Association of injection drug use with incidence of HIV-associated non-AIDS-related morbidity by age, 1995–2014

Catherine R. Lesko[a], Richard D. Moore[a], Weiqun Tong[a] and Bryan Lau[a]

Objective: Incidence of HIV-associated non-AIDS (HANA) related comorbidities is increasing in HIV-infected individuals. Our objective was to estimate the risk of HANA comorbidity associated with history of injection drug use (IDU) correctly accounting for higher death rates among people who inject drugs (PWID).

Design: We followed HIV-infected persons aged 25–59 years who enrolled in the Johns Hopkins HIV Clinical Cohort between 1995 and May 2014, from enrollment until HANA comorbidity diagnosis, death, age 60, or administrative censoring.

Methods: We compared cumulative incidence ('risk'), by age, of validated diagnoses of HANA comorbidities among HIV-infected PWID and non-IDU; specifically, we considered end-stage renal disease (ESRD), end-stage liver disease (ESLD), myocardial infarction, stroke, and non-AIDS-defining cancer. We used competing risk methods appropriate to account for death, standardized to the marginal distribution of baseline covariates, and adjusted for potential differential loss-to-clinic.

Results: Of 5490 patients included in this analysis, 37% reported IDU as an HIV transmission risk. By age 55 years, PWID had higher risk of ESLD [risk difference = 6.8, 95% confidence interval (CI): −1.9, 15.5] and ESRD (risk difference = 11.1, 95% CI: 1.2, 21.0) than did non-IDU. Risk of myocardial infarction and stroke were similar among PWID and non-IDU. Risk of non-AIDS-defining cancer was lower among PWID than among non-IDU (risk difference at 55 years: −4.9, 95% CI: −11.2, 1.3).

Conclusion: Not all HANA comorbidities occur with higher incidence in PWID compared with non-IDU. However, higher incidence of ESRD and ESLD among PWIDs highlights the importance of recognition and management of markers of these comorbidities in early stages among PWID.

AIDS 2016, **30**:1447–1455

Keywords: cancer, competing risks, end-stage liver disease, end-stage renal disease, injection drug use, myocardial infarction, stroke

Introduction

AIDS-related comorbidity and mortality in the modern antiretroviral therapy (ART) era has declined rapidly and non-AIDS-related causes of morbidity and death represent an increasing share of the burden of disease among HIV-infected persons [1–4]. The apparent high incidence of HIV-associated non-AIDS (HANA) comorbidities in HIV-infected persons [3,4] is thought to be associated with persistent immunodeficiency, residual inflammation caused by HIV even among people with suppressed viral load [5], direct effects of antiretroviral drugs [6,7], and with lifestyle characteristics that are more prevalent in HIV-infected persons than among uninfected persons [8], including hepatitis C virus (HCV) infection, smoking, and alcohol use [9,10].

[a]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health[b] School of Medicine, Johns Hopkins University, Baltimore, Maryland, USA.

Correspondence to Catherine R. Lesko, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe St, E7139, Baltimore, MD 21205, USA.

Tel: +1 410 614 6517; e-mail: clesko2@jhu.edu

Received: 22 November 2015; revised: 3 March 2016; accepted: 7 March 2016.

DOI:10.1097/QAD.0000000000001087

ISSN 0269-9370

Since early in the epidemic in the United States, injection drug use (IDU) has been an important risk factor for HIV acquisition. IDU is associated with poorer HIV-related outcomes and faster progression of HIV disease and death [11]. Furthermore, compared with persons who do not inject drugs (non-IDU) persons who inject drugs (PWID) have a higher prevalence of many risk factors for HANA comorbidities, in particular HCV coinfection, smoking, and alcohol use. Thus, a history of IDU may be an important predictor for incident HANA comorbidity. Yet, to our knowledge, the cumulative incidence of HANA comorbidities among PWIDs has not been described.

Our goal was to describe the occurrence of major HANA comorbidities among PWID compared with non-IDU, using competing risk methodologies to appropriately account for differences in survival between the two groups. Because PWID experiences higher risk of death than non-IDU, standard Cox proportional hazards models for HANA events may lead to incorrect inferences regarding the risk of HANA events (see statistical methods for more details). Competing risk methods facilitate fuller description of the risk of HANA comorbidities among PWIDs compared with non-IDU individuals.

Methods

Study population

The Johns Hopkins HIV Clinical Cohort (JHHCC) consists of all HIV-infected persons aged 18 years or older who enroll in HIV care at Johns Hopkins outpatient HIV clinic and consent to share their data (approximately >95% of persons who enroll into continuity care). The HIV-infected population in Baltimore, Maryland has a high prevalence of IDU, making the JHHCC well suited to study morbidity and mortality associated with IDU. For this study, we included all HIV-infected persons who enrolled in the JHHCC from January 1995 to May 2014. We excluded persons from analyses of specific HANA comorbidities if they had a validated diagnosis of the HANA comorbidity prior to the start of follow-up, with one exception: when modeling cancer incidence, we included all persons, regardless of prior cancer diagnosis, but only analyzed cancers that occurred in a different site as incident cancers. Collection of data on patients in the JHHCC, and this analysis of that data were approved by the Johns Hopkins Hospital institutional review board.

Patient characteristics including sex, race, age, HIV transmission risk factors, prior AIDS diagnosis, and prior use of any antiretroviral drugs were ascertained through conversations between patient and physician at enrollment. Patients who reported IDU as a possible source of their HIV infection were classified as PWID. Patients could report more than one possible source of their HIV infection (e.g., IDU and being a MSM). Baseline laboratory values and BMI were defined as those measured closest to the date of study enrollment, within a window 6 months prior to and 1 month after enrollment. Starting in 1996, tobacco use (ever/never), alcohol use (hazardous/any/none), cocaine use (ever/never), heroin use (ever/never), and marijuana use (any current/none) were abstracted from patients' medical records every 6 months; we assigned patients to baseline categories for substance use based on the earliest data available. Because loss-to-clinic was not negligible and differential by IDU, if the (unobservable) incidence of HANA was different among patients lost-to-clinic than among those retained in care, a complete-cohort analysis may be biased. We controlled for this potential selection bias using inverse probability of censoring weights (see below) that were estimated based on time-updated laboratory values, BMI, AIDS diagnoses, and ART initiation. Time-varying covariates were updated whenever a patient was seen for routine clinical care. Median time between visits was 3 months [interquartile range (IQR): 2–4].

Outcome validation

We examined the incidence of non-AIDS-defining cancers, end-stage liver disease (ESLD), end-stage renal disease (ESRD), stroke and myocardial infarction (MI). Cancer diagnoses were validated at Johns Hopkins according to a protocol defined by the Centers for AIDS Research Network of Integrated Clinical Systems [12]. Possible ESRD diagnoses and ESLD diagnoses were identified according to a screening protocol developed by the North American AIDS Cohort Collaboration on Research and Design and validated by standardized medical records review at Johns Hopkins [13,14]. Possible MIs and strokes were identified according to screening criteria standardized for the Centers for AIDS Research Network of Integrated Clinical Systems and subsequently validated by physicians participating in cardiovascular disease cohort studies [15,16].

Analysis

We completed separate analyses for each of five HANA comorbidities: ESLD, ESRD, stroke, MI, and non-AIDS cancers. Because HANA comorbidities were analyzed separately, patients could contribute HANA events to more than one HANA analysis. In each analysis, we followed patients from the latest of either enrollment into the JHHCC or their 25th birthday until they were diagnosed with an incident HANA event (type specific to the HANA being analyzed), died, were lost to clinic (1 year without having $CD4^+$ cell count or viral load measured), or were administratively censored (at 60 years or the end of administrative follow-up). End of administrative follow-up depended on the specific HANA comorbidity under investigation (MI, July 2012; stroke, September 2012; ESLD, May 2013; ESRD and cancer, May 2014).

We ran Cox proportional hazards models ('standard methods') to get cause-specific hazard ratios, and use competing risk methods [17,18] to get cumulative incidence functions and calculate risk differences and risk ratios. Cause-specific hazard ratios provide insight into whether, among persons surviving to a given age, PWID have a higher instantaneous risk of developing a HANA. However, because risk of death is higher for PWID than for non-IDU, cause-specific hazard ratios may not correlate with the actual lifetime probability of developing HANA comorbidity [19]. Risk estimates from standard survival analyses (e.g., Kaplan–Meier curves, where people are censored when they die) are sometimes termed 'conditional' risks [20] because they represent risk of HANA comorbidity in a hypothetical world in which the competing event (in this study, death) does not exist. Appropriately accounting for competing risks results in a cumulative incidence or unconditional risk function (henceforth 'risk') that corresponds, more intuitively, to the proportion of the cohort who would experience the event by a given age. Cause-specific hazard ratios provide a summary of the relative rate of HANA comorbidities for IDU versus non-IDU, averaged across all ages. The absolute risks of each HANA comorbidity for IDU versus non-IDU at given ages may be more useful for planning and may be more intuitive when communicating with patients, because lay persons understand absolute changes in risk better than relative changes [21].

We estimated the cumulative incidence of each HANA comorbidity according to age (25–60 years) to improve interpretation and to account for the strong association between older age and HANA comorbidity.

We adjusted for imbalances in the distribution of baseline covariates among PWIDs and non-IDUs using an inverse probability weights. Inverse probability of exposure weights (IPEW) [22] is a semiparametric extension of direct standardization. IPEW allowed for the estimation of disparities in the hazard and risk of HANA comorbidities and death associated with IDU that are not because of baseline covariates already known to be associated with HANA comorbidity risk, such as race, access to ART, or clinical stage at entry to care. The use of inverse probability of censoring weights (IPCW) [23] controlled for the possibility that loss-to-clinic was differential by IDU and that HANA comorbidity risk among those retained in care was different compared with those lost-to-clinic. Final weights were the product of IPEW and IPCW. Applying these weights resulted in cause-specific hazard ratios and relative risks that represent disparities in HANA diagnoses associated with IDU, assuming all baseline covariates in the IPEW model had been equal for the two groups, and assuming we had been able to observe the entire cohort until an incident HANA, death, or age 60 (i.e. had no one been lost-to-clinic) [17,24]. Risk differences and risk ratios were calculated empirically from cumulative incidence curves. Cause-specific hazard ratios were estimated from inverse probability-weighted Cox proportional hazards models [25]. The proportional hazards assumption was checked by visualizing log (−log(survival)) curves.

We estimated the denominator of the IPEW [22] using a logistic regression model for the probability of baseline IDU, conditional on all covariates Table 1 excepting hepatitis B and C virus infection, and cocaine, heroin, or marijuana use. We did not adjust for hepatitis virus infection or illicit drug use because we believe they mediate the association between IDU and risk of HANA comorbidity. As mediators, they are potential targets for reducing disparities in HANA comorbidity risk associated with IDU [26]. We estimated the denominator of the IPCW [23] using a pooled logistic regression, pooling over age (in quarters), for the probability of remaining in care up to a specific age, conditional on covariates in the IPEW model, and time-varying ART initiation, $\log_{10}$ HIV-1 RNA, $CD4^+$ cell count, and AIDS diagnosis. We stabilized IPEW and IPCW by the marginal probability of baseline IDU or remaining in care, respectively. Categorical variables were modeled with disjoint indicator variables and continuous variables were modeled using quadratic and cubic terms. We checked mean and range of the weights, expecting mean weight close to 1. Because some weights were large (>40), we also ran analyses using weights winsorized at the 0.1st and 99.9th percentiles [27].

We used multiple imputations to handle missing data on baseline covariates (Table 1). We generated 20 data sets in which we imputed missing values based on all available baseline data, age at end of follow-up, and incidence of any HANA event or death, stratified on IDU. We conducted all analyses outlined above in each of the 20 data sets, and combined estimates using Rubin's method [28]. We calculated the standard error for risk differences and risk ratios within each imputed data set from the standard deviation of estimates from 200 nonparametric bootstrap random samples drawn with replacement [29]. We calculated the standard error for hazard ratios within each imputed data set using a robust variance estimator [30].

Results

Of 5490 HIV-infected persons enrolled in the JHHCC between 1995 and May 2014, the majority were men (66%), black (76%), and heterosexual (51%). The median age at enrollment was 40 years (IQR: 34, 46), median $CD4^+$ cell count was 268 cells/μl (IQR: 91, 463), and median $\log_{10}$ HIV1 RNA was 4.3 copies/ml (IQR: 2.9, 5.0). Half of persons (55%) had prior exposure to antiretroviral medications and 27% had a prior AIDS diagnosis at enrollment. PWID comprised 37% of the

Table 1. Characteristics of 5490 HIV-infected persons upon enrollment in the Johns Hopkins Clinical Cohort, 1995–2014, stratified by self-report of injection drug use as their likely route of HIV acquisition.

	PWID	Non-IDU	Total
N	2028	3462	5490
Male sex[a]	1366 (67%)	2286 (66%)	3652 (67%)
Age[b]	41 (37, 47)	38 (32, 45)	40 (34, 46)
Race			
Black	1682 (83%)	2466 (71%)	4148 (76%)
White	323 (16%)	848 (25%)	1171 (21%)
Other	23 (1%)	148 (4%)	171 (3%)
Transmission risk			
MSM	173 (9%)	1308 (38%)	1481 (27%)
Heterosexual	925 (46%)	1879 (54%)	2804 (51%)
Ever smoked[c]	1007 (70%)	1192 (43%)	2199 (53%)
Missing	597	705	1302
Alcohol use[c]			
Hazardous use	525 (28%)	485 (15%)	1010 (19%)
Any use	969 (51%)	1699 (51%)	2668 (51%)
Missing	126	124	250
Ever used cocaine[c]	685 (46%)	361 (14%)	1046 (26%)
Missing	546	959	1505
Ever used heroin[c]	715 (48%)	189 (8%)	904 (23%)
Missing	546	959	1505
BMI[b]	24.1 (21.7, 27.6)	24.9 (22.0, 28.6)	24.5 (21.9, 28.2)
Missing	754	1278	2032
Hepatitis B exposure[d]	293 (14%)	384 (11%)	677 (12%)
Hepatitis C exposure[d]	1800 (89%)	832 (24%)	2632 (48%)
History of any ART use	1101 (54%)	1898 (55%)	2999 (55%)
AIDS	564 (28%)	939 (27%)	1503 (27%)
$CD4^+$ cell count (cells/μl)[b]	270 (99, 466)	267 (87, 462)	268 (91, 464)
<50	325 (17%)	607 (19%)	932 (18%)
50–199 cells/μl	451 (23%)	721 (22%)	1172 (22%)
200–349	436 (22%)	667 (20%)	1103 (21%)
≥350 cells/μl	735 (38%)	1270 (39%)	2005 (38%)
Missing	81	197	278
Viral load (HIV RNA $\log_{10}$ copies/ml)[b]	4.3 (3.1, 5.0)	4.3 (2.9, 5.0)	4.3 (2.9, 5.0)
≤400	333 (20%)	652 (22%)	985 (22%)
>400	1330 (80%)	2248 (78%)	3578 (78%)
Missing	365	562	927

ART, antiretroviral therapy; PWID, persons who inject drugs.
[a]*N* (%) unless otherwise specified.
[b]Median (IQR).
[c]Based on a review of the medical record, for example, physician notes, physical signs and symptoms, etc.
[d]As measured by any positive laboratory test for antibody, antigen, or DNA/RNA.

study sample ($n = 2028$). PWID were slightly older than non-IDU and greater proportion were black, ever smokers, hazardous drinkers, and coinfected with HCV. A smaller proportion of PWID reported MSM as another risk factor for HIV infection. IDU was not substantively associated with the probability of reporting any alcohol consumption, being coinfected with hepatitis B virus, having a prior AIDS diagnosis or prior exposure to antiretroviral medications. Median $CD4^+$ cell count and HIV1 RNA did not differ substantively by IDU (Table 1).

The highest crude incidence rate of major HANA comorbidities was for non-AIDS-defining cancer (8.90/1000 person-years), followed by ESRD (5.22/1000 person-years). The rate of ESLD was lowest among the HANA comorbidities investigated (2.08/1000 person-years) (Table 2). The most common incident non-AIDS-defining cancers were lung ($n = 30$), skin (excludes Kaposi's sarcoma; $n = 22$), anal ($n = 19$), and breast ($n = 17$).

PWID consistently had higher risk of death prior to any HANA comorbidity diagnosis than non-IDU at all ages (Fig. 1) For example, by age 55, risk of death prior to an ESLD diagnosis was 13.1% [95% confidence interval (CI): 6.5%, 19.6%] higher among PWIDs than among non-IDU (Table 1). Risk of death before any other HANA diagnosis was similar, although not identical; risk of death before HANA diagnosis was higher for HANA comorbidities that tended to occur at older ages (data not presented). Even given higher risk of death, after standardizing on baseline covariates and adjusting for loss-to-clinic, PWID had higher risk of ESLD and ESRD than did non-IDU (Fig. 1). The risk difference at age 55 for ESLD and ESRD was 6.8% (95% CI: −1.9, 15.5%) and 11.1% (95% CI: 1.2, 21.0%), respectively, comparing PWID to non-IDU. The magnitude of the risk difference

Table 2. Crude cause-specific events, person-years, rates[a], rate ratios and hazard ratios, and adjusted[b] hazard ratios for HANA comorbidity and death, among 5490 HIV-infected persons in the Johns Hopkins Clinical Cohort, 1995–2014.

	PWID			Non-IDU					
	Events	Person-years	Rate[a]	Events	Person-years	Rate[a]	Crude rate ratio	Crude hazard ratio	Adjusted hazard ratio
HANA comorbidity									
ESLD	29	6822.5	4.25	14	13840.3	1.01	4.20 (2.22, 7.95)	3.63 (1.86, 7.09)	2.99 (1.30, 6.88)[d]
ESRD	61	6964.7	8.76	51	14493.7	3.52	2.49 (1.72, 3.61)	2.58 (1.76, 3.78)	2.29 (1.43, 3.69)
Stroke	28	6636.2	4.22	19	13173.2	1.44	2.93 (1.63, 5.24)	2.63 (1.46, 4.76)	1.57 (0.80, 3.06)[d]
MI	40	6540.7	6.12	50	12920.9	3.87	1.58 (1.04, 2.40)	1.34 (0.89, 2.02)	0.82 (0.49, 1.39)[d]
Non-AIDS cancer[c]	62	7035.6	8.81	127	14201.9	8.94	0.99 (0.73, 1.34)	0.80 (0.59, 1.09)	0.79 (0.52, 1.21)
Death									
ESLD	424	6822.5	62.15	417	13840.3	30.13	2.06 (1.80, 2.36)	2.04 (1.77, 2.35)	1.39 (1.15, 1.69)
ESRD	407	6964.7	58.44	394	14493.7	27.18	2.15 (1.87, 2.47)	2.12 (1.84, 2.46)	1.39 (1.14, 1.69)
Stroke	431	6636.2	64.95	418	13173.2	31.73	2.05 (1.79, 2.34)	2.01 (1.75, 2.32)	1.43 (1.18, 1.73)
MI	420	6540.7	64.21	393	12920.9	30.42	2.11 (1.84, 2.42)	2.08 (1.80, 2.41)	1.48 (1.22, 1.80)
Non-AIDS cancer[c]	415	7035.6	58.99	382	14204.9	26.90	2.19 (1.91, 2.52)	2.22 (1.92, 2.57)	1.50 (1.24, 1.83)

ESLD, end-stage liver disease; ESRD, end-stage renal disease; HANA, HIV-associated non-AIDS-related; MI, myocardial infarction; PWID, persons who inject drugs.
[a]Per 1000 person-years.
[b]PWID and non-IDU groups standardized on: sex, age, race, baseline HIV transmission risk because of MSM or high-risk heterosexual sex, baseline smoking, alcohol use, BMI, prior antiretroviral therapy use, prior AIDS diagnosis, $CD4^+$ cell count, and viral load; also adjusted for potentially differential loss-to-clinic associated with all baseline variables listed here, IDU, and time-varying $CD4^+$ cell count, viral load, BMI, AIDS diagnosis, and ART initiation.
[c]AIDS-defining cancers include invasive cervical cancer, non-Hodgkin's lymphoma, and Kaposi's sarcoma.
[d]Some evidence of proportional hazards assumption violated as the log of the cumulative hazard curves crossed or were not parallel) for AIDS-defining cancer, ESLD, MI, and stroke, therefore, the HR should be interpreted as a time-averaged estimate.

for ESLD was driven in large part by one early ESLD case when there were few other PWID in the age risk set (see the large step in Fig. 1). Deleting the early ESLD case, brought the risk difference of ESLD at age 55 down slightly to 5.0% (95% CI: −3.2, 13.2%). Risk of stroke, MI, and non-AIDS-defining cancer were not significantly different among PWIDs and non-IDUs, although risk of non-AIDS-defining cancers was slightly lower among PWIDs compared with non-IDUs (risk difference at age 55 years = −4.9%, 95% CI: −11.2, 1.3%). The most common non-AIDS-defining cancers among PWIDs were lung (19%) and liver (15%), compared with skin (12%), anal (11%), and lung (11%) among non-IDU.

Cause-specific hazards ratios showed similar trends to those seen in risk differences. PWID had a mortality hazard between 39 and 50% higher than non-IDU (Table 2). PWID had a higher cause-specific hazard of ESLD (inverse probability-weighted hazard ratio = 2.99, 95% CI: 1.30, 6.88%) and ESRD (inverse probability-weighted hazard ratio = 2.29, 95% CI: 1.43, 3.69%) compared with non-IDU. The cause-specific hazard of stroke was elevated among PWIDs but the association was not statistically significant (inverse probability-weighted hazard ratio = 1.57, 95% CI: 0.80, 3.06%). The cause-specific hazard of non-AIDS-defining cancer and MI was similar for PWID and non-IDU. The proportional hazards assumption was violated for ELSD, stroke, and MI, meaning that the cause-specific hazard ratios for these events varied over the 35 years of follow-up and the hazard ratios presented in Table 2 and herein are time-averaged summary measures.

Discussion

In this cohort, cause-specific mortality hazard was approximately 50% higher among PWIDs than among non-IDU. The hazard of ESLD and ESRD were higher among PWID, which led to a higher risk of ESLD and ESRD among PWID at nearly all ages, even though fewer PWID survived to be diagnosed with a HANA comorbidity. This association remained even after standardizing on baseline covariates and potentially differential loss-to-clinic. However, PWID did not have a higher risk of all HANA comorbidities. Although the cause-specific hazard ratio for stroke comparing PWID and non-IDU was suggestive of a strong association, risk of stroke was similar in PWID and non-IDU, and possibly lower among PWIDs until age 40. The cause-specific hazard and risk of MI and non-AIDS-defining cancers was lower among PWIDs compared with non-IDU, although associations failed to reach statistical significance.

In this study, we examined risk of HANA comorbidities according to history of IDU. Our results should not be interpreted as the causal effect of continuous IDU. Because some persons reporting history of IDU subsequently ceased injecting drugs (and few if any persons with no history of IDU initiated injecting drugs) results probably underestimate the association between continuous IDU and HANA comorbidity and death. Furthermore, 'the' effect of IDU on HANA comorbidity risk likely varies according to type of drug injected, and frequency and duration of injection. Although we had some information on use of specific drugs from medical

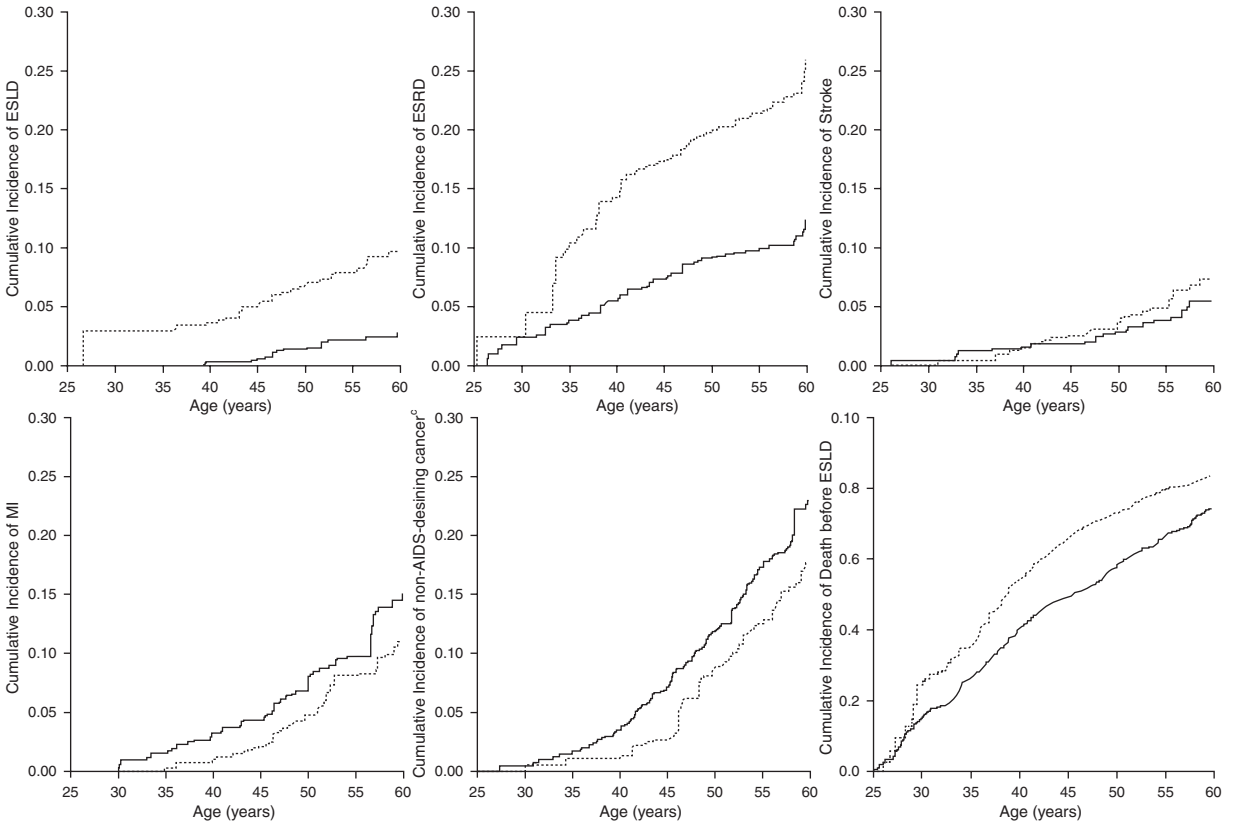

Fig. 1. Adjusted[a] cumulative incidence of five HANA comorbidities and cumulative incidence of death before ESLD diagnosis[b], stratified by baseline IDU (dashed line, $n = 2028$) or non-IDU (solid line, $n = 3462$), by age, Johns Hopkins Clinical Cohort, 1995–2014. HANA, HIV-associated non-AIDS-related; ESLD, end-stage liver disease; ESRD, end-stage renal disease; MI, myocardial infarction. [a]PWID and non-IDU groups standardized on: sex, age, race, baseline HIV transmission risk because of MSM or high-risk heterosexual sex, baseline smoking, alcohol use, BMI, prior antiretroviral therapy use, prior AIDS diagnosis, $CD4^+$ cell count, and viral load; also adjusted for and potentially differential loss-to-clinic associated with all baseline variables listed here, IDU, and time-varying $CD4^+$ cell count, viral load, BMI, AIDS diagnosis and ART initiation. [b]Cumulative incidence of death, as well as risk difference and risk ratio associated with IDU were similar for all HANA comorbidities; we present death before ESLD as a representative example of the association between IDU and death before HANA comorbidity diagnosis. [c]AIDS-defining cancers include invasive cervical cancer, non-Hodgkin's lymphoma, and Kaposi's sarcoma.

record review, we did not have information on frequency and duration of drug use over time. Furthermore, documentation of drug use in the medical record was likely differential according to history of IDU. If we had attempted to estimate an association between time-varying use of specific drugs and HANA, such an imperfect measure of 'exposure' could lead to biased results [31]. History of IDU may be a more discriminating indicator of future HANA comorbidity risk than time-varying injecting behavior, anyway, because of the long induction period for all HANA comorbidities we investigated. Despite not distinguishing the many specific effects of IDU in this study, we believe our results are useful to HIV providers who may know patients' history of IDU but who do not have time or resources to collect current injecting behavior.

We estimated that IDU was associated with increased risk of ESRD. IDU was previously noted as highly prevalent among persons diagnosed with HIV-1-associated nephropathy [32]. In contrast to our results, in the ART Cohort Collaboration (ART-CC), IDU was not associated with hazard of renal-related mortality [2]. The ART-CC examined non-AIDS-related causes of death and is one of the only other studies to report cumulative incidence functions, which appropriately account for competing events by not censoring individuals experiencing a competing event. However, the ART-CC examined causes of death, not incident diagnoses, and therefore, may have been underpowered to detect an association between IDU and renal-related morbidity. We analyzed validated clinical diagnoses of HANA comorbidities rather than causes of death, which increased power (because individuals could contribute events to more than one analysis), and was more sensitive for the outcome (because a HANA comorbidity did not have to cause death to be included). Our findings suggest that IDU should be considered an important risk factor for ESRD.

Table 3. Crude and adjusted[a] risk differences and risk ratios at age 35, 40, 45, 50, and 55 years for five HANA comorbidities and death (before ESLD)[b] comparing PWID (n = 2028) to non-IDU (n = 3462) individuals in the Johns Hopkins Clinical Cohort, 1995–2014.

	Crude		Adjusted	
Age	Risk difference	Risk ratio	Risk difference	Risk ratio
ESLD				
35	3.7 (−3.7, 11.0)	–	4.0 (−4.4, 12.3)	–
40	4.6 (−2.9, 12.1)	10.69 (1.24, 92.02)	4.3 (−4.1, 12.7)	13.59 (0.91, 203.30)
45	5.6 (−2.0, 13.1)	8.17 (1.54, 43.28)	5.7 (−2.9, 14.2)	10.24 (1.59, 67.25)
50	7.0 (−0.5, 14.5)	5.97 (1.95, 18.32)	6.5 (−2.1, 15.1)	5.57 (1.36, 22.87)
55	7.7 (0.1, 15.2)	4.75 (1.80, 12.57)	6.8 (−1.9, 15.5)	4.10 (1.17, 14.41)
ESRD				
35	6.3 (−5.7, 18.4)	2.64 (0.59, 11.92)	6.2 (−3.4, 15.7)	2.58 (0.74, 9.03)
40	8.8 (−3.4, 20.9)	2.69 (0.93, 7.78)	8.4 (−1.5, 18.3)	2.55 (1.00, 6.50)
45	10.4 (−1.5, 22.3)	2.61 (1.13, 6.04)	9.7 (−0.2, 19.6)	2.34 (1.14, 4.77)
50	12.2 (0.6, 23.8)	2.61 (1.31, 5.19)	10.4 (0.6, 20.3)	2.15 (1.16, 3.99)
55	12.8 (1.2, 24.3)	2.46 (1.31, 4.62)	11.1 (1.2, 21.0)	2.12 (1.20, 3.75)
Stroke				
35	−0.1 (−2.7, 2.6)	0.96 (0.21, 4.40)	−0.9 (−2.7, 0.8)	0.32 (0.07, 1.56)
40	0.8 (−2.3, 3.9)	1.51 (0.27, 8.38)	−0.2 (−2.5, 2.0)	0.86 (0.15, 5.03)
45	2.3 (−1.0, 5.6)	2.30 (0.66, 7.96)	0.6 (−1.8, 3.0)	1.31 (0.37, 4.63)
50	2.6 (−0.8, 6.1)	2.07 (0.83, 5.18)	0.8 (−2.1, 3.6)	1.26 (0.51, 3.12)
55	3.5 (−0.2, 7.2)	2.03 (0.99, 4.20)	1.0 (−2.2, 4.1)	1.24 (0.59, 2.61)
MI				
35	−1.0 (−2.8, 0.8)	0.36 (0.10, 1.28)	−1.4 (−3.0, 0.2)	0.15 (0.04, 0.56)
40	−1.6 (−4.0, 0.9)	0.48 (0.13, 1.80)	−2.4 (−4.7, 0.0)	0.30 (0.07, 1.18)
45	−1.1 (−3.9, 1.7)	0.73 (0.30, 1.80)	−2.5 (−5.2, 0.3)	0.45 (0.17, 1.20)
50	−0.2 (−3.7, 3.2)	0.96 (0.53, 1.73)	−2.2 (−6.0, 1.7)	0.69 (0.35, 1.35)
55	0.1 (−3.9, 4.2)	1.02 (0.64, 1.62)	−1.8 (−6.8, 3.2)	0.82 (0.47, 1.44)
Non-AIDS cancer[c]				
35	0.3 (−3.2, 3.8)	1.16 (0.25, 5.44)	−0.3 (−2.9, 2.2)	0.79 (0.16, 3.89)
40	−1.4 (−5.1, 2.3)	0.64 (0.13, 3.07)	−1.9 (−4.7, 0.8)	0.45 (0.10, 2.00)
45	−3.0 (−7.0, 1.1)	0.60 (0.26, 1.38)	−4.3 (−7.7, −1.0)	0.41 (0.17, 0.98)
50	−4.3 (−9.0, 0.5)	0.66 (0.40, 1.10)	−3.3 (−8.5, 1.9)	0.73 (0.42, 1.27)
55	−5.9 (−11.5, −0.3)	0.68 (0.46, 1.00)	−4.9 (−11.2, 1.3)	0.72 (0.46, 1.13)
Death (before ESLD)[b]				
35	14.9 (3.3, 26.6)	1.63 (1.17, 2.27)	7.0 (-6.4, 20.3)	1.27 (0.83, 1.95)
40	20.0 (10.9, 29.1)	1.56 (1.29, 1.87)	13.2 (1.7, 24.6)	1.33 (1.06, 1.69)
45	25.5 (18.5, 32.4)	1.59 (1.40, 1.79)	15.9 (6.8, 25.0)	1.33 (1.14, 1.55)
50	26.0 (20.1, 31.8)	1.51 (1.37, 1.66)	14.4 (6.6, 22.2)	1.25 (1.11, 1.41)
55	24.4 (19.3, 29.4)	1.42 (1.31, 1.53)	13.1 (6.5, 19.6)	1.20 (1.10, 1.31)

ESLD, end-stage liver disease; ESRD, end-stage renal disease; HANA, HIV-associated non-AIDS-related; HIV, human immunodeficiency virus; IDU, injection drug use; MI, myocardial infarction; PWID, persons who inject drugs.

[a]PWID and non-IDU groups standardized on: sex, age, race, baseline HIV transmission risk because of MSM or high-risk heterosexual sex, baseline smoking, alcohol use, BMI, prior antiretroviral therapy use, prior AIDS diagnosis, $CD4^+$ cell count, and viral load; also adjusted for and potentially differential loss-to-clinic associated with all baseline variables listed here, IDU, and time-varying $CD4^+$ cell count, viral load, BMI, AIDS diagnosis, and ART initiation.

[b]Cumulative incidence of death, as well as risk difference and risk ratio associated with IDU were similar for all HANA comorbidities; we present death before ESLD as a representative example of the association between IDU and death before HANA comorbidity diagnosis

[c]AIDS-defining cancers include invasive cervical cancer, non-Hodgkin's lymphoma, and Kaposi's sarcoma

Our finding that IDU is associated with ESLD is not surprising, given high prevalence of HCV coinfection and alcohol consumption among PWIDs [33]. Furthermore, among those with HIV/HCV coinfection, IDU is associated with increased rate of HCV disease progression [34] and liver-related mortality [2]. An estimate of how much of the increased risk of ESLD among PWIDs is mediated by HCV coinfection would be particularly useful in light of new, highly effective direct-acting antiviral treatment regimens for HCV. It is possible that new direct-acting antivirals for treatment of HCV [35] will reduce incidence of ESLD for both PWID and non-IDU in the future. However, IDU may be a barrier to HCV treatment [36] and it will be important to assess trends in HCV treatment and liver disease progression in this population.

Cause-specific hazard for non-AIDS-defining cancer was lower among PWIDs than among non-IDU in this cohort. In the ART-CC, IDU was associated with higher hazard of non-AIDS-related cancer death [2]. Few studies of cancer incidence among HIV-infected persons have specifically stratified on IDU. Investigations into incidence of specific cancers and their association with IDU could provide insight into these results, but we did not have enough incident cancers to stratify cancers further.

Although we did not observe increased risk of cardiovascular events among IDUs, PWID had a higher crude cause-

specific hazard of MI and stroke. There is other evidence that PWID have a higher cause-specific hazard of cardiovascular causes of death [2]. Both heroin and cocaine use are in Baltimore, and cocaine is associated with acute MI and stroke [37]. The lack of association between IDU and risk of cardiovascular events may be because of high prevalence of noninjection illicit drug use among the non-IDU in our cohort. However, it may also be the result of appropriately accounting for competing events.

Our analysis has several strengths, including, first, proper accounting for death as a competing risk. Most prior studies have not used competing risk methods, which may explain some of the disagreement in the literature as to the association between IDU and HANA comorbidities or non-AIDS-related causes of death [2,38]. Second, we used validated HANA comorbidity diagnoses, rather than relying on clinical diagnoses or cause-specific mortality. Third, we allowed individuals to contribute diagnoses to more than one HANA analysis. Because older HIV-infected patients often have multimorbidity [39] this increased our power. Indeed, 49 individuals in our cohort had more than one HANA comorbidity diagnosis. Finally, by presenting cumulative incidence curves (Fig. 1) we have increased the interpretability of our results. Because not everyone enters the cohort at age 25 (i.e. we have late entries), one limitation of our analysis is that we must assume that HANA comorbidity incidence among younger PWIDs is a good substitute for the HANA incidence among older PWIDs, had we been able to observe them when they were younger. If older and younger PWID who entered our cohort were not comparable, we may have over (or under) estimated the risk of HANA comorbidities (Table 3).

In conclusion, the increased risk of ESRD and ESLD among HIV-infected PWIDs should be recognized and monitored. It will be particularly important to understand the mediating effect of HCV infection on this increased risk in light of the new treatments for HCV. Notably, we did not find evidence of an association between IDU and risk of stroke or MI, although the cause-specific hazard of stroke was slightly elevated among PWIDs. Finally, the risk of non-AIDS-defining cancers was actually lower among PWIDs than among non-IDU. PWID in our cohort have higher mortality rates than non-IDU and it will be important to understand the reasons for these higher rates. Our analysis indicates that to date, after for death as a competing event, PWID are not at increased risk compared with non-IDU for several HANA comorbidities that have become of increasing concern as HIV-infected persons survive longer.

Acknowledgements

C.R.L. conducted analyses and drafted the manuscript. R.D.M oversaw collection of data, conceived of the research question, and provided substantive expertise and guidance. W.T. assisted in cleaning of data and data management. B.L. conceived of the research question and provided methodological expertise and guidance. All authors have read and approved the final manuscript. This work was supported by NIH grants U01 DA036935, U01 HL121812, and P30 AI094189.

Conflicts of interest

There are no conflicts of interest.

References

1. Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, d'Arminio Monforte A, *et al*. **Decline in the AIDS and death rates in the EuroSIDA study: an observational study.** *Lancet* 2003; **362**:22–29.
2. Antiretroviral Therapy Cohort Collaboration. **Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996–2006: collaborative analysis of 13 HIV cohort studies.** *Clin Infect Dis* 2010; **50**:1387–1396.
3. Deeks SG, Phillips AN. **HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity.** *BMJ* 2009; **338**:a3172.
4. Whiteside YO, Selik R, An Q, Huang T, Karch D, Hernandez AL, *et al*. **Comparison of rates of death having any death-certificate mention of heart, kidney, or liver disease among persons diagnosed with HIV infection with those in the general US population, 2009–2011.** *Open AIDS J* 2015; **9**:14–22.
5. Kuller LH, Tracy R, Belloso W, De Wit S, Drummond F, Lane HC, *et al*. **Inflammatory and coagulation biomarkers and mortality in patients with HIV infection.** *PLoS Med* 2008; **5**:e203.
6. Friis-Moller N, Worm SW. **Can the risk of cardiovascular disease in HIV-infected patients be estimated from conventional risk prediction tools?** *Clin Infect Dis* 2007; **45**:1082–1084.
7. Group DADS, Sabin CA, Worm SW, Weber R, Reiss P, El-Sadr W, *et al*. **Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multicohort collaboration.** *Lancet* 2008; **371**:1417–1426.
8. Goulet JL, Fultz SL, Rimland D, Butt A, Gibert C, Rodriguez-Barradas M, *et al*. **Aging and infectious diseases: do patterns of comorbidity vary by HIV status, age, and HIV severity?** *Clin Infect Dis* 2007; **45**:1593–1601.
9. Kakinami L, Block RC, Adams MJ, Cohn SE, Maliakkal B, Fisher SG. **Risk of cardiovascular disease in HIV, hepatitis C, or HIV/hepatitis C patients compared to the general population.** *Int J Clin Pract* 2013; **67**:6–13.
10. Lucas GM, Jing Y, Sulkowski M, Abraham AG, Estrella MM, Atta MG, *et al*. **Hepatitis C viremia and the risk of chronic kidney disease in HIV-infected individuals.** *J Infect Dis* 2013; **208**:1240–1249.
11. Lucas GM, Griswold M, Gebo KA, Keruly J, Chaisson RE, Moore RD. **Illicit drug use and HIV-1 disease progression: a longitudinal study in the era of highly active antiretroviral therapy.** *Am J Epidemiol* 2006; **163**:412–420.
12. Achenbach CJ, Cole SR, Kitahata MM, Casper C, Willig JH, Mugavero MJ, *et al*. **Mortality after cancer diagnosis in HIV-infected individuals treated with antiretroviral therapy.** *AIDS* 2011; **25**:691–700.
13. Abraham AG, Althoff KN, Jing Y, Estrella MM, Kitahata MM, Wester CW, *et al*. **End-stage renal disease among HIV-infected adults in North America.** *Clin Infect Dis* 2015; **60**:941–949.
14. Kitahata MM, Drozd DR, Crane HM, Van Rompaey SE, Althoff KN, Gange SJ, *et al*. **Ascertainment and verification of end-stage renal disease and end-stage liver disease in the north american AIDS cohort collaboration on research and design.** *AIDS Res Treat* 2015; **2015**:923194.
15. Crane HM, Heckbert SR, Drozd DR, Budoff MJ, Delaney JA, Rodriguez C, *et al*. **Lessons learned from the design and implementation of myocardial infarction adjudication tailored for HIV clinical cohorts.** *Am J Epidemiol* 2014; **179**:996–1005.

16. Rosamond WD, Folsom AR, Chambless LE, Wang CH, McGovern PG, Howard G, *et al*. **Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort.** *Stroke* 1999; **30**:736–743.
17. Cole SR, Lau B, Eron JJ, Brookhart MA, Kitahata MM, Martin JN, *et al*. **Estimation of the standardized risk difference and ratio in a competing risks framework: application to injection drug use and progression to AIDS after initiation of antiretroviral therapy.** *Am J Epidemiol* 2015; **181**:238–245.
18. Fine JP, Gray RJ. **A proportional hazards model for the subdistribution of a competing risk.** *J Am Stat Assoc* 1999; **94**:496–509.
19. Allignol A, Schumacher M, Wanner C, Drechsler C, Beyersmann J. **Understanding competing risks: a simulation point of view.** *BMC Med Res Methodol* 2011; **11**:86.
20. Rothman KJ, Greenland S, Lash TL. *Modern epidemiology*. 3rd ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.
21. Visschers VH, Meertens RM, Passchier WW, de Vries NN. **Probability information in risk communication: a review of the research literature.** *Risk Anal* 2009; **29**:267–287.
22. Robins J, Hernan MA, Brumback B. **Marginal structural models and causal inference in epidemiology.** *Epidemiology* 2000; **11**:550–560.
23. Robins JM, Finkelstein DM. **Correcting for noncompliance and dependent censoring in an AIDS Clinical Trial with inverse probability of censoring weighted (IPCW) log-rank tests.** *Biometrics* 2000; **56**:779–788.
24. Cole SR, Hernan MA. **Adjusted survival curves with inverse probability weights.** *Comput Methods Programs Biomed* 2004; **75**:45–49.
25. Cox DR. **Regression models and life tables.** *J R Stat Soc Series B, Stat Methodol* 1972; **34**:187–220.
26. VanderWeele TJ, Robinson WR. **On the causal interpretation of race in regressions adjusting for confounding and mediating variables.** *Epidemiology* 2014; **25**:473–484.
27. Cole SR, Hernan MA. **Constructing inverse probability weights for marginal structural models.** *Am J Epidemiol* 2008; **168**:656–664.
28. Rubin DB. **Multiple imputation after 18+ years.** *J Am Stat Assoc* 1996; **91**:473–489.
29. Efron B, Tibshirani R. *An introduction to the bootstrap*. New York: Chapman & Hall; 1993.
30. Lin DY, Wei LJ. **The robust inference for the proportional hazards model.** *J Am Stat Assoc* 1989; **84**:1074–1078.
31. Thomas D, Stram D, Dwyer J. **Exposure measurement error: influence on exposure-disease. Relationships and methods of correction.** *Annu Rev Public Health* 1993; **14**:69–93.
32. Klotman PE. **HIV-associated nephropathy.** *Kidney Int* 1999; **56**:1161–1176.
33. Galvan FH, Bing EG, Fleishman JA, London AS, Caetano R, Burnam MA, *et al*. **The prevalence of alcohol consumption and heavy drinking among people with HIV in the United States: results from the HIV Cost and Services Utilization Study.** *J Stud Alcohol* 2002; **63**:179–186.
34. Greub G, Ledergerber B, Battegay M, Grob P, Perrin L, Furrer H, *et al*. **Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study.** *Lancet* 2000; **356**:1800–1805.
35. When and in whom to initiate HCV therapy. In: *Recommendations for testing, managing, and treating hepatitis C*. Edited by Diseases AAftSoL, America IDSo.
36. McGowan CE, Fried MW. **Barriers to hepatitis C treatment.** *Liver Int* 2012; **32 (Suppl 1)**:151–156.
37. McCord J, Jneid H, Hollander JE, de Lemos JA, Cercek B, Hsue P, *et al*. **Management of cocaine-associated chest pain and myocardial infarction: a scientific statement from the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology.** *Circulation* 2008; **117**:1897–1907.
38. Lucas GM, Eustace JA, Sozio S, Mentari EK, Appiah KA, Moore RD. **Highly active antiretroviral therapy and the incidence of HIV-1-associated nephropathy: a 12-year cohort study.** *AIDS* 2004; **18**:541–546.
39. Salter ML, Lau B, Go VF, Mehta SH, Kirk GD. **HIV infection, immune suppression, and uncontrolled viremia are associated with increased multimorbidity among aging injection drug users.** *Clin Infect Dis* 2011; **53**:1256–1264.