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Trends in Incidences and Risk Factors for Hepatocellular Carcinoma and Other Liver Events in HIV and Hepatitis C Virus–coinfected Individuals From 2001 to 2014: A Multicohort Study

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Background. While liver-related deaths in human immunodeficiency virus (HIV) and hepatitis C virus (HCV)–coinfected individuals have declined over the last decade, hepatocellular carcinoma (HCC) may have increased. We describe the epidemiology of HCC and other liver events in a multicohort collaboration of HIV/HCV–coinfected individuals.

Methods. We studied 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 7229 HIV/HCV–coinfected 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 1000 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. Older 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–coinfected 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.

Keywords. HIV; hepatitis C virus; hepatocellular carcinoma; liver disease; cohort study.

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–coinfected individuals [6], but at the same time, national cohort studies have shown an increasing rate of HCC [7–9].

Our aim was to study HIV/HCV–coinfected 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–coinfected individuals in 4 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–coinfected individuals from 18 centers across Canada; and the Swiss HIV

Cohort Study [13]. All cohorts collect and update data at least every 6 months using standardized collection forms.

We defined HCV coinfection as being HCV antibody-positive. Baseline was defined as the latest of first cohort or clinic visit; first positive HCV antibody test; or 1 January 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 2 separate outcomes: HCC and 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 death 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 Analyses

Crude incidence rates of both HCC and other liver events were calculated by calendar time, grouped into 2-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 autoregressive (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 ($P < .1$) were included in multivariate regression models. Sensitivity analyses were performed that excluded HCC cases with HIV/HCV/hepatitis B virus (HBV) coinfection or those with any cancer diagnosis (other than HCC) prior to the end of follow-up.

All statistical tests were 2 sided with a type I error rate of 5%. Statistical analyses were performed using SAS 9.3 (Statistical Analysis Software, Cary, North Carolina).

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*, HBV coinfection*, ever HBV active drugs*, ever HCV active drugs*, ever combination

antiretroviral therapy (cART)*, ever AIDS*, detectable HIV RNA*, CD4 cell count current*, CD4 cell count nadir*, cirrhosis*, and calendar year of event. Asterisk indicates 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. Where available, alcohol abuse was defined as consuming more than 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 coinfection was defined as the presence of hepatitis B surface antigen in serum, and cART was defined as receiving at least 3 antiretrovirals from any class. Detectable HIV RNA was defined as having plasma HIV RNA >400 copies/mL.

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, then aspartate aminotransferase-to-platelet ratio index (APRI) of ≥2, and then plasma hyaluronic acid level of ≥200 ng/mL. A patient was assumed cirrhotic from the date of measurement and onward if the measurement fulfilled at least 1 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 "unknown."

RESULTS

Baseline Characteristics

We included 7229 individuals in our study (4132 from the EuroSIDA study; 2044 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 western Europe (58%). Median age was 38 years (interquartile range [IQR]: 36, 43). The main HIV risk group was IDU (59%), and 5% were HIV/HCV/HBV–coinfected.

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 1000 person-years of follow-up and 8.6 (95% CI, 7.8, 9.5) cases of other liver events per 1000 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%; $P = .002$), from 0.4 cases per 1000 person-years of follow-up

Table 1. Baseline Characteristics of 7229 Human Immunodeficiency Virus/Hepatitis C Virus–Coinfected Individuals

Characteristic	N (%)
Age, years, median (IQR)	38.1 (32.6, 43.4)
Female sex, N (%)	2304 (31.9)
White race, N (%)	6530 (90.3)
Region, N (%)	
Western Europe	4200 (58.1)
Eastern Europe/Argentina	1976 (27.3)
Canada	1053 (14.6)
HIV risk group, N (%)	
Men who have sex with men	834 (11.5)
Injection drug use	4289 (59.3)
Heterosexual	1188 (16.4)
Other/unknown	918 (12.7)
Body mass index category, N (%)[a]	
Underweight	111 (4.1)
Normal weight	2003 (74.5)
Overweight	496 (18.5)
Obese	78 (2.9)
Ever smoked, N (%)[b]	2168 (71.7)
Ever abused alcohol, N (%)[c]	165 (13.3)
Diabetes mellitus, N (%)	200 (2.8)
HBV coinfection, N (%)[d]	329 (5.1)
Ever HBV active drugs, N (%)	381 (5.3)
Ever hepatitis C virus active drugs, N (%)	735 (10.2)
Ever combination antiretroviral therapy, N (%)	5138 (71.1)
Ever AIDS, N (%)	1822 (25.2)
Detectable HIV RNA, N (%)[e]	2540 (41.6)
CD4 cell count, cells/mm^3, median (IQR)[f]	388 (240, 571)
CD4 cell count nadir, cells/mm^3, median (IQR)[g]	208 (95, 351)
Cirrhosis, N (%)[h]	342 (5.9)
Year of baseline[i], N (%)	
2001–2002	3185 (44.1)
2003–2004	799 (11.1)
2005–2006	892 (12.3)
2007+	2353 (32.5)

Abbreviations: HBV, hepatitis B virus; HIV, human immunodeficiency virus; IQR, interquartile range.

[a] Body mass index was categorized in 2668 individuals.
[b] Smoking status was determined in 3025 individuals.
[c] Alcohol abuse was determined in 1241 individuals.
[d] HBV coinfection was determined in 6485 individuals.
[e] Detectable HIV RNA was determined in 6099 individuals.
[f] CD4 cell count was determined in 6802 individuals.
[g] CD4 cell count nadir was determined in 7098 individuals.
[h] Cirrhosis was determined in 5799 individuals.
[i] Baseline was defined as the latest of first visit; first positive hepatitis C virus antibody test; or 1 January 2001.

in 2001–2002 to 2.3 cases per 1000 person-years of follow-up in 2013–2014. In contrast, the incidence of other liver events decreased by 4% per year (95% CI, 2%, 7%; $P = .002$) from 9.9 cases per 1000 person-years of follow-up in 2003–2004 to 5.2 cases per 1000 person-years of follow-up in 2013–2014.

In cirrhotics, the overall incidence rate of HCC was 7.9 (95% CI, 5.9, 10.5) cases per 1000 person-years of follow-up compared with 0.5 (95% CI, .3, .7) cases per 1000 person-years of follow-up in noncirrhotics. 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 1000 person-years of follow-up for cirrhotics and noncirrhotics, respectively.

In both cirrhotics and noncirrhotics, the incidence rates of both outcomes were lower in those with a current CD4 cell count >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 1000 person-years of follow-up in those with a CD4 cell count <350 cells/mm^3 to 6.1 (95% CI, 3.8, 9.7) cases per 1000 person-years of follow-up in those with a CD4 cell count >350 cells/mm^3. For other liver events, the effect was more drastic, as the incidence rate went from 58.7 (95% CI, 49.2, 70.0) to 20.1 (95% CI, 15.5, 26.4) cases per 1000 person-years of follow-up, respectively. There was no significant interaction between cirrhosis and current CD4 cell count for any outcome (both $P > .2$), 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 the end of follow-up in the remaining cohort. Median age at event was 49.6 years for HCC vs 43.9 years for other liver events. Within 2 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–coinfected. Thirty-two percent of HCC cases had ever received HCV active drugs vs 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 6 months) CD4 cell counts were quite low with a median of 286 cells/mm^3 (IQR, 201, 438) in HCC cases and 242 cells/mm^3 (IQR, 110, 397) in other liver event cases.

Of the 11 who developed HCC and had an HCV RNA measurement at least 6 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, being older, HBV coinfection, 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, .98, 1.13).
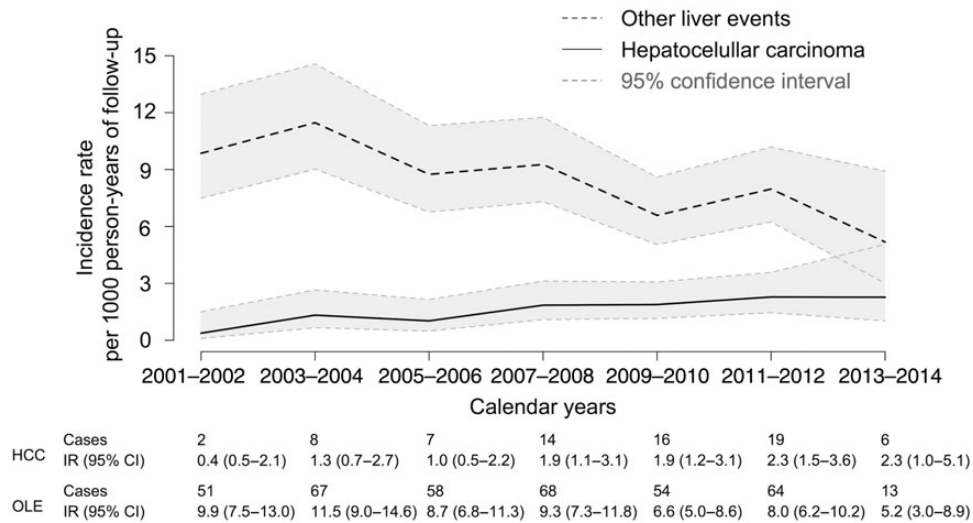
Figure 1. Trend in incidence rates (with 95% confidence intervals [CI]) of hepatocellular carcinoma (HCC) and other liver events in 7229 human immunodeficiency virus/ hepatitis C virus coinfected individuals from 2001 to 2014. Abbreviations: IR, incidence rate; OLE, other liver event.

The multivariate analysis of other liver events yielded similar risk factors (Figure 3 and Supplementary 1). Being older, lower CD4 cell count, and cirrhosis (but not HBV coinfection) were associated with a higher incidence of other liver events. Additionally, the 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. In both uni- and multivariate analysis, later calendar years were associated with a lower incidence of other liver events with statistical significance.

Exclusion of those with HBV coinfection 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 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–coinfected individuals from 2001 to 2014. HCC increased from 0.4 to 2.3 cases per 1000 person-years of follow-up, whereas other liver events decreased from 9.9 to 5.2 cases per 1000 person-years of follow-up.

An increase in HCC incidence has previously been shown in retrospective national studies of HIV/HCV–coinfected individuals. In Spain, Merchante et al [8] showed that the incidence increased from 2000 to 2010 (0.2–1.4 cases per 1000 person-years of follow-up). 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 linked 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, that is, liver decompensations and liver-related deaths, decreased, even after adjustment. Other recent studies of HIV/HCV–coinfected individuals, but not all [19], have shown similar trends [5–7, 20]. This could be explained by the increased uptake of cART (which have been found to lower the progression
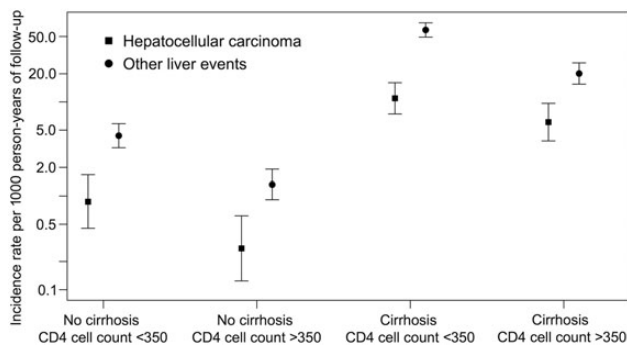

Figure 2. Incidence rates (with 95% confidence intervals) for hepatocellular carcinoma and other liver events in human immunodeficiency virus/hepatitis C virus coinfected individuals stratified by cirrhosis status and current CD4 cell count (cells/mm³). Note: Formal analysis of interaction between cirrhosis and current CD4 cell count was not significant for both outcomes (all *P* values >.2).

Table 2. Characteristics of Human Immunodeficiency Virus/Hepatitis C Virus–Coinfected Individuals Within 6 Months of Diagnosis of Hepatocellular Carcinoma or Other Liver Event or Within 6 Months of End of Follow-Up in the Remaining Cohort

Characteristic	No HCC or Other Liver Event (n = 6787)	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 (%)	2182 (32.1)	17 (23.6)	106 (28.3)
White race, N (%)	6124 (90.2)	68 (94.4)	343 (91.5)
Region, N (%)			
Western Europe	3882 (57.2)	55 (76.4)	266 (70.9)
Eastern Europe /Argentina	1898 (28.0)	6 (8.3)	73 (19.5)
Canada	1007 (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	4003 (59.0)	40 (55.6)	249 (66.4)
Heterosexual	1129 (16.6)	17 (23.6)	43 (11.5)
Other/unknown	853 (12.6)	9 (12.5)	56 (14.9)
Body mass index category, N (%)[a]			
Underweight	179 (6.8)	3 (12.0)	23 (13.9)
Normal weight	1794 (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 coinfection, N (%)[d]	292 (4.5)	6 (8.3)	23 (6.3)
Ever HBV active drugs, N (%)	2633 (38.8)	34 (47.2)	136 (36.3)
Ever hepatitis C virus active drugs, N (%)	1537 (14.6)	23 (31.9)	68 (18.1)
Ever combination antiretroviral therapy, N (%)	5964 (87.9)	71 (98.6)	340 (90.7)
Ever AIDS, N (%)	2163 (31.9)	28 (38.9)	167 (44.5)
Detectable HIV RNA, N (%)[e]	1189 (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 (%)[g]	1447 (25.0)	45 (75.4)	189 (69.7)

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; IQR, interquartile range.

[a] Body mass index was categorized in 2615 individuals without an event, 25 individuals with HCC, and 166 individuals with other liver events.

[b] Smoking status was determined in 3728 individuals without an event, 33 individuals with HCC, and 208 individuals with other liver events.

[c] Alcohol abuse was determined in 3278 individuals without an event, 20 individuals with HCC, and 72 individuals with other liver events.

[d] HBV coinfection was determined in 6489 individuals without an event, 69 individuals with HCC, and 366 individuals with other liver events.

[e] Detectable HIV RNA was determined in 4746 individuals without an event, 58 individuals with HCC, and 320 individuals with other liver events.

[f] CD4 cell count current was determined in 6254 individuals without an event, 69 individuals with HCC, and 349 individuals with other liver events.

[g] Cirrhosis was determined in 5799 individuals without an event, 61 individuals with HCC, and 271 individuals with other liver events.

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. However, an increase in current CD4 cell count did protect against other liver events, and the population had higher CD4 cell counts at the 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 have yet to be accounted for.

It seems paradoxical that improvements in liver-related morbidity in HIV/HCV–coinfected 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 cirrhotic HIV/HCV–coinfected 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 <350 cells/mm^3 to those with a count >350 cells/mm^3, though formal analysis for interaction between cirrhosis and current CD4 cell count was not statistically significant.

Table 3. Univariate and Multivariate Analyses of Hepatocellular Carcinoma in Human Immunodeficiency Virus/Hepatitis C Virus–Coinfected Individuals

Variates	Univariate Analysis		Multivariate Analysis[a]	
	IRR (95% CI)	P Value	IRR (95% CI)	P Value
Age at baseline, per 10-y increase	2.43 (2.06, 2.88)	<.01	2.36 (1.89, 2.94)	<.01
Sex, female vs male	0.61 (.36, 1.06)	.08	1.01 (.58, 1.77)	.96
Race, other/unknown vs white	0.65 (.24, 1.77)	.40		
Region				
Western Europe	Reference		Reference	
Eastern Europe /Argentina	0.32 (.14, 0.74)	.01	0.65 (.28, 1.51)	.31
Canada	1.27 (.6, 2.42)	.47	0.68 (.32, 1.45)	.32
HIV risk group				
Men who have sex with men	Reference			
Injection drug use	1.06 (.45, 2.50)	.89		
Heterosexual	1.79 (.71, 4.51)	.22		
Other/unknown	1.07 (.38, 3.01)	.89		
Body mass index category				
Underweight	2.40 (.70, 8.22)	.16		
Normal weight	Reference			
Overweight	0.91 (.31, 2.71)	.87		
Obese	1.26 (.17, 9.39)	.82		
Unknown	1.14 (.65, 1.98)	.65		
Ever smoked				
No	Reference			
Yes	0.84 (.38, 1.85)	.66		
Unknown	1.07 (.50, 2.28)	.87		
Ever abused alcohol				
No	Reference			
Yes	1.34 (.45, 4.01)	.61		
Unknown	0.66 (.38, 1.15)	.14		
Diabetes mellitus, yes vs no	1.95 (.86, 4.46)	.11		
HBV coinfection				
No	Reference		Reference	
Yes	2.17 (.94, 5.02)	.07	2.46 (1.03, 5.87)	.04
Unknown	0.72 (.23, 2.28)	.58	0.96 (.31, 2.96)	.95
Ever HBV active drugs, yes vs no	1.92 (1.12, 3.04)	<.01	1.00 (.59, 1.68)	.99
Ever hepatitis C virus active drugs, yes vs no	2.06 (1.26, 3.38)	<.01	1.27 (.74, 2.16)	.39
Ever combination antiretroviral therapy, yes vs no	12.03 (1.67, 86.58)	<.01	5.79 (.77, 43.69)	.09
Ever AIDS, yes vs no	1.51 (.94, 2.42)	.09	1.20 (.69, 2.06)	.52
Detectable HIV RNA				
No	Reference			
Yes	0.56 (.28, 1.14)	.11		
Unknown	0.83 (.46, 1.50)	.53		
CD4 cell count current, per $\log_2$ increase in cells/mm^3	0.74 (.66, .83)	<.01	0.78 (.65, .95)	.01
CD4 cell count nadir, per $\log_2$ increase in cells/mm^3	0.88 (.80, .97)	<.01	1.07 (.90, 1.27)	.43
Cirrhosis				
No	Reference		Reference	
Yes	17.21 (9.74, 30.41)	<.01	12.92 (6.97, 23.95)	<.01
Unknown	5.51 (2.56, 11.87)	<.01	5.80 (2.52, 13.39)	<.01
Calendar year of event, per year increase	1.11 (1.04, 1.19)	<.01	1.05 (.98, 1.13)	.17

Abbreviations: CI, confidence interval; HBV, hepatitis B virus; HIV, human immunodeficiency virus; IRR, incidence rate ratio.

[a] Variables with a P value of <.10 in the univariate analysis were included in the multivariate analysis.

In our multivariate analysis, the major risk factor for HCC was cirrhosis. We found that 74% of individuals with HCC had cirrhosis within 6 months of HCC diagnosis. As "unknown" 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
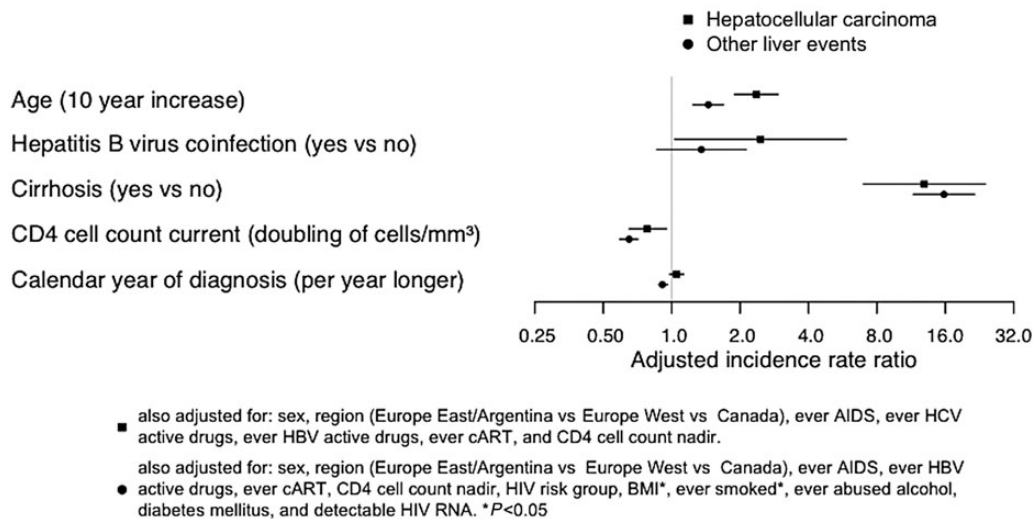
■ Hepatocellular carcinoma
● Other liver events

Age (10 year increase)
Hepatitis B virus coinfection (yes vs no)
Cirrhosis (yes vs no)
CD4 cell count current (doubling of cells/mm³)
Calendar year of diagnosis (per year longer)

0.25 0.50 1.0 2.0 4.0 8.0 16.0 32.0
Adjusted incidence rate ratio

■ 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

Figure 3. Adjusted incidence rate ratios (with 95% confidence intervals) for a selection of risk factors for hepatocellular carcinoma and other liver events in multivariate time-updated Poisson regression models. Abbreviations: BMI, body mass index; cART, combination antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

same noninvasive 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–coinfected individuals. Previous studies have also shown this in HIV individuals in general [9, 25, 26], but in HCV/HIV–coinfected 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/ mm³ (compared with >350 cells/mm³) was associated with a 1.7 times greater hazard of HCC and that the association remained when the subgroup with cirrhosis was analyzed. 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 coinfection and being older were independent risk factors for HCC. However, these factors (except HBV coinfection) were also risk factors for other liver events. Even though the effect sizes were different, 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 have been associated with an increased risk of HCC among HCV-monoinfected individuals. We 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. We 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 noninvasive 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 coinfection by the presence of HCV antibodies. Since 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 was taken from prospective cohorts, representing a large portion of Europe and Canada and with a relatively large proportion of females.

In conclusion, we observed that from 2001 to 2014, the incidence of HCC in HIV/HCV–coinfected 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. Older 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. However, as HCC can develop after SVR is achieved [31], or as a consequence of long-tern alcohol abuse, nonalcoholic steatohepatitis, or other hepatotoxic exposures, continuous surveillance of incidence trends is needed.

Supplementary Data

Notes

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