding 70%.

ESRD:

The crude HR for death after ESRD diagnosis associated with history of IDU was 1.29 (95% CI: 0.89, 1.87, Table 2). After adjustment, there was no association between history of IDU and death (HR=0.98, 95% CI: 0.57, 1.68). Adjusted mortality risk curves after ESRD diagnosis (Figure 2) were very similar for PWID and non-IDU. Median survival was between 2.5 and 3.5 years and 5-year mortality risk exceeded 60%.

Cancer:

The crude HR for death after cancer diagnosis comparing PWID to non-IDU was 1.90 (95% CI: 1.47, 2.45, Table 2). Differences were attenuated by adjustment, but PWID still had a hazard of mortality that was 1.45 times the hazard of mortality among non-IDU (95% CI: 1.02, 2.07). However, the proportional hazards assumption was not met, and thus this adjusted HR represents an average HR across the 5 years after cancer diagnosis. Examining the standardized mortality risk curves (Figure 2), it appeared that risk was similar for the first 6 months or so after cancer diagnosis, and then the risk curves began to diverge, so we stratified follow-up at 6-months. The HR for mortality following cancer diagnosis associated with history of IDU was 0.97 (95% CI: 0.58, 1.62) in the first 6 months and then 2.03 (95% CI: 1.26, 3.27) between 6 months and 5 years after diagnosis. The proportional hazards assumption was met in these two strata of follow-up time. Median survival was around 2 years for PWID but around 5 years for non-IDU. The 5-year RD associated with history of IDU was 17.8% (95% CI: -31.4%, 67.0%) (Web Table 1).

MI/stroke:

Although the crude HR for mortality following MI or stroke associated with history of IDU was elevated (HR=1.52, 95% CI: 1.04, 2.21, Table 2), the adjusted HR was attenuated (HR=1.21, 95% CI: 0.80, 1.83). Although the risk of death after MI or stroke was consistently higher among PWID than among non-IDU, risk estimates were quite close (Figure 2). Median survival was around, or just after, 5 years after MI or stroke diagnosis.

DISCUSSION

The 5-year mortality risk of persons with HIV was close to 50% or higher after all of the NCD diagnoses we examined. This mortality hazard is comparable to the general population for ESLD, ESRD, MI and stroke. In the general population, median survival of patients with compensated versus decompensated cirrhosis is >12 years versus approximately 2 years (29). The 5-year mortality risk in the general population is approximately 65% for persons with ESRD on dialysis (30), 49% for MI (31), and 60% for stroke (32). The 5-year mortality risk after cancer diagnosis in our cohort was higher than mortality after cancer diagnosis in the general population (33%) although mortality risk after specific cancer subtypes varies and this difference may be the result of different mixes of cancer subtypes (33).

Persons with and without a history of IDU had similar mortality risk after ESLD, ESRD and MI or stroke; it is possible that the force of mortality is so strong after diagnosis with one of these comorbidities that few risk factors can increase (or decrease) it further. Only for cancer did PWID have higher mortality following diagnosis than did non-IDU, with the difference beginning to manifest approximately 6 months after diagnosis. Differences in survival may be attributable to differences in cancer type, differences in cancer stage at diagnosis and thus prognosis, or differences in cancer treatment; we did not link to specific information about site, stage or treatment of cancer for this study. In a prior analysis of this cohort, the incidence of non-AIDS-defining cancer was higher for non-IDU than for PWID (9).

This analysis is unique in that, in attempting to identify differences in outcomes following diagnosis with a NCD comorbid condition, we restricted our analysis of deaths to the subset of patients that survived and remained in care in the JHHCC long enough to receive a NCD diagnosis. Furthermore, we considered all-cause mortality rather than cause-specific mortality; cause of death on death certificates is frequently misclassified (34). As such, our results do not reflect the total effect of injection drug use on liver-related, kidney-related, cancer or cardiovascular mortality. However, our estimand of interest is more akin to a controlled direct effect (35). That is, we are asking: is a person with a history of IDU at higher risk for death after a NCD diagnosis compared to the same person had she been infected with HIV through another route? We know that PWID experience higher rates of ESLD and ESRD; our analysis gives some indication of what might happen to survival if we could eliminate disparities leading to the diagnosis.

Persons with HIV, and in particular persons co-infected with HIV and HCV, have a higher rate of ESLD than the general population (36), making this a key population in which to study survival with ESLD. In a Spanish cohort of HIV/HCV co-infected individuals with decompensated cirrhosis diagnosed between 1997 and 2004 (37), as in our cohort, active drug use during follow-up was not associated with survival. Beyond increasing the risk for *development* of ESLD, mediated by HCV infection, it does not appear that history of or ongoing drug use increases the risk of death *after* ESLD diagnosis.

Survival after diagnosis with ESRD has improved on dialysis and after kidney transplantation (38). Progression to ESRD among persons with HIV who have chronic kidney disease is faster among black persons than among white persons (39), which is manifest in the proportion of the cohort with ESRD who were black (94%). Progression to ESRD is faster among persons with a history of IDU, with or without HIV infection (40). However, based on our study, survival after ESRD does not appear to be associated with history of IDU.

One limitation of our ability to describe survival after ESLD and ESRD is our lack of data on whether or not patients received a liver or kidney transplant. Liver or kidney transplant are not truly competing events for death after ESLD or ESRD diagnosis, but they could dramatically change survival probabilities. If they were unevenly distributed between PWID and non-IDU (or persons who did or did not recently use illicit drugs), liver or kidney transplants could have explained lack of differences in survival. However, during the period under study, liver transplants among PWH were exceptionally rare (41). Opportunities for kidney and liver transplantation in PWH improved late in the study period, based on recognition that outcomes from HIV-negative donor kidneys were comparable in HIV-positive versus HIV-negative transplant recipients (42) and increased acceptability of transplanting HIV-positive donor kidneys into HIV-positive ESRD patients (43). As transplant options improve for PWH (43, 44), survival following ESLD and ESRD may also improve.

We did find a higher hazard of death after 6 months after a cancer diagnosis associated with a history of IDU. This may be because the cancer subtypes diagnosed among PWID have a worse prognosis than those diagnosed in non-IDU or because PWID are diagnosed at later

stages. We did not have sufficient numbers to directly compare survival after specific cancer diagnoses, however, the distribution of cancer types differed for PWID and non-IDU. The most common cancer types among PWID included lung (n=31, 22% of all cancers among PWID), non-Hodgkin's lymphoma (n=25, 18%) and liver (n=17, 12%); the most common cancer types among non-IDU were non-Hodgkin's lymphoma (n=55, 19%), Kaposi's sarcoma (n=44, 15%), skin (n=23, 8%), lung (n=21, 7%) and anal (n=21, 7%). Another explanation for why PWID had higher all-cause mortality after cancer diagnosis compared to non-IDU could be because they had worse treatment outcomes, either because of their response to cancer treatment directly or because their health is poorer at the time of the cancer diagnosis. We did adjust for CD4 cell count to attempt to control for immune health, but other biomarkers or indicators may be important in this setting. As we discuss in more detail below, PWID did also have a higher prevalence of HCV infection, which could explain some of the survival differences seen among PWID and non-IDU.

PWID had a slightly higher hazard of mortality after MI or stroke than did non-IDU, but the cumulative incidence curves were very similar; it seems the excess mortality hazard is incurred very early on – at the time of the event – and then deficits in survival among PWID cannot be made up. This early disparity in survival may be associated with the acute event that precipitated the MI or stroke or with the medical care and interventions at the time of the MI or stroke. Persons with a history of substance use at the time of a hospital admission for acute MI had higher inpatient mortality and lower rates of catheterization or revascularization (45).

We were limited in our ability to differentiate effects of history of IDU and HCV infection on survival after NCD diagnosis because IDU and HCV infection are so collinear (46, 47). HCV infection independently increases all-cause, liver-related, kidney-related, malignancy and cardiovascular mortality risk, both among persons with and without HIV infection (48–51). In one prior study, adjusting for HCV infection attenuated the association between history of IDU and all-cause and liver-related mortality among people with HIV (52). That said, we found no strong evidence of an effect of history of IDU on increasing mortality risk after diagnosis of ESLD, ESRD or MI or stroke, suggesting, therefore, that the impact of HCV Infection on mortality is on the development of disease rather than on accelerating its progression.

We were also limited in our ability to describe effects of recent illicit drug use on survival after NCD diagnosis. PWID may have ceased injecting and non-IDU may use illicit drugs through non-injection routes. We did not examine recent illicit drug use for several reasons. First, because this is a clinical cohort, we do not have reliable, standardized measure of time-updated injection drug use. The limited information in this cohort about recent illicit drug use is limited and certainly misclassifies individuals' use (53). Second, using history of IDU as a risk factor allows the disparities (or lack of disparities) described herein to be interpreted with respect to the existing literature. Finally, even if we had had perfect data on time-updated injection drug use, the window of susceptibility in which injection drug use would act to increase mortality is unknown. For example, for death due to overdose, drug use just prior to death is most relevant, but for death due to cancer treatment failure, is drug use just prior to death also most relevant or should we use some measure of cumulative

exposure to injection drugs? Using history of IDU as a risk factor does not require we specify a relevant exposure window.

PWID and non-IDU had strikingly similar risk and hazard of mortality after several major NCD diagnoses. In particular, even though PWID have higher incidence of ESLD and ESRD (9), following diagnosis, survival probabilities were similar for PWID and non-IDU. PWID had lower longer-term (5-year) survival after cancer diagnosis than did non-IDU, although this may be due to the sites and stages of cancers PWID versus non-IDU were diagnosed with.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Crude risk of death for persons with a history of injection drug use (PWID) and those without a history of injection drug use (non-IDU) following validated first diagnosis of end-stage liver disease (ESLD), end-stage renal disease (ESRD), cancer, or myocardial infarction (MI) or stroke

^a Standardized on black race; HBV infection; FIB-4; hazardous alcohol use; and calendar year of ESLD diagnosis

^b Standardized on age; body-mass index (BMI); hypertension; diabetes; hemoglobin A1C; LDL cholesterol; FIB-4; CD4 cell count; hazardous alcohol use; and year of ESRD diagnosis

^c Standardized on black race; age; BMI; hypertension; diabetes; FIB-4; CD4 cell count; log₁₀ HIV viral load; hazardous alcohol use; cigarette smoking; and year of cancer diagnosis

^d Standardized on sex; black race; age; BMI; hypertension; diabetes; LDL cholesterol; CD4 cell count; cigarette smoking; prior use of ART; and year of MI or stroke diagnosis

Figure 2.

Standardized risk of death for persons with a history of injection drug use (PWID) and those without a history of injection drug use (non-IDU) following validated first diagnosis of end-stage liver disease (ESLD)^a, end-stage renal disease (ESRD)^b, cancer^c, or myocardial infarction (MI) or stroke (cardiovascular disease [CVD])^d

Table 1.

Characteristics (N[%] or median[IQR]) of persons diagnosed with ESLD (n=67), ESRD (n=187), cancer (n=424) and MI or stroke (n=213) in the JHHCC at the time of diagnosis^a, stratified by history of injection drug use (PWID) or not (non-IDU)

	ESLD		ESRD		Cancer		MI or Stroke	
	PWID	Non-IDU	PWID	Non-IDU	PWID	Non-IDU	PWID	Non-IDU
N	47	20	94	93	138	286	113	100
Male	41 (87)	17 (85)	59 (63)	61 (66)	96 (70)	214 (75)	78 (69)	57 (57)
Age, years	50 (44, 55)	46 (40, 52)	47 (40, 53)	44 (36, 55)	51 (46, 55)	47 (40, 54)	49 (44, 53)	48 (41, 56)
Black race	36 (77) ^b	9 (45)	85 (90)	89 (96)	112 (81)	191 (67)	103 (91)	86 (86)
Diagnosis year	2005 ('01, '08)	2005 ('01, '07)	2004 ('00, '09)	2006 ('02, '12)	2006 ('02, '10)	2006 ('02, '09)	2006 ('02, '08)	2007 ('03, '09)
ART	36 (77)	13 (65)	63 (67)	73 (78)	111 (80)	236 (83)	92 (81)	79 (79)
CD4, cells/ μ L	239 (92, 346)	191 (90, 410)	203 (110, 425)	239 (47, 418)	224 (83, 372)	290 (112, 453)	202 (92, 370)	270 (92, 486)
Missing	2	2	11	3	20	22	7	6
Log ₁₀ viral load, cells/mL	2.8 (1.7, 4.6)	3.3 (1.9, 4.8)	3.3 (1.9, 4.9)	3.2 (1.7, 4.9)	2.5 (1.7, 4.5)	2.4 (1.7, 4.1)	3.1 (1.7, 4.6)	2.6 (1.7, 4.6)
Missing	2	2	13	6	23	29	6	6
HBV infection	14 (30)	9 (45)	21 (22)	24 (26)	25 (18)	56 (20)	16 (14)	14 (14)
HCV infection	47 (100)	17 (85)	88 (94)	36 (39)	129 (93)	90 (31)	109 (96)	41 (41)
BMI, kg/m ²	23.6 (21.8, 28.5)	24.2 (19.8, 27.1)	22.5 (20.9, 25.2)	24.8 (21.4, 28.5)	23.2 (20.5, 25.7)	24.0 (20.7, 27.6)	23.0 (20.1, 26.7)	24.1 (20.8, 29.3)
Missing	23	10	40	42	44	101	31	36
FIB-4	9.8 (6.4, 16.9)	7.1 (4.7, 12.5)	2.1 (1.4, 4.7)	1.4 (1.0, 2.4)	1.9 (1.2, 3.9)	1.3 (0.8, 2.2)	2.4 (1.4, 6.0)	1.4 (1.0, 2.6)
Missing	1	1	9	6	16	26	1	3
Hypertension	14 (30)	7 (35)	67 (71)	52 (56)	55 (40)	94 (33)	61 (54)	54 (54)
Diabetes	8 (17)	3 (15)	12 (13)	21 (23)	20 (14)	30 (10)	20 (18)	16 (16)
HgBA1C	5.4 (5.3, 5.8)	5.4 (5.0, 6.0)	5.6 (5.2, 5.9)	6.0 (5.2, 7.2)	6.2 (5.1, 7.1)	6.2 (5.6, 6.7)	5.6 (5.2, 6.0)	5.8 (5.5, 6.2)
Missing	36	16	77	64	107	250	70	61
LDL cholesterol	59 (48, 76)	73 (40, 83)	69 (50, 89)	85 (63, 116)	75 (58, 115)	91 (67, 116)	65 (51, 95)	89 (66, 113)
Missing	31	14	53	50	78	162	38	29
Haz. alcohol use	13 (29)	2 (11)	11 (14)	8 (9)	17 (31)	26 (10)	21 (20)	13 (14)
Missing	2	1	14	5	19	25	10	6

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	ESLD		ESRD		Cancer		MI or Stroke	
	PWID	Non-IDU	PWID	Non-IDU	PWID	Non-IDU	PWID	Non-IDU
N	47	20	94	93	138	286	113	100
Smoking	20 (61)	8 (57)	43 (75)	31 (48)	86 (86)	103 (52)	66 (74)	48 (61)
Missing	14	6	37	29	39	86	24	21

* Abbreviations: IQR, interquartile range; ESLD, end-stage liver disease; ESRD, end-stage renal disease; MI, myocardial infarction; JHHCC, Johns Hopkins HIV Clinical Cohort; IDU, injection drug use (history of); ART, antiretroviral therapy; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; BMI, body mass index; FIB-4, fibrosis-4 index; HgBA1C, hemoglobin A1C; LDL, low-density lipoprotein

^a Approximately 1986–2014, depending on the diagnosis

^b Shaded cells denote patient characteristics used to standardize associations between illicit drug use and risk of death following each of the non-communicable disease diagnoses

Table 2.

Number of deaths and person-years, and crude and standardized HRs of death comparing PWID and non-IDU, and comparing persons with and without an indication that they were actively using cocaine or heroin (illicit drug use), following validated first diagnosis of ESLD, ESRD, cancer, or MI or stroke

	PWID		Non-IDU		HR	
	Deaths/PY	Rate/100 PY	Deaths/PY	Rate/100 PY	Crude	Standardized
ESLD	40/77.5	51.6	13/48.9	26.6	1.64 (0.85, 3.17)	1.17 (0.63, 2.19) ^a
ESRD	67/219.9	30.5	48/198.5	24.2	1.29 (0.89, 1.87)	0.98 (0.57, 1.68) ^b
Cancer	99/273.7	36.2	131/811.6	16.4	1.90 (1.47, 2.45)	1.45 (1.02, 2.07) ^c
MI/Stroke	68/310.3	21.9	44/317.3	13.9	1.52 (1.04, 2.21)	1.21 (0.80, 1.83) ^d

Abbreviations: HR, hazard ratio; PWID, persons with a history of injection drug use as an HIV acquisition risk factor; non-IDU, persons without a history of injection drug use; ESLD, end-stage liver disease; ESRD, end-stage renal disease; MI, myocardial infarction; PY, person-years

^aStandardized on black race; HBV infection; FIB-4; hazardous alcohol use; and calendar year of ESLD diagnosis; illicit drug use also standardized on history of injection drug use

^bStandardized on age; body-mass index (BMI); hypertension; diabetes; hemoglobin A1C; LDL cholesterol; FIB-4; CD4 cell count; hazardous alcohol use; and year of ESRD diagnosis; illicit drug use also standardized on history of injection drug use

^cStandardized on black race; age; BMI; hypertension; diabetes; FIB-4; CD4 cell count; log10 HIV viral load; hazardous alcohol use; cigarette smoking; and year of cancer diagnosis; illicit drug use also standardized on history of injection drug use

^dStandardized on sex; black race; age; BMI; hypertension; diabetes; LDL cholesterol; CD4 cell count; cigarette smoking; prior use of ART; and year of MI or stroke diagnosis; illicit drug use also standardized on history of injection drug use

^eBased on a single imputed dataset; exact numbers may differ depending on value of illicit drug use imputed for persons whose drug use was missing in the original data