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

Running title: HCC in HIV/HCV co-infected individuals.

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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 word count: 248 words

Text word count: 2,999 words

Display items: 3 tables and 3 figures

Supplementary material: 1 table

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.

TEXT

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]. It is therefore not surprising that 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 incidence 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 HIV-positive individuals from 107 clinics across Europe, Israel, and Argentina; the Southern Alberta Clinic Cohort [11], which enrolls individuals receiving HIV care in Southern Alberta, Canada; the Canadian Co-infection Cohort study (CTN222) [12], which enrolls HCV co-infected HIV-positive individuals from 18 centers across Canada; and the Swiss HIV Cohort Study [13], which enrolls HIV-positive individuals from Switzerland. 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], which is freely available at www.hicdep.org.

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 from the hospitalization or clinic. 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.

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 the 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 considered for inclusion in the regression models: 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 (per doubling), CD4 cell count nadir, cirrhosis, and calendar year of event*. Asterisks indicate time-fixed variables; all other variables 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 units per week for men and 20 units per week for women. 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 using cutoffs from earlier publications [15-17]: A liver biopsy with a METAVIR score of F4 was considered the highest level of evidence, followed by a FibroScan elasticity of 12.5 kPa or above, then an aspartate aminotransferase-to-platelet ratio index (APRI) of 2 or above, and then a plasma hyaluronic acid level of 200 ng/ml or above. The individual patient was assumed cirrhotic from the date of measurement and onwards if the measurement fulfilled at least one of the criteria mentioned above. If different markers were incon-

sistent, 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 individuals with cirrhosis, 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 individuals who did not have cirrhosis according to our definition. 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 in cirrhotics and non-cirrhotics, respectively.

When further stratifying for current CD4 cell count, we found that the incidence rates of both outcomes were lower in those with a current CD4 cell count above 350 cells/mm^3 in both those with and without cirrhosis (Figure 2). For individuals with cirrhosis, 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 of current CD4 cell count 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. Formal statistical interaction analyses did not identify a 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 those who developed HCC and 70% of those who developed other liver events had cirrhosis. Only 8% of HCC cases and 6% of other liver events cases were HBV co-infected. 32% of those who developed HCC had ever taken HCV active drugs versus 18% of those who developed other liver events. Almost all had ever taken cART (99% of HCC cases and 91% of other liver events cases), but their most recent (within six months) CD4 cell counts were however still quite low with a median of 286 (IQR: 201, 438) cells/mm^3 for those who developed HCC and 242 (IQR: 110, 397) cells/mm^3 for those who developed another liver event.

Of the 11 of those who developed HCC that 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 of HCC (Table 3), higher age, HBV co-infection, lower current CD4 cell count, and cirrhosis were associated with a higher incidence of HCC. 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 events in univariate analysis, but not in multivariate analysis, indicating that changes in some of the 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. However, the HIV risk group "other/unknown" compared with MSM, being underweight, and having ever smoked were also significant risk factors for other liver events. The decrease in other liver events per calendar year in the univariate analysis did remain significant in multivariate analysis.

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).

DISCUSSION

We observed opposing trends in the 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.

The increase in HCC incidence has previously been shown in national and mostly retrospective 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 a study of 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. The authors of these studies point to the increased survival in individuals with HIV as an explanation for the rise in incidence, 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 we found to increase by 8% per year in a post-hoc analysis (data not shown) – mostly explained the increase in HCC per calendar year in multivariate analysis.

However, while the proportion of cirrhotics and incidence of HCC was increasing, we found that the incidence of other liver events, i.e. liver decompensations and liver-related deaths, decreased. Other recent studies of HIV/HCV co-infected individuals, but not all [19], have shown similar trends [5-7, 20]. This could potentially 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 switch from older hepatotoxic antiretrovirals such as zidovudine, didanosine, and stavudine to newer drugs [24]. In our analysis, prior cART and and prior HCV active drug treatment did not impact on the decrease of other liver events per calendar year in multivariate analysis, but an increase of CD4 cell count did protect against the development of other liver events, and the population as a whole had higher CD4 cell counts at end-of-follow-up. Improvements in HIV and HCV treatment have undoubtedly reduced the risk of liver decompensations or liver-related death in the last decade, but our data suggest that other explanatory factors are yet to be accounted for.

Thus, taken together, our study has shown opposing shifts in the incidence of HCC and other liver events. 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 at the same time yield a higher incidence of HCC. One explanation could be that 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 to a point where viral hepatocarcinogenesis has had 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 true cirrhotics, rather than an actual situation in which 26% of individuals developed HCC without cirrhosis. However, as liver biopsies are being continuously replaced by the same non-invasive markers, our results 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]. But in a more recent study, 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 the association remained when analyzing a subgroup with cirrhosis. In our study – where we treated CD4 cell count as a continuous variable – we found a statistically 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 of HCC.

In addition to cirrhosis and CD4 cell count, HBV co-infection and higher age were significant risk factors for HCC. All these are clinically relevant parameters that can help the treating physician assess each HIV/HCV co-infected individual's risk of liver malignancy. However, the risk

factors we identified for HCC were also independent risk factors for other liver events (except for HBV co-infection). The effect sizes were different, but for a singular case, the clinician should perceive the aforementioned risk factors as more general predictors of liver disease and death, and not HCC exclusively, especially as the incidence of HCC, though increasing, remains low.

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. Third, data on alcohol abuse were only recently added to some of our cohorts and thus very limited. 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 counts were independent risk factors for both HCC and other liver events. New treatment of HCV with direct acting antivirals and earlier HIV treatment will likely reduce the rates of HCC and other liver events, but as HCC still 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.

NOTES

Funding

This work was supported within the framework of the EuroSIDA Study (supported by the European Commission BIOMED 1 [CT94-1637], BIOMED 2 [CT97-2713], the 5th Framework [QLK2-2000-00773], the 6th Framework [LSHP-CT-2006-018632] and the 7th Framework [FP7/ 2007-2013, EuroCoord grant agreement number 260694] programmes, the Swiss National Science Foundation [grant number 108787], and unrestricted grants by Janssen R&D, Merck and Co. Inc., Pfizer Inc., and GlaxoSmithKline LLC), the Swiss HIV Cohort Study (supported by the Swiss National Science Foundation [grant number 148522] and the Swiss HIV Cohort Study research foundation), and the Canadian Co-Infection Cohort (supported by the Canadian Institutes of Health Research [CIHR MOP-79529], Fonds de la recherche du Québec-Santé (FRQ-S): Réseau SIDA/maladies infectieuses, and the Canadian HIV Trials Network (CTN-222). M.B.K. is supported by the "Chercheurs Nationaux" career award from the FRQ-S).

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Conflict of interest

L.I.G., L.S., A.L., M.R., K.D., M.B., D.B., V.M.L., J.D.L., J.K.R., J.G., M.B.K., and L.P. have no conflict of interest. E.J. have held lectures sponsored by AbbVie, MSD, Gilead, Janssen, and BMS and have received honoraria for advisory boards from Gilead, Janssen, Glaxo, and BMS. A.R. received honoraria for advisory boards, unrestricted grants, and travel grants from Janssen-Cilag, MSD, Gilead Sciences, ViiV, Abbvie, Bristol-Myers Squibb, and Boehringer Ingelheim, all remuneration went to his home institution and not to A.R. personally. A.M. received honoraria, travel support, speaker and or consultancy fees from BMS, BI, Gilead, Pfizer, Merck and Wragge LLC.

Acknowledgements

Members of the Swiss HIV Cohort Study: Aubert V, Battegay M, Bernasconi E, Böni J, Braun DL, Bucher HC, Burton-Jeangros C, Calmy A, Cavassini M, Dollenmaier G, Egger M, Elzi L,

Fehr J, Fellay J, Furrer H (Chairman of the Clinical and Laboratory Committee), Fux CA, Gorgievski M, Günthard H (President of the SHCS), Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Kahlert C, Kaiser L, Keiser O, Klimkait T, Kouyos R, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Marzolini C, Metzner K, Müller N, Nadal D, Nicca D, Pantaleo G, Rauch A (Chairman of the Scientific Board), Regenass S, Rudin C (Chairman of the Mother & Child Substudy), Schöni-Affolter F (Head of Data Centre), Schmid P, Speck R, Stöckle M, Tarr P, Trkola A, Vernazza P, Weber R, Yerly S. Data from the Swiss HIV Cohort Study are gathered by the five Swiss University Hospitals, two Cantonal Hospitals, 15 affiliated hospitals and 36 private physicians (listed in http://www.shcs.ch/180-health-care-providers).

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The Canadian Co-Infection Cohort would like to acknowledge the participants of the Canadian Co-Infection Cohort (CTN 222) and thank Olugbenga Adebayo, Claire Allen, Brenda Beckthold, Claire Casavant, Isabelle Chabot, Warmond Chan, Victor Chiang, Sarah De Coutere, Bruce Ganase, Laurie Gokool, Sandy Kassir, Jennifer Kocilowicz, Judy Latendre-Paquette, Nancy McFarland, Anja Mcneil, Jessica Milloy, Chantal Morrisseau, Mina Perez, Marie-Claude Plaisance, Laura Puri, Annie Qiu, for their assistance with study coordination, participant recruitment and care. Co-Investigators of the Canadian Co-Infection Cohort are Drs. Lisa Barrett, Jeff Cohen, Brian Conway, Curtis Cooper, Pierre Côté, Joseph Cox, John Gill, Shariq Haider, Mark Hull, Valerie Martel-Laferriere, Julio Montaner, Erica Moodie, Neora Pick, Anita Rachlis, Danielle Rouleau, Aida Sadr, Stephen Sanche, Roger Sandre, Mark Tyndall, Marie-Louise Vachon, Sharon Walmsley, Alexander Wong, David Wong.

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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 ami-notransferase-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