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Trends in incidences and risk factors for hepatocellular carcinoma and other liver events in HIV and hepatitis C virus co-infected individuals from 2001 to 2014: a multi-cohort study

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Summary: We examined the epidemiology of HCC and other liver events in a multi-cohort collaboration of HIV/HCV co-infected individuals. We observed shifts in incidence from 2001 to 2014 and identified age, cirrhosis, and low current CD4 cell count as risk factors.

ABSTRACT

Background: While liver-related deaths in HIV and hepatitis C virus (HCV) co-infected individuals have declined over the last decade, hepatocellular carcinoma (HCC) may have increased. We described the epidemiology of HCC and other liver events in a multi-cohort collaboration of HIV/HCV co-infected individuals.

Methods: We studied all HCV antibody-positive adults with HIV in the EuroSIDA Study, the Southern Alberta Clinic Cohort, the Canadian Co-infection Cohort, and the Swiss HIV Cohort Study from 2001 to 2014. We calculated the incidence of HCC and other liver events (defined as liver-related deaths or decompensations, excluding HCC) and used Poisson regression to estimate incidence rate ratios.

Results: Our study comprised 7,229 HIV/HCV co-infected individuals (68% male, 90% white). During follow-up, 72 cases of HCC and 375 other liver events occurred, yielding incidence rates of 1.6 (95% confidence interval (CI): 1.3, 2.0) and 8.6 (95% CI: 7.8, 9.5) cases per 1,000 person-years of

follow-up, respectively. The rate of HCC increased 11% per calendar year (95% CI: 4%, 19%) and decreased 4% for other liver events (95% CI: 2%, 7%), but only the latter remained statistically significant after adjustment for potential confounders. High age, cirrhosis, and low current CD4 cell count were associated with a higher incidence of both HCC and other liver events.

Conclusions: In HIV/HCV co-infected individuals, the crude incidence of HCC increased from 2001 to 2014, while other liver events declined. Individuals with cirrhosis or low current CD4 cell count are at highest risk of developing HCC or other liver events.

BACKGROUND

As hepatitis C virus (HCV) and human immunodeficiency virus (HIV) have shared modes of transmission, individuals with HIV are more often infected with HCV than the general population [1]. HCV can cause chronic hepatic inflammation leading to liver fibrosis and cirrhosis that entails a risk of liver decompensation and hepatocellular carcinoma (HCC) [2]. Concomitant HIV infection accelerates this process [3, 4], and liver disease is one of the main causes of death in people with HIV [5]. Some studies indicate that the overall rate of liver-related death is declining in HIV/HCV co-infected individuals [6], but at the same time, national cohort studies have shown an increasing rate of HCC [7-9].

We aimed to study HIV/HCV co-infected individuals in Europe and Canada and describe trends in the incidences of HCC and other liver events from 2001 to 2014 and identify risk factors for the development of HCC and other liver events.

METHODS

Study population

We included all HIV/HCV co-infected individuals in four prospective cohorts of HIV-positive individuals: the EuroSIDA study [10], which enrolls from 111 clinics across Europe, Israel, and Argentina; the Southern Alberta Clinic Cohort [11], which enrolls from Southern Alberta, Canada; the Canadian Co-infection Cohort study (CTN222) [12], which enrolls HIV/HCV co-infected individuals from 18 centers across Canada; and the Swiss HIV Cohort Study [13]. All cohorts collect and update data at least every six months using standardized collection forms.

We defined HCV co-infection as being HCV antibody-positive. Baseline was defined as the latest of first cohort or clinic visit; first positive HCV antibody-test; or January 1, 2001 (since data on non-AIDS defining cancers, including HCC, were collected prospectively from this date).

Data from all participating cohorts were pooled together by use of the HIV Cohort Data Exchange Protocol [14].

Outcomes

We studied two separate outcomes: 1) HCC, and 2) other liver events, defined as liver decompensation or liver-related death. Liver decompensation was defined as hepatic encephalopathy (grade 3 or 4), hepatorenal syndrome, ascites, variceal bleeding, or spontaneous bacterial peritonitis. Liver-related death was defined as deaths caused by chronic viral hepatitis or other liver failure, excluding HCC. The diagnoses were based on pathology reports, hospital discharge summaries, or consultation notes. For HCC, in the absence of the above, the diagnosis could also be based on a strong suspicion supported by evidence from radiological imaging or biochemical assay. All events were subsequently centrally reviewed.

Statistical analysis

Crude incidence rates of both HCC and other liver events were calculated by calendar time, grouped into two-year periods, and stratified by latest cirrhosis status and CD4 cell count, also testing for interaction between cirrhosis status and current CD4 cell count. When calculating incidence of other liver events, individuals with a liver decompensation prior to baseline were excluded from follow-up (N = 179).

Poisson generalized estimating equations assuming auto-regressive (AR1) correlation were used to investigate the association between various demographic, HIV, and lifestyle related characteristics and the incidence of HCC and other liver related events, separately. Variables significant in the univariate regression models ($P<0.1$) were included in multivariate regression models. Sensitivity analyses were performed which excluded HCC cases with HIV/HCV/HBV co-infection or those with any cancer diagnosis (other than HCC) prior to end-of-follow-up.

All statistical tests were two sided with a type I error rate of 5%. Statistical analyses were performed using SAS 9.3 (Statistical Analysis Software, Cary NC, USA).

Predictor variables

The following variables were analyzed: age*, sex, race (white, other/unknown), region (Europe East/Argentina, Europe West, Canada), HIV risk group (men who have sex with men (MSM), injection drug use (IDU), heterosexual, other/unknown), body mass index (BMI) category*, ever smoked*, ever abused alcohol*, diabetes mellitus*, hepatitis B virus (HBV) co-infection*, ever HBV active drugs*, ever HCV active drugs*, ever combination antiretroviral therapy (cART)*, ever acquired immunodeficiency syndrome (AIDS)*, detectable HIV RNA*, CD4 cell count current*, CD4 cell count nadir*, cirrhosis*, and calendar year of event. Asterisks indicate variables that were updated at each visit.

BMI was calculated as weight in kilograms / squared height in meters and categorized as either underweight (BMI <20), normal weight (BMI 20-25), overweight (BMI 25-30), or obese (BMI > 30). Alcohol use was not uniformly collected in all cohorts, but where available, alcohol abuse was defined as consuming above 25 and 20 units per week for men and women, respectively. Diabetes mellitus was defined as having a diagnosis of insulin-dependent diabetes mellitus or taking diabetic medication or insulin. HBV co-infection was defined as the presence of hepatitis B surface antigen in serum. cART was defined as receiving at least three antiretrovirals from any class. Detectable HIV RNA was defined as having plasma HIV RNA above 400 copies per milliliter.

Cirrhosis was defined using a hierarchical structure with cutoffs from earlier publications [15-17]: Liver biopsy with a METAVIR score of F4 was considered the highest level of evidence, followed by FibroScan elasticity of 12.5 kPa or above, then aspartate aminotransferase-to-platelet ratio index (APRI) of 2 or above, and then plasma hyaluronic acid level of 200 ng/ml or above. A patient was assumed cirrhotic from the date of measurement and onwards if the measurement fulfilled at least one of the criteria mentioned above. If markers were inconsistent, the marker of highest evidence level decided the cirrhosis status. Individuals in whom we could not assess cirrhosis status were classified as “missing”.

RESULTS

Baseline characteristics

We included 7,229 individuals in our study (4,132 from the EuroSIDA Study; 2,044 from the Swiss HIV Cohort Study; 840 from the Canadian Co-infection Cohort; 213 from the Southern Alberta Clinic Cohort). Table 1 shows the baseline characteristics of our study population. The majority were male (68%), white (90%), and primarily from Europe West (58%). Median age was 38 (inter-quartile range (IQR): 36, 43) years. The main HIV risk group was IDU (59%), and 5% were HIV/HCV/HBV co-infected.

Incidence rates of HCC and other liver events

From 2001 to 2014, 72 cases of HCC (with 45,192 person-years of follow-up) and 375 cases of other liver events (with 43,718 person-years of follow-up) occurred, resulting in overall incidence rates of 1.6 (95% confidence interval (CI): 1.3, 2.0) cases of HCC per 1,000 person-years of follow-up and 8.6 (95% CI: 7.8, 9.5) cases of other liver events per 1,000 person-years of follow-up. Figure 1 shows the incidence rates of HCC and other liver events as a function of calendar years. The incidence of HCC increased by 11% per year (95% CI: 4%, 19%, p = 0.002), from 0.4 cases per 1,000 person-years of follow-up in 2001-02 to 2.3 cases per 1,000 person-years of follow-up in 2013-14. In contrast, the incidence of other liver events decreased by 4% per year (95% CI: 2%, 7%, p = 0.002) from 9.9 cases per 1,000 person-years of follow-up in 2003-04 to 5.2 cases per 1,000 person-years of follow-up in 2013-14.

In cirrhotics, the overall incidence rate of HCC was 7.9 (95% CI: 5.9, 10.5) cases per 1,000 person-years of follow-up against 0.5 (95% CI: 0.3, 0.7) cases per 1,000 person-years of follow-up in non-cirrhotics. For other liver events, the incidence rates were 35.9 (95% CI: 31.1, 41.4) and 2.4 (95% CI: 1.9, 3.0) cases per 1,000 person-years of follow-up for cirrhotics and non-cirrhotics, respectively.

In both cirrhotics and non-cirrhotics, the incidence rates of both outcomes were lower in those with a current CD4 cell count above 350 cells/mm^3 (Figure 2). In cirrhotics, the incidence

rate of HCC decreased from 10.9 (95% CI: 7.4, 16.1) cases per 1,000 person-years of follow-up in those with a CD4 cell count below 350 cells/mm^3 to 6.1 (95% CI: 3.8, 9.7) cases per 1,000 person-years of follow-up in those with a CD4 cell count above 350 cells/mm^3. For other liver events, the effect was more drastic, as the incidence rate here went from 58.7 (95% CI: 49.2, 70.0) to 20.1 (95% CI: 15.5, 26.4) cases per 1,000 person-years of follow-up, respectively. There was no significant interaction between cirrhosis and current CD4 cell count for any outcome (both $p > 0.2$), but the analyses had low power.

Characteristics at event

Table 2 shows the characteristics at event in those who developed HCC or other liver events and at end-of-follow-up in the remaining cohort. Median age at event was 49.6 years for HCC versus 43.9 years for other liver events. Within two years of event, 75% of HCC cases and 70% of other liver events cases had cirrhosis. Only 8% of HCC cases and 6% of other liver events cases were HBV co-infected. 32% of HCC cases had ever received HCV active drugs versus 18% of other liver events cases. Almost all had ever received cART (99% of HCC cases and 91% of other liver events cases), but their most recent (within six months) CD4 cell counts were quite low with a median of 286 (IQR: 201, 438) cells/mm^3 in HCC cases and 242 (IQR: 110, 397) cells/mm^3 in other liver event cases.

Of the 11 who developed HCC and had an HCV RNA measurement at least six months after completing interferon-based treatment, none had achieved a sustained virologic response (SVR).

Risk factors for HCC and other liver events

In multivariate analysis, higher age, HBV co-infection, lower current CD4 cell count, and cirrhosis were associated with a higher incidence of HCC (Table 3). Notably, we found no impact of alcohol abuse, diabetes mellitus, or detectable HIV RNA on the incidence of HCC in univariate analysis.

Later calendar years were significantly associated with a higher incidence of HCC in univariate analysis, but not in multivariate analysis, indicating that changes in other variables explained the increase over time. In a supplementary analysis, increases in the proportion with cirrhosis mostly explained the increase in HCC over time, as it was only after adjustment for cirrhosis that there no longer was a significant increase in HCC over time (adjusted incidence rate ratio per calendar year increase 1.05, 95% CI: 0.98, 1.13).

The multivariate analysis of other liver events yielded similar risk factors (Figure 3 and Supplementary Table 1): higher age, lower CD4 cell count, and cirrhosis (but not HBV co-infection) were associated with a higher incidence of other liver events. Additionally, HIV risk group "other/unknown" compared with MSM, being underweight, and having ever smoked were also associated with a higher incidence of other liver events. Later calendar years were in both uni- and multivariate analysis associated with a lower incidence of other liver events with statistical significance.

Excluding those with HBV co-infection or those with any other cancer diagnosis prior to end-of-follow-up did not change the results (data not shown).

In a supplementary analysis of individuals with cirrhosis (Supplementary Table 2), we found that having a current APRI >3 (compared with current APRI between 2 and 3) was independently associated with a higher incidence of other liver events. For HCC, the trend was similar, but not statistically significant.

DISCUSSION

We observed opposing trends in the crude incidence of HCC and other liver events in HIV/HCV co-infected individuals from 2001 to 2014: HCC increased from 0.4 to 2.3 cases per 1,000 person-years of follow-up, whereas other liver events decreased from 9.9 to 5.2 cases per 1,000 person-years of follow-up.

An increase in HCC incidence has previously been shown in retrospective national studies of HIV/HCV co-infected individuals: in Spain, Merchante et al. [8] showed that the incidence

increased from 2000 to 2010 (0.2 to 1.4 cases per 1,000 person-years of follow-up), and, in the Veterans Affairs Cohort in the United States, Ioannou et al. [9] found that the age-adjusted prevalence of HCC increased from 0.15% in 1996 to 1.06% in 2009. They link the rise in incidence with the increased survival in individuals with HIV, as HCV-related development of cirrhosis and subsequent HCC takes several years [18]. Our results support this reasoning as changes in the proportion of individuals with cirrhosis – which increased by 8% per year (data not shown) – mostly explained the increase in HCC per calendar year in multivariate analysis.

However, while the proportion of cirrhotics and crude incidence of HCC was increasing, we found that the incidence of other liver events, i.e. liver decompensations and liver-related deaths, decreased, even after adjustment. Other recent studies of HIV/HCV co-infected individuals, but not all [19], have shown similar trends [5-7, 20]. This could be explained by the increased uptake of cART, which has been found to lower the progression of hepatic fibrosis and disease [21, 22], improved HCV treatment uptake [23], and possibly the discontinuation of older hepatotoxic antiretrovirals [24]. In our multivariate analysis, having ever received cART or HCV active drugs did not affect the decrease of other liver events per calendar year, but an increase in current CD4 cell count did protect against other liver events, and the population had higher CD4 cell counts at end-of-follow-up. Improvements in HIV and HCV treatment have undoubtedly reduced the risk of liver decompensations and liver-related death in the last decade, but our data suggest that other explanatory factors are yet to be accounted for.

It seems paradoxical that improvements in liver-related morbidity in HIV/HCV co-infected patients, demonstrated by a lower incidence of other liver events, would simultaneously yield a higher incidence of HCC. Perhaps an improved management of liver cirrhosis and HIV treatment can increase the threshold for liver decompensation in the cirrhotic HIV/HCV co-infected individuals, but thus increasing longevity such that viral hepatocarcinogenesis has enough time to manifest itself as HCC. This hypothesis is somewhat supported in our finding that for cirrhotics, the decrease in incidence rate was much more pronounced for other liver events than for HCC when comparing those with a current CD4 cell count less than 350 cells/mm^3 to those with a count above 350 cells/mm^3,

though formal analysis for interaction between cirrhosis and current CD4 cell count was not statistically significant.

In our multivariate analysis, the major risk factor for HCC was cirrhosis. We found that 74% of individuals with HCC had cirrhosis within six months of HCC diagnosis. As "missing" cirrhosis status also was associated with a higher incidence of HCC, it is likely that the markers used in our definition of cirrhosis have not identified all cirrhotics, rather than an actual situation in which 26% of individuals developed HCC without cirrhosis. However, as liver biopsies are being replaced by the same non-invasive markers, our result warns that HCC can develop in individuals who do not seem to have cirrhosis based on these markers.

We also found that lower current CD4 cell count was associated with HCC in HIV/HCV co-infected individuals. Previous studies have also shown this in HIV individuals in general [9, 25, 26], but in HCV/HIV co-infected individuals, the results have been conflicting: Salmon et al. [27] did not find an association, arguing that any association is likely confounded by cirrhosis as concomitant splenic sequestration of lymphocytes artificially lowers the CD4 cell count [28]. However, Kramer et al. [29] found that having a CD4 cell count of <200 cells/mm^3 (compared with >350 cells/mm^3) was associated with a 1.7 times greater hazard of HCC, and that the association remained when analyzing the subgroup with cirrhosis. In our study, we found a significant protective effect of a doubling in current CD4 cell count after adjustment for cirrhosis, corroborating the independent effect of current immunosuppression as a risk factor for HCC.

In addition to cirrhosis and CD4 cell count, HBV co-infection and higher age were independent risk factors for HCC. However, these factors (except HBV co-infection) were also risk factors for other liver events. The effect sizes were different, but for a singular case, the clinician should perceive the aforementioned risk factors as general predictors of liver disease and death, and not HCC exclusively, especially as the incidence of HCC, though increasing, remains low.

Alcohol abuse and diabetes mellitus has been associated with an increased risk of HCC amongst HCV mono-infected individuals. Our study found no influence of a history of alcohol abuse on the risk of HCC (or other liver events after adjustment), but since our data on alcohol abuse were

heterogeneous and scarce, we cannot rule out that (continued) alcohol abuse impacts the risk of developing HCC or other liver events. Our study found no association between diabetes mellitus and HCC or other liver events, consistent with other studies [9, 27], although the latter study found an association between insulin resistance and the risk of HCC.

Our study has several limitations: First, our diagnosis of cirrhosis was based primarily on non-invasive techniques. However, the measurements and their respective cutoffs have been validated [30], and possible misclassifications would underestimate any real effect of cirrhosis in our analyses, where it in fact was the strongest predictor. Second, we defined (chronic) HCV co-infection by the presence of HCV antibodies, and as around 20% can clear the infection spontaneously, we might have included some individuals with resolved HCV infection, which may have diluted the incidence rates reported. Third, data on alcohol abuse were only recently added to some of our cohorts and were thus very limited. Fourth, we only had data on HCV treatment, but not treatment outcome (SVR rates), which likely would have been a more precise covariate to include in our regression models. The major strength of our study is that our population is taken from prospective cohorts, representing a large portion of Europe and Canada and with a relatively large proportion of females rendering our results readily applicable to the Caucasian population.

In conclusion, we observed that from 2001 to 2014, the incidence of HCC in HIV/HCV co-infected individuals increased – largely explained by an increase in the number of individuals with cirrhosis – whereas the rate of other liver events (liver decompensations and liver-related deaths) decreased. Higher age, cirrhosis, and lower current CD4 cell count were independent risk factors for both HCC and other liver events. New HCV treatment with direct-acting antivirals and earlier HIV treatment will likely reduce the rates of HCC and other liver events, but as HCC can develop after achieving SVR [31], or as a consequence of long-tern alcohol abuse, non-alcoholic steatohepatitis, or other hepatotoxic exposures, continuous surveillance of incidence trends is needed.

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Conflict of interest

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Table 1. Baseline Characteristics of 7,229 HIV/Hepatitis C Virus Co-Infected Individuals

Characteristic	
Age, years, median (IQR)	38.1 (32.6, 43.4)
Female sex, N (%)	2,304 (31.9)
White race, N (%)	6,530 (90.3)
Region, N (%)	
Europe West	4,200 (58.1)
Europe East/Argentina	1,976 (27.3)
Canada	1,053 (14.6)
HIV risk group, N (%)	
Men who have sex with men	834 (11.5)
Injection drug use	4,289 (59.3)
Heterosexual	1,188 (16.4)
Other/unknown	918 (12.7)
BMI category, N (%)[a]	
Underweight	111 (4.1)
Normal weight	2,003 (74.5)
Overweight	496 (18.5)
Obese	78 (2.9)
Ever smoked, N (%)[b]	2,168 (71.7)
Ever abused alcohol, N (%)[c]	165 (13.3)
Diabetes mellitus, N (%)	200 (2.8)
HBV co-infection, N (%)[d]	329 (5.1)
Ever HBV active drugs, N (%)	381 (5.3)
Ever HCV active drugs, N (%)	735 (10.2)
Ever cART, N (%)	5,138 (71.1)

Ever AIDS, N (%)	1,822 (25.2)
Detectable HIV RNA, N (%)[f]	2,540 (41.6)
CD4 cell count, cells/mm^3, median (IQR)[g]	388 (240, 571)
CD4 cell count nadir, cells/mm^3, median (IQR)[h]	208 (95, 351)
Cirrhosis, N (%)[i]	342 (5.9)
Year of baseline[j], N (%)	
2001-02	3,185 (44.1)
2003-04	799 (11.1)
2005-06	892 (12.3)
2007+	2,353 (32.5)

Abbreviations: IQR, inter-quartile range; BMI, body mass index; AIDS, acquired immunodeficiency syndrome; cART, combination antiretroviral therapy; HCV, hepatitis C virus; HBV, hepatitis B virus.

[a] Body mass index was categorized in 2,668 individuals.

[b] Smoking status was determined in 3,025 individuals.

[c] Alcohol abuse was determined in 1,241 individuals.

[d] HBV co-infection was determined in 6,485 individuals.

[f] Detectable HIV RNA was determined in 6,099 individuals.

[g] CD4 cell count was determined in 6,802 individuals.

[h] CD4 cell count nadir was determined in 7,098 individuals.

[i] Cirrhosis was determined in 5,799 individuals.

[j] Baseline was defined as the latest of first visit; first positive HCV-antibody test; or January 1, 2001.

Table 2. Characteristics of HIV/Hepatitis C Virus Co-Infected Individuals Within Six Months of Diagnosis of Hepatocellular Carcinoma or Other Liver Event or Within Six Months of End-of-Follow-Up in the Remaining Cohort

Characteristic	No HCC or other liver event (n = 6,787)	HCC (n = 72)	Other liver event (n = 375)
Age, years, median (IQR)	44.8 (37.6, 50.8)	49.6 (46.0, 55.8)	43.9 (38.6, 49.6)
Follow-up time, years, median (IQR)	5.3 (2.5, 9.7)	6.0 (2.4, 9.2)	3.9 (1.6, 6.7)
Female sex, N (%)	2,182 (32.1)	17 (23.6)	106 (28.3)
White race, N (%)	6,124 (90.2)	68 (94.4)	343 (91.5)
Region, N (%)			
Europe West	3,882 (57.2)	55 (76.4)	266 (70.9)
Europe East/Argentina	1,898 (28.0)	6 (8.3)	73 (19.5)
Canada	1,007 (14.8)	11 (15.3)	36 (9.6)
HIV risk group, N (%)			
Men who have sex with men	802 (11.8)	6 (8.3)	27 (7.2)
Injection drug use	4,003 (59.0)	40 (55.6)	249 (66.4)
Heterosexual	1,129 (16.6)	17 (23.6)	43 (11.5)
Other/unknown	853 (12.6)	9 (12.5)	56 (14.9)
BMI category, N (%)[a]			
Underweight	179 (6.8)	3 (12.0)	23 (13.9)
Normal weight	1,794 (68.6)	17 (68.0)	109 (65.7)
Overweight	527 (20.2)	4 (16.0)	27 (16.3)
Obese	115 (4.4)	1 (4.0)	7 (4.2)

Ever smoked, N (%)[b]	2987 (80.1)	25 (75.8)	180 (86.5)
Ever abused alcohol, N (%)[c]	610 (18.6)	4 (20.0)	22 (30.6)
Diabetes mellitus, N (%)	313 (4.6)	6 (8.3)	29 (7.7)
HBV co-infection, N (%)[d]	292 (4.5)	6 (8.3)	23 (6.3)
Ever HBV active drugs, N (%)	2,633 (38.8)	34 (47.2)	136 (36.3)
Ever HCV active drugs, N (%)	1,537 (14.6)	23 (31.9)	68 (18.1)
Ever cART, N (%)	5,964 (87.9)	71 (98.6)	340 (90.7)
Ever AIDS, N (%)	2,163 (31.9)	28 (38.9)	167 (44.5)
Detectable HIV RNA, N (%)[e]	1,189 (25.1)	9 (15.5)	123 (38.4)
CD4 cell count current, cells/mm^3, median (IQR)[f]	470 (289, 670)	286 (201, 438)	242 (110, 397)
Cirrhosis, N (%)[h]	1,447 (25.0)	45 (75.4)	189 (69.7)

Abbreviations: HCC, hepatocellular carcinoma; IQR, inter-quartile range; BMI, body mass index; AIDS, acquired immunodeficiency syndrome; cART, combination antiretroviral therapy; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HBV, hepatitis B virus; APRI, aspartate aminotransferase-to-platelet ratio index.

[a] Body mass index was categorized in 2,615 individuals without an event, 25 individuals with HCC, and 166 individuals with other liver events.

[b] Smoking status was determined in 3,728 individuals without an event, 33 individuals with HCC, and 208 individuals with other liver events.

[c] Alcohol abuse was determined in 3,278 individuals without an event, 20 individuals with HCC, and 72 individuals with other liver events.

[d] HBV co-infection was determined in 6,489 individuals without an event, 69 individuals with HCC, and 366 individuals with other liver events.

[e] Detectable HIV RNA was determined in 4,746 individuals without an event, 58 individuals with HCC, and 320 individuals with other liver events.

[f] CD4 cell count current was determined in 6,254 individuals without an event, 69 individuals with HCC, and 349 individuals with other liver events.

[g] CD4 cell count nadir was recorded in 6,773 individuals without an event, all individuals with HCC and 370 individuals with other liver events.

[h] Cirrhosis was determined in 5,799 individuals without an event, 61 individuals with HCC, and 271 individuals with other liver events.

Table 3. Univariate and Multivariate Analyses of Hepatocellular Carcinoma in HIV/Hepatitis C Virus Co-Infected Individuals

	Univariate analysis		Multivariate analysis[a]	
	IRR (95% CI)	p-value	IRR (95% CI)	p-value
Age at baseline, per 10 year increase	2.43 (2.06, 2.88)	< 0.01	2.36 (1.89, 2.94)	< 0.01
Sex, female vs. male	0.61 (0.36, 1.06)	0.08	1.01 (0.58, 1.77)	0.96
Race, other/unknown vs. white	0.65 (0.24, 1.77)	0.40		
Region				
Europe West	Reference		Reference	
Europe East/Argentina	0.32 (0.14, 0.74)	0.01	0.65 (0.28, 1.51)	0.31
Canada	1.27 (0.6, 2.42)	0.47	0.68 (0.32, 1.45)	0.32
HIV risk group				
Men who have sex with men	Reference			
Injection drug use	1.06 (0.45, 2.50)	0.89		
Heterosexual	1.79 (0.71, 4.51)	0.22		
Other/unknown	1.07 (0.38, 3.01)	0.89		
BMI category				
Underweight	2.40 (0.70, 8.22)	0.16		
Normal weight	Reference			
Overweight	0.91 (0.31, 2.71)	0.87		
Obese	1.26 (0.17, 9.39)	0.82		
Unknown	1.14 (0.65, 1.98)	0.65		
Ever smoked				
No	Reference			

Yes	0.84 (0.38, 1.85)	0.66		
Unknown	1.07 (0.50, 2.28)	0.87		
Ever abused alcohol				
No	Reference			
Yes	1.34 (0.45, 4.01)	0.61		
Unknown	0.66 (0.38, 1.15)	0.14		
Diabetes mellitus, yes vs. no	1.95 (0.86, 4.46)	0.11		
HBV co-infection				
No	Reference		Reference	
Yes	2.17 (0.94, 5.02)	0.07	2.46 (1.03, 5.87)	0.04
Unknown	0.72 (0.23, 2.28)	0.58	0.96 (0.31, 2.96)	0.95
Ever HBV active drugs, yes vs. no	1.92 (1.12, 3.04)	< 0.01	1.00 (0.59, 1.68)	0.99
Ever HCV active drugs, yes vs. no	2.06 (1.26, 3.38)	< 0.01	1.27 (0.74, 2.16)	0.39
Ever cART, yes vs. no	12.03 (1.67, 86.58)	< 0.01	5.79 (0.77, 43.69)	0.09
Ever AIDS, yes vs. no	1.51 (0.94, 2.42)	0.09	1.20 (0.69, 2.06)	0.52
Detectable HIV RNA				
No	Reference			
Yes	0.56 (0.28, 1.14)	0.11		
Unknown	0.83 (0.46, 1.50)	0.53		
CD4 cell count current, per log2 increase in cells/mm^3	0.74 (0.66, 0.83)	< 0.01	0.78 (0.65, 0.95)	0.01
CD4 cell count nadir, per log2 increase in cells/mm^3	0.88 (0.80, 0.97)	< 0.01	1.07 (0.90, 1.27)	0.43
Cirrhosis				
No	Reference			
Yes	17.21 (9.74, 30.41)	< 0.01	12.92 (6.97, 23.95)	< 0.01

Unknown	5.51 (2.56, 11.87)	< 0.01	5.80 (2.52, 13.39)	< 0.01
Calendar year of event, per year increase	1.11 (1.04, 1.19)	< 0.01	1.05 (0.98, 1.13)	0.17

Abbreviations: IRR, incidence rate ratio; CI, confidence interval; BMI, body mass index; AIDS, acquired immunodeficiency syndrome; HCV, hepatitis C virus; HBV, hepatitis B virus; cART, combination antiretroviral therapy.

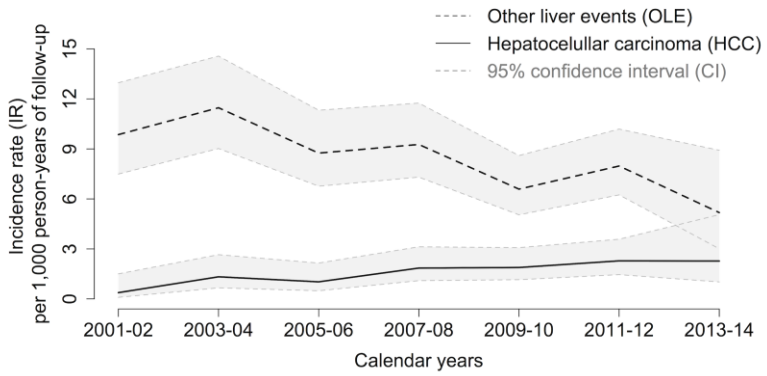
[a] Variables with a p-value of < 0.10 in the univariate analysis were included in the multivariate analysis.

FIGURE LEGENDS

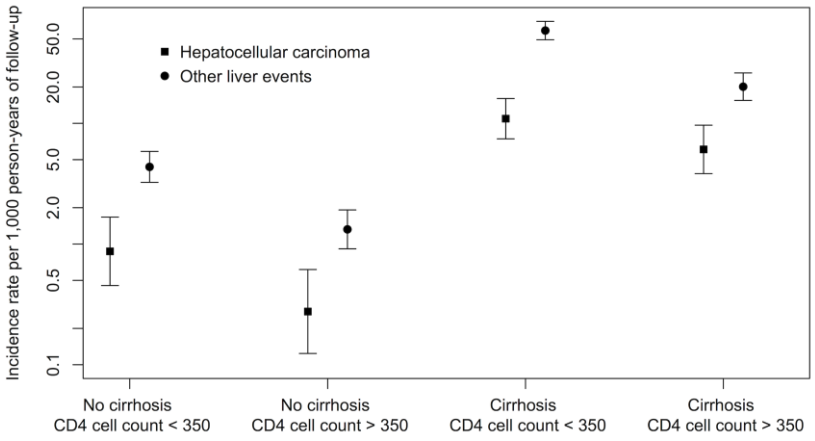
Figure 1 Trend in Incidence Rates (with 95% Confidence Intervals) of Hepatocellular Carcinoma and Other Liver Events in 7,229 HIV/Hepatitis C Virus Co-Infected Individuals from 2001 to 2014

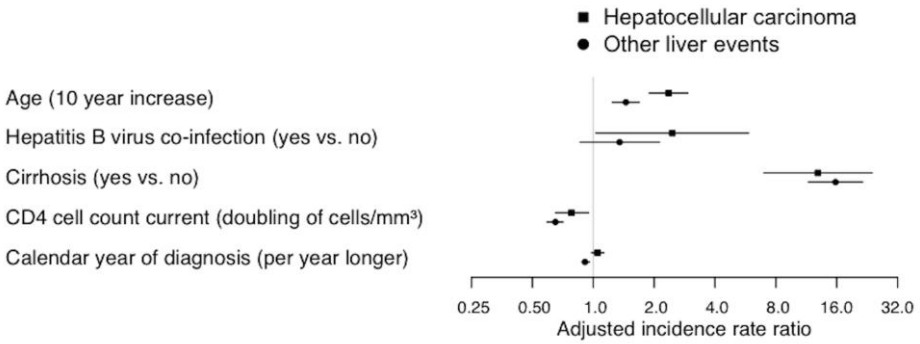
Figure 2 Incidence Rates (with 95% Confidence Intervals) for Hepatocellular Carcinoma and Other Liver Events in HIV/Hepatitis C Virus Co-Infected Individuals Stratified by Cirrhosis Status and Current CD4 Cell Count (Cells per mm^3). Note: Formal Analysis of Interaction between Cirrhosis and Current CD4 Cell Count was Non-Significant for Both Outcomes (All P-values > 0.2)

Figure 3 Adjusted Incidence Rate Ratios (with 95% Confidence Intervals) for a Selection of Risk Factors for Hepatocellular Carcinoma (HCC) and Other Liver Events in Multivariate Time-Updated Poisson Regression Models



HCC	Cases	2	8	7	14	16	19	6
	IR (95% CI)	0.4 (0.5-2.1)	1.3 (0.7-2.7)	1.0 (0.5-2.2)	1.9 (1.1-3.1)	1.9 (1.2-3.1)	2.3 (1.5-3.6)	2.3 (1.0-5.1)
OLE	Cases	51	67	58	68	54	64	13
	IR (95% CI)	9.9 (7.5-13.0)	11.5 (9.0-14.6)	8.7 (6.8-11.3)	9.3 (7.3-11.8)	6.6 (5.0-8.6)	8.0 (6.2-10.2)	5.2 (3.0-8.9)





■ also adjusted for: sex, region (Europe East/Argentina vs. Europe West vs. Canada), ever AIDS, ever HCV active drugs, ever HBV active drugs, ever cART, and CD4 cell count nadir.

● also adjusted for: sex, region (Europe East/Argentina vs. Europe West vs. Canada), ever AIDS, ever HBV active drugs, ever cART, CD4 cell count nadir, HIV risk group, BMI*, ever smoked*, ever abused alcohol, diabetes mellitus, and detectable HIV RNA. *p<0.05