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Hepatitis C coinfection and extrahepatic cancer incidence among people living with HIV

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Abstract

Objectives: We assessed incidence of extrahepatic cancer among people with HIV/HCV coinfection and the potential impact of direct-acting antivirals (DAAs) on extrahepatic cancer risk among people with HIV/HCV coinfection.

Design: Our study cohort included adults who initiated HIV care at a CNICS site in the U.S. during 1995-2017, excluding those with previous cancer and without HCV testing.

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CONFLICTS OF INTEREST:

Sarah Willis is participating in research funded by Pfizer and paid to Harvard Pilgrim Health Care Institute outside of the submitted work.

Edward Cachay has received research grants paid to UC Reagents from Gilead Sciences and Merck and has been on an advisory board for Gilead Sciences.

Michael Silverberg has received a grant paid to his institution from Gilead Sciences.

Phyllis Tien's institution received funding from Merck to support her research and Gilead to support an industry-funded clinical trial.

Julia Marcus has previously consulted for Kaiser Permanente Northern California on a research grant from Gilead Sciences outside of the submitted work.

Methods: We used Cox regression to estimate hazard ratios for extrahepatic cancer incidence among patients with HIV/HCV coinfection compared with those with HIV monoinfection. Standardized morbidity ratio (SMR) weights were used to create a "pseudopopulation" in which all patients were treated with antiretroviral therapy (ART), and to compare extrahepatic cancer incidence among patients with untreated HIV/HCV coinfection with the incidence that would have been observed if they had been successfully treated for HCV.

Results: Of 18,422 adults, 1,775 (10%) had HCV RNA and 10,899 (59%) were on ART at baseline. Incidence rates of any extrahepatic cancer among patients with HIV/HCV coinfection and HIV monoinfection were 1,027 and 771 per 100,000 person-years, respectively. In SMR-weighted analyses, the risk of any extrahepatic cancer among patients with untreated HCV coinfection at baseline was similar to the risk if they had been successfully treated for HCV. Patients with untreated HCV coinfection at baseline had higher incidence of kidney, lung, and inflammation-related cancers than if their HCV had been successfully treated, but these associations were not statistically significant.

Conclusions: We did not find evidence that treating HCV coinfection with DAAs would reduce incidence of extrahepatic cancers among people with HIV receiving ART.

Keywords

Hepatitis C; chronic; HIV Infection; HIV Coinfection; Antiviral Agents; Extrahepatic Cancer

INTRODUCTION

Hepatitis C virus (HCV) infection is the most common chronic bloodborne infection in the United States (U.S.), with particularly severe outcomes in people with HIV. People with HIV/HCV coinfection have three-fold risk of cirrhosis progression compared with people with HCV monoinfection [1,2]. HCV-associated liver disease is also a leading cause of non-AIDS-related death among people with HIV [3].

Few studies have explored the relationship between HCV infection and extrahepatic outcomes, particularly among people with HIV/HCV coinfection. HCV infection may increase the risk of non-liver-related outcomes, including extrahepatic cancers such as non-Hodgkin lymphoma (NHL), lung cancer, and anal cancer [4-8], due to increased immunosuppression, immune activation, and chronic inflammation [9,10]. However, previous studies that examined the association between HCV infection and extrahepatic cancers among people with HIV/HCV coinfection were limited by small sample size, incomplete adjustment for confounders such as smoking and substance use, and reliance on the general population as a comparison group rather than an internal control group of persons with HIV but not HCV infection [11-14].

Initial uptake of HCV treatment using direct-acting antiviral (DAA) agents was hindered by high cost and policies restricting access to patients with advanced liver fibrosis, cirrhosis, and those without active substance use [15-17]. In recent years, DAA uptake has increased as generic formulations have been introduced [19], increasing market competition and driving down prices [18], and as more patients have become eligible to be treated. To ensure

that the expansion of HCV treatment continues, it is important to understand secondary and longer-term benefits of curing HCV infection. Thus, the objectives of our analyses were to assess the incidence of extrahepatic cancer among people with HIV/HCV coinfection and to estimate the potential impact of DAAs on extrahepatic cancer risk among people with HIV/HCV coinfection.

METHODS

Study population

Our study population included individuals 18 years of age or older living with HIV who initiated care at one of eight Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) sites between January 1, 1995 and November 1, 2017 and had at least one follow-up visit 180 days or more later. CNICS is a dynamic clinical cohort that collects longitudinal data on demographic characteristics, HIV-related diagnoses, laboratory information, and patient-reported outcomes from over 34,000 people with HIV in the U.S [20]. CNICS sites included in this analysis were Case Western Reserve University, University of Alabama at Birmingham, University of Washington, University of California San Diego, Fenway Health, University of North Carolina at Chapel Hill, and Johns Hopkins University [20].

We defined HCV infection as having documented detectable HCV RNA before baseline. HCV-seropositive patients without confirmatory HCV RNA results available were classified as missing HCV status and were excluded from the primary analyses. We also excluded patients with HCV infection who initiated DAA therapy before baseline. For our study, baseline was defined as 180 days after the first clinical visit to allow time for patients to establish HIV care at a CNICS site and have HCV- and HIV-related labs drawn.

The outcomes of interest were extrahepatic cancer diagnoses after baseline. We examined the most common site-specific cancers, including anal cancer, kidney cancer, lung cancer, NHL, prostate cancer, and Kaposi sarcoma (KS). Given small numbers of site-specific cancers, we also examined several combinations of extrahepatic cancers, grouped as any extrahepatic cancer, viral infection-related cancers, and inflammation-related cancers. Infection-related extrahepatic cancers included malignancies of the anus, rectum, cervix, and oropharyngeal cavity (human papillomavirus), as well as Hodgkin's lymphoma, NHL (Epstein-Barr virus), and KS (human herpesvirus 8) [21,22]. Inflammation-related cancers included malignancies of the bladder, colon, esophagus, lung, pancreas, and stomach, as well as multiple myeloma [23]. Cancer diagnoses were available from January 1995 through April 2018; cancer validations are done in waves in CNICS and all cancers diagnosed through December 31, 2016 were verified by medical record review. Patients who had a record of a cancer diagnosis before baseline were excluded from our analyses.

Covariate assessment

Covariates were measured at baseline and included age, sex, race/ethnicity, calendar year of CNICS entry, alcohol use disorders, smoking, drug use, chronic hepatitis B infection, CD4 cell count, HIV RNA suppression, and liver fibrosis. Data on HIV transmission risk

factor are available in CNICS, but these are determined at the time of infection and may not reflect later behavior. Therefore, these data were not included in our models. Age was included as a continuous variable using restricted quadratic splines with four knots at the 5th, 35th, 65th, and 95th percentiles [24]. Race/ethnicity was categorized as non-Hispanic White, non-Hispanic Black, non-Hispanic Asian/Pacific Islander, Hispanic, or "other." Calendar years of CNICS entry were grouped as 1995-1999, 2000-2004, 2005-2009, 2010-2014, or 2015-2017. Alcohol use disorders were defined as a clinical diagnosis of alcohol dependence or alcohol non-dependent abuse on or before CNICS enrollment. Smoking was defined as a clinical diagnosis of current tobacco use or history of tobacco use at CNICS enrollment. Drug use included a clinical diagnosis of amphetamine, cocaine, hallucinogen, inhalant, marijuana, illicit opioid, or other substance use on or before CNICS enrollment. Chronic HBV infection was defined as ever having a positive HBV DNA (quantitative or qualitative), HBV surface antigen, or HBV e antigen result. CD4 cell counts were categorized as <200 cells/μL, 200-500 cells/μL, or >500 cells/μL. HIV RNA suppression was defined as a viral load <200 copies/mL. Liver fibrosis was measured by the FIB-4 index and categorized as <1.45, 1.45-3.25, or >3.25 [25]. Patients who were missing data on HIV RNA level, CD4 cell count, or race/ethnicity at baseline were excluded from the study.

Statistical Analysis

Patients were followed from baseline until the earliest occurrence of extrahepatic cancer or censoring due to loss to follow-up or death. For each extrahepatic cancer outcome, patients were followed from baseline until they were diagnosed with the site-specific cancer or cancer category. These diagnoses could have been patients' second, third, or fourth cancer diagnosis if previously diagnosed cancers were in other categories or sites. Patients who remained in the study were administratively censored on April 30, 2018.

Cox proportional hazards regression models were used to estimate crude hazard ratios (HR) and 99.5% confidence intervals (CI) for extrahepatic cancer incidence among patients with HIV/HCV coinfection compared to patients with HIV monoinfection. We used 99.5% CI, rather than 95% CI, because we examined nine distinct extrahepatic cancer outcomes [26].

To estimate the potential effect of HCV treatment and HIV treatment among patients who received the respective treatment, we used two sets of standardized morbidity ratio (SMR) weights [27]. The first set of SMR weights was used to estimate the effect of HIV/HCV coinfection on extrahepatic cancer incidence in a cohort of patients who were all receiving ART. In these weights, patients who had not yet initiated ART at baseline were weighted to reflect the distribution of covariates among participants who had initiated ART before baseline. In 2012, U.S. treatment guidelines recommended ART for all people with HIV, regardless of CD4 cell count [28]. We believed that our results would have greater clinical relevance if we estimated the effect of HCV treatment on extrahepatic cancers in a cohort of patients with HIV who were all receiving the standard of care for HIV. ART-naïve patients were assumed to be conditionally exchangeable with patients who had already initiated ART given baseline covariates. Logistic regression was used to estimate these weights in a model that included age, calendar year of CNICS entry, CD4 cell count, HIV suppression, and HCV status.

We used a second set of SMR weights to compare extrahepatic cancer incidence among patients with HIV/HCV coinfection with the incidence we would have observed if all patients with HIV/HCV coinfection were treated with DAAs and achieved sustained virologic response (SVR) at baseline. This approach was used so that we could compare the natural course—i.e. incidence of extrahepatic cancers among patients with HIV/HCV coinfection, some of whom subsequently received interferon-based regimens and/or DAAs—to a hypothetical scenario in which there was universal access to DAAs and elimination of HCV infection among patients living with HIV.

To create the second set of SMR weights, we assumed that extrahepatic cancer risk was the same for patients who never had HCV infection and those who were successfully treated for HCV infection with DAAs, given baseline fibrosis levels and confounders. In other words, we assumed that a patient who never had HCV could "stand in" for a patient who had been successfully treated for HCV with DAAs if the two had similar age, race, CD4 cell count, and importantly, liver fibrosis. Given this assumption, we then estimated SMR weights to allow patients with HIV monoinfection to reflect the distribution of covariates and liver fibrosis among patients with HIV/HCV coinfection, and thus "stand in" for patients with HIV/HCV coinfection if, counter to fact, those patients had been treated with DAAs and achieved SVR. We used logistic regression to estimate the second set of weights in a model with age, sex, race/ethnicity, calendar year of CNICS entry, HBV status, alcohol, drug, and smoking diagnoses, CD4 cell count, liver fibrosis, and HIV suppression.

The product of the ART and HCV SMR weights was used in weighted Cox proportional hazards regression models; we used robust standard errors to estimate 99.5% confidence intervals. The estimated weights ranged from 0.001 to 21.77 with a mean of 0.24; we trimmed the weights at the 1^{st} and 99^{th} percentile to reduce the variability of the estimated effect of HCV coinfection on extrahepatic cancer outcomes.

We conducted a sensitivity analysis to explore potential misclassification of HCV. In this analysis, we redefined HCV infection as evidence of HCV antibodies or HCV RNA before baseline. HCV-seropositive patients without confirmatory HCV RNA results, who were excluded from the primary analyses, were included in the group of patients with HIV/HCV coinfection. We then re-estimated the SMR weights and ran the unweighted and weighted Cox models comparing extrahepatic cancer incidence among patients with untreated HIV/HCV coinfection at baseline to the hypothetical scenario in which all patients with HIV/HCV coinfection were successfully treated for HCV.

RESULTS

There were 30,489 patients 18 years of age or older who attended at least one HIV care visit at a CNICS site between January 1, 1995 and November 1, 2017 and had a follow-up visit 180 days or more afterwards. We excluded 1,343 patients with a previous cancer diagnosis, 6,731 patients who were missing HCV antibody or HCV RNA test results, and 3,985 patients missing HIV RNA levels, CD4 cell counts, or race/ethnicity information at baseline. An additional eight patients with HIV/HCV coinfection were excluded because

they initiated DAAs before baseline. Thus, 18,422 patients were eligible for our primary analyses.

Of those 18,422 patients, 1,775 (10%) had HCV infection at baseline (Table 1). The median age of patients was 39 years (interquartile range (IQR) 31, 47), one-fifth were female, and approximately 40% were non-Hispanic Black. The most common HIV-transmission risk factors among patients with HCV infection were injection drug use (44%) and being men who have sex with men (MSM; 38%). Among patients with HIV monoinfection, the most common HIV-transmission risk factors were MSM (64%) and heterosexual transmission (30%). The percentages of patients with HCV infection who had alcohol, smoking, or drug use diagnoses were 21%, 35%, and 43% respectively, and these percentages were slightly higher than in patients with HIV monoinfection. In addition, 17% of patients with HCV infection had FIB-4 scores that indicated advanced liver fibrosis (FIB-4 >3.25), compared with only 2% among patients with HIV monoinfection. Approximately 60% of the overall study sample had initiated ART before baseline.

Patients in our study sample accrued 110,321 person-years of follow-up and median follow-up was 4.6 person-years (IQR 1.7, 9.2). Among patients with HIV/HCV coinfection, 142 (8%) initiated an interferon-based regimen and 412 (23%) initiated DAAs during follow-up. This resulted in 2001.9 person-years (18%) occurring during or after HCV treatment among patients with HIV/HCV coinfection. A total of 878 patients were diagnosed with an extrahepatic cancer during follow-up (Table 2). The incidence rates of extrahepatic cancer were 1,027 and 771 per 100,000 person-years for people with and without HCV infection, respectively. The site-specific cancers with the highest incidence rates overall were NHL (127 cases per 100,000 person-years) and KS (116 cases per 100,000 person-years).

The crude HR for any extrahepatic cancer was 1.33 (99.5% CI 1.00, 1.78) among patients with HIV/HCV coinfection compared to those with HIV monoinfection (Table 3). The crude models also showed that patients with HIV/HCV coinfection were at increased risk for lung cancer (HR 2.52; 99.5% CI 1.26, 5.01) and inflammation-related extrahepatic cancers (HR 2.50; 99.5% CI 1.46, 4.25) compared to those with HIV monoinfection. In addition, patients with HIV/HCV coinfection had increased risks for kidney cancer, prostate cancer, and NHL, and decreased risks for anal cancer, KS, and infection-related extrahepatic cancers, when compared with patients with HIV monoinfection, but these results were not statistically significant.

In SMR-weighted models, there was no association between untreated HCV infection at baseline and risk of any extrahepatic cancer (HR 0.96; 99.5% CI 0.68, 1.37). Patients with untreated HCV infection at baseline had higher risks for kidney cancer (HR 1.51; 99.5% CI 0.26, 8.89), lung cancer (HR 1.56; 99.5% CI 0.65, 3.75), and inflammation-related extrahepatic cancer (HR 1.49; 99.5% CI 0.75, 3.00) than we would expect had they been successfully treated for HCV infection, but these results were not statistically significant. Protective associations between untreated HCV infection at baseline and anal cancer (HR 0.51, 99.5% CI 0.15, 1.75), KS (HR 0.50; 99.5% CI 0.11, 2.16), and infection-related extrahepatic cancers (HR 0.68; 99.5% CI 0.39, 1.21) were also identified in weighted models, but again, these results were not statistically significant.

Sensitivity analysis

When we redefined HCV infection as evidence of HCV RNA or HCV antibodies there were a total of 20,099 patients and 3,452 (17%) had HCV infection. The results of the sensitivity analyses were generally consistent with our primary weighted analysis (Supplemental Materials Table 1). The risk of any extrahepatic cancer among patients with untreated HCV infection at baseline was similar to the risk they would have experienced if they were successfully treated for HCV infection (HR 0.88; 99.5% CI 0.67, 1.16). Patients with untreated HCV infection at baseline also had elevated risks for kidney (HR 2.25; 99.5% CI 0.64, 7.71), lung (HR 1.35; 99.5% CI 0.67, 2.71), and inflammation-related extrahepatic cancers (HR 1.32; 99.5% CI 0.76, 2.31) and decreased risks for anal cancer (HR 0.58; 99.5% 0.24, 1.39), KS (HR 0.38; 99.5% 0.14, 1.08), and infection-related extrahepatic cancers (HR 0.68; 99.5% 0.44, 1.03). As in the primary analysis, none of the results were statistically significant.

DISCUSSION

In this large cohort of adults receiving HIV care in the U.S., individuals who were not yet treated for HCV at baseline had essentially the same risk of extrahepatic cancer as estimated under the hypothetical scenario in which all patients with HIV/HCV coinfection were treated with DAAs and achieved SVR. Results were similar when we redefined HCV infection as evidence of HCV antibodies or HCV RNA.

We hypothesized that people with untreated HCV infection at baseline would be at greater risk for extrahepatic cancers than if they had been successfully treated with DAAs because of increased immunosuppression, immune activation, and chronic inflammation associated with HCV [9,10] and previous studies identifying an association between HCV and extrahepatic cancer among people with HIV [11-14,29]. However, in the present study we found no association between untreated HCV infection at baseline and subsequent risk of extrahepatic cancers. The incidence of kidney cancer, lung cancer, and inflammation-related extrahepatic cancers was elevated, but not significantly, among people with untreated HCV infection at baseline. Several previous studies have identified associations between HCV infection and these cancers [6,30,31]. A 2016 meta-analysis found an elevated risk for kidney cancer among people with HCV infection compared with those without HCV infection [30]. People with HIV/HCV coinfection were also shown to be at greater risk for kidney disease, a risk factor for kidney cancer, compared with people with HIV monoinfection [31]. Similarly, the incidence of lung cancer and other cancers related to inflammation, such as pancreatic cancer, has also been shown to be elevated among people with chronic HCV infection when compared to the general population [6].

There are several limitations to this study. First, this is an observational study and our results could be biased by unmeasured or uncontrolled confounding in the models used to estimate ART and HCV treatment weights. The extent to which people who never had HCV are an appropriate stand-in for people who were successfully treated for HCV is also unknown. Second, the estimated associations between HCV and extrahepatic cancer outcomes may have limited generalizability to all people with HCV and HIV. We excluded approximately 37% of CNICS participants because they did not have HCV test results or

complete covariate data at baseline. While the CNICS cohort is generally representative of people receiving HIV care in the U.S., we cannot guarantee that people who were excluded from our sample would have had the same results, on average, that we estimated in this study. Third, confidence intervals were wide, and we may have had limited statistical power to detect true associations between chronic HCV infection and extrahepatic cancers. Fourth, we censored participants at death rather than conducting competing risk analyses. However, only four participants were censored due to death and we do not expect this limitation to have had a meaningful effect on our findings. Fifth, cancer outcomes after December 31, 2016 have not been adjudicated in the CNICS cohort and may have been misclassified. Because misclassification of cancer outcomes is unlikely to differ by HCV status, misclassification likely would have underestimated the true effect of untreated HCV coinfection on extrahepatic cancer incidence. Sixth, the median number of days between the last detectable HCV RNA test and the start of follow-up was 190 days, and some patients could have spontaneously cleared infection or have been successfully treated with an interferon-based regimen during this time, resulting in misclassification of HCV status at baseline. However, to minimize such misclassification, patients who had a subsequent negative RNA result before baseline were removed. Finally, we examined several cancer outcomes in our analysis and there is the potential for spurious results because of the number of comparisons. We used 99.5% confidence intervals, rather than 95% confidence intervals, to reduce the likelihood that our findings could be due to chance.

Despite limitations, our analyses provide a novel look at several types of extrahepatic cancers among people with HIV/HCV coinfection and extend prior work in several important ways. We followed a large cohort of over 18,000 patients with HIV from 1995 through 2018, a period of 23 years. Data were available on important confounders, including clinical diagnoses of alcohol use disorders, drug use, and smoking. We also estimated the potential effect of HCV and HIV treatment on extrahepatic cancer risk by using SMR weights. The SMR weights created a “pseudopopulation” in which we could model all people with HIV being treated with ART, and likewise, could model individuals with HIV/HCV coinfection being successfully treated with DAAs. As ART is now recommended for all people with HIV and DAA uptake is increasing, the results of our study are relevant to current and future clinical practice.

CONCLUSIONS

Among people with HIV on ART, we did not find evidence that successfully treating HCV infection would reduce the incidence of extrahepatic cancer. Our results suggest that health care providers should remain vigilant about screening for extrahepatic cancers among people with HIV/HCV infection, even after HCV cure. We also recommend additional studies that evaluate longer-term benefits of DAAs on hepatic and extrahepatic outcomes, particularly among people with HIV/HCV coinfection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Baseline characteristics of 18,422 people with HIV who initiated care at a CNICS site during January 1995 – November 2017, by HCV status

	HCV RNA+ (n=1,775)		HCV Ab- or HCV RNA− (n=16,647)		Total (n=18,422)	
	Median or n	IQR or %	Median or n	IQR or %	Median or n	IQR or %
Median age at 180 days after enrollment (years)	45	39, 51	38	31, 46	39	31, 47
Sex						
Male	1,382	77.9%	13,554	81.4%	14,936	81.1%
Female	393	22.1%	3,093	18.6%	3,486	18.9%
Race/ethnicity						
Asian, non-Hispanic	21	1.2%	293	1.8%	314	1.7%
Black, non-Hispanic	813	45.8%	6,992	42.0%	7,805	42.4%
Hispanic	142	8.0%	2,076	12.5%	2,218	12.0%
Other	56	3.2%	390	2.3%	446	2.4%
White, non-Hispanic	743	41.9%	6,896	41.4%	7,639	41.5%
Calendar year of CNICS entry						
1995-1999	95	5.4%	1,219	7.3%	1,314	7.1%
2000-2004	504	28.4%	4,073	24.5%	4,577	24.8%
2005-2009	562	31.7%	4,157	25.0%	4,719	25.6%
2010-2014	475	26.8%	4,768	28.6%	5,243	28.5%
2015-2017	139	7.8%	2,430	14.6%	2,569	13.9%
HIV transmission risk factor						
Heterosexual	260	14.6%	4,941	29.7%	5,201	28.2%
Injection drug use	773	43.5%	422	2.5%	1,195	6.5%
Men who have sex with men	682	38.4%	10,621	63.8%	11,303	61.4%
Other	42	2.4%	412	2.5%	454	2.5%
Unknown	18	1.0%	251	1.5%	269	1.5%
Alcohol related diagnosis[a]	380	21.4%	1,274	7.7%	1,654	9.0%
Smoking related diagnosis[b]	626	35.3%	2,979	17.9%	3,605	19.6%
Drug use related diagnosis[c]	755	42.5%	2,696	16.2%	3,451	18.7%
Family history of cancer	53	3.0%	309	1.9%	362	2.0%
Chronic HBV[d]	108	6.1%	922	5.5%	1,030	5.6%
ART initiation on/before baseline	1,082	61.0%	9,817	59.0%	10,899	59.2%
CD4 cell count (cells/μL)						
<200	451	25.4%	3,504	21.0%	3,955	21.5%
200-500	754	42.5%	6,965	41.8%	7,719	41.9%
>500	570	32.1%	6,178	37.1%	6,748	36.6%
Suppressed HIV RNA (<200 copies/mL)	901	50.8%	9,159	55.0%	10,060	54.6%
FIB-4 index						
<1.45	875	49.3%	14,128	84.9%	15,003	81.4%

	HCV RNA+ (n=1,775)		HCV Ab- or HCV RNA− (n=16,647)		Total (n=18,422)	
	Median or n	IQR or %	Median or n	IQR or %	Median or n	IQR or %
1.45-3.25	606	34.1%	2,172	13.0%	2,778	15.1%
>3.25	294	16.6%	347	2.1%	641	3.5%

HIV – Human Immunodeficiency Virus, CNICS - Center for AIDS Research Network of Integrated Clinical Systems, HCV – hepatitis C virus, RNA – ribonucleic acid, Ab – antibody, IQR – interquartile range, HBV – hepatitis B virus

[a] Diagnosis of alcohol dependence or alcohol non-dependent abuse on or before CNICS enrollment

[b] Diagnosis of current tobacco use or history of tobacco use on or before CNICS enrollment

[c] Diagnosis of amphetamine, cocaine, hallucinogen, inhalant, marijuana, opiate, or other substance use ever on or before CNICS enrollment

[d] Chronic HBV was defined as a positive HBV DNA quantitative, HBV DNA qualitative, HBV surface antigen, or HBV e antigen test result ever

Table 2.

Number of cancer events, deaths and person-years at risk among 18,422 persons with HIV who initiated care at a CNICS site during January 1995 – November 2017, by HCV status

	HCV RNA+ (n=1,775)			HCV Ab- or HCV RNA− (n=16,647)			Total (n=18,422)		
	Number of events	Person-years	Incidence rate[a]	Number of events	Person-years	Incidence rate[a]	Number of events	Person-years	Incidence rate[a]
Anal	6	10878.4	55.2	85	102338.1	83.1	91	113216.5	80.4
Kidney	4	10883.4	36.8	20	102628.9	19.5	24	113512.3	21.1
Lung	21	10882.1	193.0	80	102630.6	77.9	101	113512.7	89.0
Non-Hodgkin lymphoma	19	10852.1	175.1	125	102318.7	122.2	144	113170.8	127.2
Prostate (men only)	14	8458.4	165.5	80	81936.4	97.6	94	90394.8	104.0
Kaposi sarcoma	5	10880.5	46.0	126	102102.8	123.4	131	112983.3	115.9
Infection-related extrahepatic cancer[b]	37	10790.4	342.9	405	100939.3	401.2	442	111729.7	395.6
Inflammation-related cancer[c]	35	10852.9	322.5	135	102509.7	131.7	170	113362.6	150.0
Extrahepatic cancers	109	10618.5	1026.5	769	99780.5	770.7	878	110399.0	795.3
Death	1	10586.6	9.4	3	99734.4	3.0	4	110321.0	3.6

HIV – Human Immunodeficiency Virus, CNICS - Center for AIDS Research Network of Integrated Clinical Systems, HCV – hepatitis C virus, RNA – ribonucleic acid, Ab – antibody

[a] Incidence rate per 100,000 person-years

[b] Infection-related extrahepatic cancers include anorectal cancers, cervical cancer, Hodgkin's lymphoma, Kaposi sarcoma, non-Hodgkin lymphoma, and cancers of the oral cavity and pharynx

[c] Inflammation-related cancers include bladder cancer, colon cancer, esophagus cancer, lung cancer, multiple myeloma, pancreas cancer, and stomach cancer

Table 3.

Associations between untreated HCV and extrahepatic cancer outcomes among 18,422 persons with HIV who initiated care at a CNICS site during January 1995 - November 2017

	Crude models	Weighted models[a]
	Hazard ratio (99.5% CI)	**Hazard ratio (99.5% CI)**
Anal	0.68 (0.21, 2.21)	0.51 (0.15, 1.75)
Kidney	1.90 (0.41, 8.82)	1.51 (0.26, 8.89)
Lung	2.52 (1.26, 5.01)	1.56 (0.65, 3.75)
Non-Hodgkin lymphoma	1.41 (0.71, 2.81)	1.01 (0.44, 2.32)
Prostate (men only)	1.72 (0.76, 3.88)	0.97 (0.41, 2.29)
Kaposi sarcoma	0.37 (0.10, 1.33)	0.50 (0.11, 2.16)
Infection-related extrahepatic cancers[b]	0.85 (0.53, 1.38)	0.68 (0.39, 1.21)
Inflammation-related extrahepatic cancers[c]	2.50 (1.46, 4.25)	1.49 (0.75, 3.00)
Extrahepatic cancers	1.33 (1.00, 1.78)	0.96 (0.68, 1.37)

HCV – hepatitis C virus, HIV – Human Immunodeficiency Virus, CNICS - Center for AIDS Research Network of Integrated Clinical Systems

[a]Standardized morbidity ratio weights for antiretroviral therapy included age, calendar year of CNICS entry, CD4 cell count, HIV suppression, and HCV status. Standardized morbidity ratio weights for HCV treatment included age, sex, race/ethnicity, calendar year of CNICS entry, HBV status, alcohol use, drug use, smoking, CD4 cell count, and HIV suppression.

[b]Infection-related extrahepatic cancers include anal cancer, anorectum cancer, cervical cancer, Hodgkin's lymphoma, Kaposi sarcoma, non-Hodgkin lymphoma, and cancer of the oral cavity and pharynx

[c]Inflammation-related extrahepatic cancers include bladder cancer, colon cancer, esophagus cancer, lung cancer, multiple myeloma, pancreas cancer, and stomach cancer