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The Effect of HIV Viral Control on the Incidence of Hepatocellular Carcinoma in Veterans with Hepatitis C and HIV Coinfection

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Abstract

Background—HIV increases the risk of progression to hepatic fibrosis and cirrhosis among individuals coinfecting with hepatitis C virus (HCV). However, the impact of HIV-related immune suppression on the risk of hepatocellular carcinoma (HCC) is currently unknown.

Methods—We used the VA HIV Clinical Case Registry to identify patients with HIV infection between 1985 and 2010 and HCV coinfection (positive HCV RNA or genotype test) between 1995 and 2010. The outcome was incident HCC as indicated by ICD-9 code (87% positive predictive value). Patients with HCV mono-infection were included as a comparison group for HCC incidence. Age-adjusted HCC incidence rates were calculated for the coinfecting cohort and HCV mono-infected cohort. Cox proportional hazards models were used to determine hazard ratios (HR) and 95% confidence intervals (CI) for each risk factor on the time to HCC diagnosis in the coinfecting cohort.

Results—There were 66,991 veterans with HIV; 8,563 had at least one positive HCV RNA test, and 234 of these developed HCC. The overall age-adjusted incidence rate of HCC in mono-infected patients was 2.99/1000 PY vs. 4.44/1000 PY in coinfecting patients. In patients with coinfection, presence of cirrhosis (HR=4.88; 95%CI: 3.30–7.21), HIV diagnosis >2002 (HR=4.65; 95%CI: 2.70–8.02), and a recent low CD4+ cell count <200 (HR=1.71; 95%CI: 1.20–2.45) were associated with an increased risk for HCC.

Conclusions—The risk of HCC in HCV-HIV coinfecting veteran men was higher than HCV mono-infection. Diagnosis of cirrhosis and low recent CD4+ cell count were the most important predictors of developing HCC in this group.

Keywords

Hepatitis C virus; coinfection; hepatocellular carcinoma; HIV-related immune suppression

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Introduction

Hepatitis C virus (HCV) coinfection is common among HIV-infected individuals worldwide; it has been estimated that 4–5 million HIV infected individuals are chronic HCV carriers. In the U.S. and Europe, approximately 10–33% of all HIV infected individuals are coinfecting with HCV.^{1,2} It is estimated that at least 20–30% of all HCV infected persons develop cirrhosis within 2 to 3 decades, of whom 1 to 4% develop hepatocellular carcinoma (HCC) per year.^{3,4} The risk for liver disease progression has been shown to be two to six times higher in HIV-HCV coinfecting patients than HCV mono-infected patients.⁵ In addition, recent studies have shown that coinfecting patients are diagnosed at a younger age, have more advanced HCC, and have shorter survival time than HCV mono-infected patients.^{6,7} A recent metanalysis of over 400,000 individuals with HIV or AIDS (with unknown HCV infection status), estimated a standardized incidence ratio for HCC of 5.2 compared with the general population.⁶ Thus, HCV associated HCC is contributing significantly to the morbidity and mortality of HIV-infected individuals.

The effect of combination antiretroviral therapy (cART) and immune status, including nadir CD4 count, last known CD4 count, and cumulative time with undetectable HIV viral load on HCC risk may play a role in cancer development, although it has not been thoroughly examined. A previous study of VA administrative data study suggested that cART may ameliorate the accelerated fibrosis progression.⁸ However, CD4 count at cART initiation, type of cART, and other HIV-related factors were not studied. A more recent study using the Swiss HIV Cohort Study found that among 24 cases of HCC, there was an increased risk of HCC associated with low CD4 count in the year preceding HCC diagnosis.⁹ While another small study conducted in France in only 16 HIV-infected cases with HCC (3 with HBV and 11 with HCV) demonstrated that current CD4+ <350 was independently associated with increased risk for HCC.¹⁰ Finally, Ioannou et al examined the prevalence of cirrhosis and HCC in US veterans with HIV and reported that a detectable HIV viral load at the time of HCC diagnosis was not associated with HCC risk, while low CD4+ count was associated with an increased risk for HCC (AOR=2.36; 95% CI: 1.3–4.2).¹¹ This study was not limited to veterans with HCV coinfection and only examined HIV viral loads and CD4+ counts in a two year period. While these studies suggest immune function does have a role in HCC risk, the results need to be confirmed in a larger, clearly defined, coinfecting population utilizing all available serially collected HIV RNA and CD4+ counts. In addition, few large studies have compared the risk for HCC in HIV/HCV co-infected compared to HCV mono-infected individuals including patients from the cART era.

The Department of Veterans Affairs (VA) Veterans Health Administration has the largest integrated health care system and is the largest provider of HIV care in the United States.¹² The VA maintains an HIV Clinical Case Registry that contains system-wide clinical information on all veterans nationwide with both HIV and HCV. Utilizing this data we aimed to determine the effect of HIV-related immune status as a risk factor for HCC among US male veterans diagnosed with HIV and HCV coinfection between 1985 and 2010.

METHODS

Data Sources

The VA HIV Clinical Case Registry (CCR) contains health-related information on all known HIV-infected individuals receiving VA care nationwide. Established in 1992, the HIV CCR extracts from the electronic medical records of over 65,000 HIV-infected patients cared for by the VA since the registry's inception and includes all demographic, laboratory, pharmacy, outpatient clinic visit, and hospitalization data and dates of death, including patients who were diagnosed as early as 1985.¹³ For this study, VA death data were supplemented with data from the VA Vital Status file, and race data were supplemented with data from the national VA MEDSAS inpatient and outpatient visit files. The Institutional Review Board for Baylor College of Medicine and Affiliated Institutions and the Michael E. DeBakey VA Medical Center Research and Development Committee approved this study.

Subjects

The study population for the main analysis was comprised of HIV and HCV co-infected veterans. Patients who were > 18 years, with at least 1 confirmed date for (1) HIV test (HIV-1 Elisa, Western Blot, or HIV viral load) or (2) ICD-9 for HIV (042 or V08) were eligible for inclusion in the cohort. Additionally, HCV infection was confirmed by positive HCV RNA or genotype test. Patients with prevalent HCC diagnosis before and up to 90 days after their earliest HIV/HCV diagnosis date were excluded from the cohort. Due to the small number of female veterans (<2%), they were also excluded. Finally, we excluded patients who did not have any CD4 cell count or HIV viral load information during follow-up. Veterans with HCV mono-infection were included as a comparison group for the HCC incidence rates. Patients who were <18 years of age, female, without documented HCV RNA, with prevalent HCC were also excluded from this group.

Study Variables

Primary Outcome—The primary outcome was incident HCC, based on ICD-9 codes (155.0 without 155.1). We previously validated this ICD-9 code algorithm for HCC using the VA electronic medical record as the gold standard.¹⁴ This algorithm had a positive predictive value of 87%, meaning 87% of the time the algorithm correctly identified HCC diagnoses. Prevalent HCC cases were excluded as defined above.

Definition of HIV-related Variables—To account for potential differences in the frequency of follow-up visits for CCR patients, each individual's follow-up duration was divided into 7-day intervals. Laboratory values were updated at the beginning of each interval, with the last observation carried forward when no new measurement was available. The nadir CD4+ cell count over the interval was captured and categorized as above or below 200 cells/ μ L. Time-updated recent CD4+ cell count was included to monitor the effects of fluctuations in immune status throughout the follow-up period modeled as <200, 200–350, and >350 (reference). We also generated a time-dependent metric to measure the cumulative percentage of follow-up time that an individual's CD4 cell count was below 200 cells/ μ L modeled as <40% (reference), 40–80%, and >80% time.

Similarly, we generated a time-dependent metric to measure the cumulative percentage of follow-up time that an individual's HIV RNA measurement was in the undetectable range. For standardization of operational procedures at different contributing VA facilities over all study years, the value for undetectable HIV RNA was established as <500 copies/cell. The percent time undetectable HIV RNA was modeled as <40% (reference), 40–80%, and >80% time. These variable definitions have been used in previous studies examining the effect of HIV related immune status and other cancers (e.g. anal cancer and Hodgkin lymphoma).^{15;16}

Definition of HCV-related Variables—HCV-related variables included receipt of HCV treatment, and HCV genotype and viral load. HCV treatment was defined as receipt of at least one prescription for pegylated-interferon and the variable was categorized as no treatment, treatment with sustained virologic response (SVR), and treatment without SVR. SVR was defined as the presence of a negative HCV RNA test 12 weeks after the treatment end date as used in previous studies using CCR data.^{17;18} Categories of HCV genotype were generated as genotyping not done, type 1 and 4, and type 2 and 3. HCV viral load was captured as the log-copies/mL using the value closest to HCV index date.

Potential Confounders—Additional demographic covariates included age at earliest infection diagnosis and race/ethnicity. Use of combination antiretroviral therapy (cART) was defined as any combination of 2 nucleoside reverse transcriptase inhibitors classes and 1 of either non-nucleoside reverse transcriptase inhibitor, protease inhibitor classes, integrase inhibitors, or CCR5 inhibitors and any combination of two classes. Era of HIV diagnosis was categorized as pre-cART (<1996), early cART (1996–2001), and late cART (2002–2010). Cirrhosis was defined by a history of ICD-9 code for cirrhosis (571.5, 571.6, or 571.2) or an aspartate aminotransferase to platelet ratio index (APRI) score greater than 2. A recent systematic review found that APRI can identify cirrhosis with moderate to high accuracy compared to liver biopsy (sensitivity at the cut-off >1.0=0.77; specificity at the cut-off >2.0=0.94).¹⁹ Information about potential screening tests for HCC was also included based on the presence of either liver ultrasound or alpha-fetoprotein tests.

Statistical Analysis

Descriptive statistics were calculated to determine the distributions of the variables in the coinfecting study population. Characteristics were described in the overall cohort and stratified by HCC cases and non-cases. T-test and chi-square statistics were derived for comparisons of means and categorical variables, respectively. Additionally, we calculated crude incidence rates of HCC in the overall coinfecting cohort and stratified by HIV diagnosis year as well as in the HCV monoinfected cohort. We used the HCV index date for the HCC incidence rate calculations to ensure the rates would be comparable between the coinfecting and HCV monoinfected cohorts. In addition, the age distribution from the US 2000 Census was used to calculate age adjusted HCC incidence rates in both the monoinfected and coinfecting cohorts.

We conducted multivariate Cox time-updated proportional hazard analyses to determine the effect of CD4+ and HIV RNA load variables on time to HCC. Two distinct models were

constructed. Our main model included nadir CD4+, time-updated recent CD4, and percent undetectable HIV RNA. Then as a sensitivity analysis we examined time-updated recent CD4 and percent time CD4+<200. Each model was adjusted for age, race/ethnicity, cART era, HCV treatment with and without SVR, HCV genotype, use of HCC screening (ultrasound or alpha-fetoprotein), and cirrhosis diagnosis. These variables were included based on their significance in the univariate analysis ($p<0.10$) or their biologic importance. For this analysis, follow-up time was calculated from the earliest date of confirmed HIV or HCV diagnosis to HCC diagnosis, last encounter date recorded in the data set before December 31, 2010 (the last date in the current CCR iteration), or death, whichever occurred first. Additional sensitivity analyses for both models were conducted in the subgroup of co-infected individuals: 1) ever using cART; and 2) diagnosed with suspected cirrhosis, defined by the presence of at least 1 cirrhosis ICD-9 code or APRI>2. The proportional hazards assumption was tested and fulfilled for all models. Statistical analyses were performed with SAS[®] version 9.1 (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Coinfection Study Cohort

Figure 1 shows the study flow chart. Of the total 66,991 patients in the HIV CCR, 9,069 had a positive test for HCV RNA. After excluding patients with prevalent HCC (N=41), females (N=154) and those missing CD4 count or HIV viral load (N=311), 8,563 patients were remaining in our study cohort for analysis.

Table 1 shows the descriptive and clinical characteristics for the overall study cohort as well as stratified by HCC status. In the 8,563 male patients in the coinfecting cohort, 244 had HCC diagnosed during mean of 10.6 years of follow-up. The mean age at HIV diagnosis was 45 years and majority was Black race (64.4%). More than half had a diagnosis of cirrhosis (56.1%) and 50% were ever screened for HCC by US or AFP test. The cohort was relatively healthy with 92.4% having a Deyo comorbidity score of zero. Approximately one-third were diagnosed in each of HIV eras (37.5% in pre-cART era, 35.9% in early-cART and 26.6% in late-cART era).

HCC Incidence Rates

Table 2 shows the crude and age-adjusted incidence rates for HCC using the HCV diagnosis dates among individuals in the HCV monoinfected cohort and the coinfecting cohort. The 189,332 HCV monoinfected veterans contributed 5249 cases of HCC in 959,032 PY yielding a crude incidence rate of 5.47/1000 PY. The 8,563 HIV-HCV coinfecting patients contributed 234 cases of HCC (10 cases occurred before the HCV index date) in 49,832 person-years, yielding a crude incidence rate of 4.70/1000 PY. The crude incidence rate in the coinfecting cohort was similar across all three cART eras resulting in 4.91/1000 PY (4.04–5.98) in the pre-cART era, 4.49/1000 PY (3.64–5.54) in the early-cART era, and 4.66/1000 PY (3.51–6.18) in the late cART era. The overall age-adjusted incidence rate in the coinfecting cohort was similar to the crude at 4.44/1000 PY. Finally, at 2.99/1000 PY, the overall age-adjusted incidence rate in the HCV monoinfected cohort was significantly lower than in the coinfecting cohort (4.44/1000 PY).

Univariate Analysis of Risk Factors for HCC in Patients with HIV-HCV Coinfection

The 244 HCC cases were slightly older, more likely to be Hispanic, diagnosed during the pre-cART era, and have cirrhosis and/or US/AFP for HCC screening. The HIV-related variables were not significantly different between the individuals with HCC and those without the diagnosis in univariate analysis when using the values closest to HCC diagnosis or censoring date. Individuals with HCC were more likely to have HCV genotype 1 or 4 compared with those without HCC. Other HCV-related variables were not significant in univariate analysis.

Multivariate Analysis of Factors Associated with Increased Risk of HCC in Patients with HIV-HCV Coinfection

Table 3 shows the results of the multivariate HRs for overall coinfecting cohort as well as restricted to individuals who ever received cART and who had a diagnosis of cirrhosis. Significant predictors for HCC included older age at HIV diagnosis, white vs. black race, diagnosis of cirrhosis, and cART era of HIV diagnosis. The most important HIV-related variable in this model was recent CD4+ count. Compared to individuals with a CD4+ cell count greater than 350, those who had a recent CD4+ cell count <200 had a 71% increased risk of HCC (HR=1.71; 95%CI: 1.20–2.45). This effect was even stronger when restricting to the cART only cohort (HR=2.20; 95%CI: 1.52–3.18) and to the cirrhosis only cohort (HR=2.33; 95%CI: 1.35–4.02). It was also significant for individuals in the cART only cohort with a recent CD4+ cell count of 200–350 vs. >350 (HR: 1.49; 95%CI: 1.05–2.10). The nadir CD4+ cell count was not significant in the overall cohort and the restricted cohorts. In addition, % time of undetectable HIV viral loads over the course of their available follow-up time was not significantly associated with HCC risk.

In order to determine if the percent of time with CD4 count < 200 was a predictor of HCC, we evaluated a second multivariate model as a sensitivity analysis replacing percent of time with undetectable HIV viral load with percent of time <200. In this analysis, similar to the primary model, we found that percent of time with CD4 <200 was not predictive of HCC risk, however, recent CD4+ cell count <200 was still a significant predictor of HCC (See appendix table, supplemental digital content).

In these models, HCV related variables that we kept in the model included HCV treatment receipt and genotype. There was a significant trend for HCV treatment to reduce the risk for HCC and was stronger in some models for treatment with a SVR, albeit not statistically significant. Also, HCV genotype 1 or 4 patients were slightly more likely to develop HCC compared with HCV genotype 2 or 3, but with borderline significance.

DISCUSSION

To our knowledge, our study includes the largest number of HCC cases among a carefully defined HIV/HCV co-infected cohort. We demonstrated that although the overall incidence of HCC is higher among the HCV mono-infected cohort, the age-adjusted incidence of HCC is higher among HIV/HCV co-infected individuals compared to HCV mono-infected individuals. However, we also found that laboratory values associated with measuring

cumulative HIV-related immunosuppression such as nadir CD4+ count, percent of time with undetectable HIV viral load were not associated with HCC, but evidence of immunosuppression at the time of HCC diagnosis, as measured by most recent CD4+ count was associated with a higher risk of HCC. We were also able to demonstrate this effect in a cohort of patients with cirrhosis diagnosis signifying the recent CD4+ effect was independent of cirrhosis.

Previously we examined the effect of HIV coinfection on HCC in HCV-infected veterans in the VA who had been hospitalized with an ICD-9 code for HCV.⁸ We did not show an increased incidence rate of HCC in the coinfecting vs. mono-infected patients. However, in this study we did not have laboratory tests to confirm HCV and HIV diagnoses, nor access to pharmacy and laboratory records to examine treatment and virologic factors, and only examined veterans who were ultimately hospitalized with HCV. Other studies examining HCC incidence have found variable results. Ioannou et al demonstrated that the prevalence of HCC among HIV/HCV co-infected individuals increased by 23 fold, however they did not compare the increased risk to HCV mono-infected individuals.¹¹ More recently, Lo et al compared the incidence of HCC among 4280 HIV/HCV coinfecting individuals compared to 6079 HCV mono-infected individuals.²⁰ Similar to our study, they found that although the incidence of HCC among the HCV mono-infected individuals and HIV/HCV coinfecting individuals were similar, when adjusted for age and additional clinical and demographic factors, the rate of HCC was higher among HIV/HCV co-infected individuals.

The findings of this study are also similar to previous reports by Clifford et al and Bruyand et al who found in smaller European HIV-infected cohorts an effect of low CD4+ cell count prior to HCC diagnosis.^{9;10} These studies only had 26 and 16 cases of HCC, respectively, and were not restricted to those with HCV coinfection. In addition, Ioannou et al examined all veterans with HIV and did not limit to those at the highest risk for HCC.¹¹ They corroborate these findings by reporting that a maximum CD4+ cell count <200 ever was associated with HCC risk. However, they did not use time dependent variables to utilize all the information available in the data.

Our findings in respect to HIV viral load are somewhat different to what we have seen in other HIV-related malignancies. For example, we published results using HIV-infected veterans from the CCR to examine the effect of HIV viral control on the risk of squamous cell cancer of the anus (SCCA) and found that % time with undetectable viral load was significantly associated with reduction of SCCA risk.¹⁶ In contrast, this study did not find that recent CD4+ cell counts were associated with developing SCCA. Our group has also recently published study evaluating the effect of HIV-related immunosuppression on Hodgkin's lymphoma (HL), another HIV-associated, virally mediated malignancy.¹⁵ In this study, we also found that the risk for HL was lowest among those individuals with a higher percentage of time with undetectable HIV viral loads. In the multivariable model adjusted for nadir and recent CD4+ counts, the risk of HL was significantly lower among those with an undetectable HIV viral load >80% of the time compared to those with undetectable HIV viral load <40% of the time (IRR=0.6, 95% CI=0.4–0.9). This demonstrates that although HCC is a virally mediated cancer, the control of HIV viral replication impacts HCC risk much less than other virally mediated HIV-associated cancers.

Our study has several limitations. First, it was a retrospective cohort study and thus may be subject to unmeasured confounders such as smoking. Smoking has not been shown to be associated with changes in CD4+ count or HIV viral load; therefore, smokers were likely evenly distributed in the CD4 and percent undetectable HIV viral load categories.²¹ We also used a relatively new measure of HIV viral load control, “percent of time with undetectable HIV viral loads,” which may not adequately describe the true time that individuals had an undetectable HIV viral load. However, we postulate that this variable is a better measure of overall HIV viral control compared with a single HIV viral load measurement. Also, since our data was extracted from clinical care there are potential variations in the frequency of follow-up visits and thus CD4+ and viral load testing. In addition, it is possible that the low CD4+ count that was observed was due to cirrhosis and sequestration of lymphocytes in the spleen, artificially decreasing the absolute CD4+ count before HCC diagnosis, however, we adjusted for cirrhosis in the analysis and conducted a sensitivity analysis in a cohort of patients with cirrhosis using cirrhosis index date as the start of follow-up time. We found that low CD4+ count at the time of HCC diagnosis remained significant. Finally, we conducted this study among male veterans. Thus, the generalizability of these data remains somewhat limited.

In conclusion, our study demonstrates that although the crude incidence of HCV-monoinfected individuals, the age-adjusted incidence of HIV/HCV co-infected individuals is higher. In addition, we found that individuals with HIV/HCV co-infection with CD4+ count <200 had a higher risk for HCC. Of note, in contrast to other HIV-associated malignancies (including anal cancer and Hodgkin’s lymphoma), we found that HIV viral load measurements were not associated with HCC risk. Thus, the interaction between the HIV and HCV viruses and the role of HIV-related immunosuppression may not play a direct role in the development of HCC. The information from this study demonstrate that HIV/HCV co-infected individuals are at high-risk for HCC and that HCC screening should be emphasized in the care of these individuals, regardless of HIV-associated immunosuppression; however, further research is necessary to determine exact impact and mechanisms of HIV infection on the tumorigenesis of HCC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Selection criteria to generate final cohort of HIV/HCV co-infected veterans

Table 1

Descriptive and clinical characteristics of the overall cohort and stratified by HCC

Variable	Overall N=8563	HCC cases n=244	No HCC n=8319	P-value
Age, median (IQR)	45 (40,50)	46 (41,51)	45 (40,50)	0.0006
Race, %				0.0005
Black	5513 (64.4)	144 (59.0)	5369 (64.5)	
White, non-Hispanic	2061 (24.1)	60 (24.6)	2001 (24.1)	
Hispanic	788 (9.2)	39 (16.0)	749 (9.0)	
Other	201 (2.3)	1 (0.4)	200 (2.4)	
Duration of follow-up, years	10.6 (6.4,14.8)	9.9 (6.5,12.9)	10.6 (6.4,14.8)	0.06
Cirrhosis, %	4804 (56.1)	211 (86.5)	4593 (55.2)	<0.0001
US/AFP for HCC screening, %	4325 (50.5)	141 (57.8)	4184 (50.3)	0.02
Deyo Comorbidity Score				0.92
0	7910 (92.4)	227 (93.0)	7683 (92.4)	
1	508 (5.9)	13 (5.3)	495 (5.9)	
2+	145 (1.7)	4 (1.7)	141 (1.7)	
<i>HIV-Related Variables</i>				
Era of HIV diagnosis, %				0.03
Pre-cART	3211 (37.5)	105 (43.0)	3106 (37.4)	
Early-cART	3072 (35.9)	91 (37.3)	2981 (35.8)	
Late-cART	2280 (26.6)	48 (19.7)	2232 (26.8)	
Nadir CD4+ cell count, median (IQR)	231 (110,363)	238 (122,374)	231 (110,363)	0.62
<200	3682 (43.0)	96 (39.3)	3586 (43.1)	
200	4881 (57.0)	148 (60.7)	4733 (56.9)	
Current CD4+ cell count*, median (IQR)	364 (183,576)	349 (200,561)	364 (182,577)	0.07
<200	2325 (27.2)	60 (24.6)	2265 (27.2)	
200–350	1791 (20.9)	62 (25.4)	1729 (20.8)	
>350	4447 (51.9)	122 (50.0)	4325 (52.0)	
% time with CD4+ cell count <200*				0.41
<40%	6580 (76.8)	192 (78.6)	6388 (76.8)	
40–80%	1151 (13.5)	26 (10.7)	1125 (13.5)	
>80%	832 (9.7)	26 (10.7)	806 (9.7)	
% time with undetectable HIV VL*				0.68
<40%	3958 (47.3)	109 (45.6)	3849 (47.4)	
40–80%	2687 (32.1)	83 (34.7)	2604 (32.0)	
>80%	1724 (20.6)	47 (19.7)	1677 (20.6)	
cART use, %	7460 (87.1)	216 (88.5)	7244 (87.1)	0.51
<i>HCV-Related Variables</i>				
HCV treatment, %				0.47
No treatment	6790 (85.3)	195 (82.6)	6595 (85.4)	

Variable	Overall N=8563	HCC cases n=244	No HCC n=8319	P-value
Treatment, SVR	282 (3.6)	9 (3.8)	273 (3.5)	0.008
Treatment, No SVR	887 (11.1)	32 (13.6)	855 (11.1)	
HCV genotype, %				
Not done	2811 (32.8)	59 (24.2)	2752 (33.1)	0.68
Type 1,4	5089 (59.4)	168 (68.8)	4921 (59.1)	
Type 2,3	663 (7.8)	17 (7.0)	646 (7.8)	
HCV viral load, log copies/mL	6.4 (5.9, 6.7)	6.4 (5.9, 6.8)	6.4 (5.9, 6.7)	0.68

* Value at HCC or censor

Table 2

Crude and age adjusted HCC incidence rates for HCV moninfected and HIV-HCV coinfecting cohorts using HCV index date

	# of HCC cases	Person-years	Crude Incidence/1000 PY (95% CI)	Age-adjusted Incidence/1000 PY (95% CI)
HCV moninfected	5249	959032	5.47 (5.33–5.62)	2.99 (2.98–2.99)
HIV-HCV coinfecting	234	49832	4.70 (4.13–5.34)	4.44 (3.31–5.56)

Table 3

Multivariate hazard ratios for the effect of specific HIV-related time dependent variables on the development of HCC (Model 1)

Variable	Overall cohort HR (95% CI)	cART only HR (95% CI)	Cirrhosis cohort HR (95% CI)
Age at HIV diagnosis	1.08 (1.06–1.10)	1.10 (1.08–1.12)	1.08 (1.05–1.11)
Race/ethnicity (vs. White)			
Black	0.86 (0.62–1.18)	0.69 (0.49–0.96)	0.53 (0.33–0.85)
Hispanic	1.48 (0.98–2.24)	1.20 (0.78–1.84)	0.93 (0.50–1.73)
Cirrhosis (vs. no)			
Yes	4.88 (3.30–7.21)	5.15 (3.43–7.71)	N/A
Ultrasound/ AFP (vs. no)			
Yes	1.15 (0.88–1.51)	1.16 (0.87–1.54)	1.14 (0.74–1.76)
cART era (vs. Pre-cART <1996)			
Early cART 1996–2001	1.92 (1.33–2.76)	1.37 (0.93–2.02)	2.12 (1.21–3.72)
Late cART 2002–2010	4.65 (2.70–8.02)	2.18 (1.21–3.91)	4.85 (1.93–12.19)
Nadir CD4+ cell count (vs. 200)			
<200	0.77 (0.58–1.03)	0.84 (0.62–1.13)	0.79 (0.50–1.25)
Recent CD4+ cell count (vs. >350)			
<200	1.71 (1.20–2.45)	2.20 (1.52–3.18)	2.33 (1.35–4.02)
200–350	1.36 (0.98–1.88)	1.49 (1.05–2.10)	1.31 (0.76–2.25)
% time undetectable VL (vs. <40%)			
40–80%	1.26 (0.92–1.71)	1.38 (0.99–1.90)	1.32 (0.81–2.17)
>80%	1.29 (0.86–1.93)	1.31 (0.85–2.01)	1.39 (0.72–2.69)
HCV treatment (vs. no treatment)			
Treatment w/o SVR	0.84 (0.57–1.25)	0.73 (0.48–1.09)	0.82 (0.45–1.52)
Treatment w/ SVR	0.90 (0.45–1.78)	0.69 (0.33–1.43)	0.46 (0.11–1.90)
HCV Genotype (vs. Type 2,3)			
Type 1,4	1.68 (0.99–2.86)	1.60 (0.92–2.77)	2.26 (0.95–5.34)
Not done	1.71 (0.96–3.05)	2.20 (1.21–3.98)	2.49 (0.98–6.32)

* Full models are presented for each analysis