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HIV RNA, CD4+ Percentage, and Risk of Hepatocellular Carcinoma by Cirrhosis Status

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ABSTRACT

Background: Despite increasing incidence of hepatocellular carcinoma (HCC) among HIV-infected patients, it remains unclear if HIV-related factors contribute to development of HCC. We examined if higher or prolonged HIV viremia and lower CD4+ cell percentage were associated with HCC.

Methods: We conducted a cohort study of HIV-infected individuals who had HIV RNA, CD4+, and CD8+ cell counts and percentages assessed in the Veterans Aging Cohort Study (1999-2015). HCC was ascertained using Veterans Health Administration cancer registries and electronic records. Cox regression was used to determine hazard ratios (HR [95% confidence interval]) of HCC associated with higher current HIV RNA, longer duration of detectable HIV viremia (≥500 copies/mL), and current CD4+ cell percentage <14%, adjusting for traditional HCC risk factors. Analyses were stratified by previously validated diagnoses of cirrhosis prior to start of follow-up.

Results: Among 35,659 HIV-infected patients, 302 (0.8%) developed HCC over 281,441 person-years (incidence rate, 107.3/100,000 person-years). Among patients without baseline cirrhosis, higher HIV RNA (1.25 [1.12-1.40] per 1.0 $\log_{10}$ copies/mL) and ≥12 months of detectable HIV (1.47 [1.02-2.11]) were independently associated with higher risk of HCC. CD4+ percentage <14% was not associated with HCC in any model. Hepatitis B and C coinfection were each significant predictors of HCC regardless of baseline cirrhosis status.

Conclusion: Among HIV-infected patients without baseline cirrhosis, higher HIV RNA and longer duration of HIV viremia increased risk of HCC, independent of

traditional HCC risk factors. This is the strongest evidence to date that HIV viremia contributes to risk of HCC in this group.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a growing cause of cancer death among people living with HIV infection.[1] Driven largely by hepatitis C virus (HCV) coinfection, hepatitis B virus (HBV) coinfection, and alcoholic liver disease, the incidence of HCC among HIV-infected persons in North America has risen more than 4-fold from 1995-2009.[2] Moreover, HIV-infected individuals have a 4-fold higher risk of HCC than uninfected persons.[3]

Despite the rising incidence of HCC among HIV-infected individuals, the determinants of this malignancy remain largely unknown in this group.[4] Three prior studies found no association between HIV suppression and risk of HCC,[5-7] but these studies did not evaluate the effects of longer durations or higher levels of HIV viremia, nor did they account for cirrhosis. Moreover, previous studies among predominantly HIV/HCV-coinfected patients reported that lower absolute CD4+ cell counts increased the risk of HCC.[6,8-12] However, absolute CD4+ cell count may decrease during cirrhosis due to portal hypertension-induced splenic sequestration.[13] Thus, studies evaluating associations between absolute CD4+ cell count and HCC risk cannot determine whether observed associations are driven by HIV-related immunosuppression or progression of liver disease. Consequently, it remains unclear if higher HIV RNA levels, longer duration of detectable HIV, and HIV-related immunosuppression contribute to development of HCC independent of traditional determinants. Identifying such factors could help define the mechanisms for the high rate of HCC among HIV-infected persons.

Cirrhosis, which represents the late stage of progressive hepatic fibrosis due to chronic liver disease, is an important step in the causal pathway towards HCC (**Figure 1**).[14] Cirrhosis promotes HCC through telomere dysfunction and alterations

of the liver milieu (e.g., increased production of toxic hepatic metabolites, cytokines, growth factors, and products of oxidative stress).[15] Since cirrhosis increases the risk of HCC substantially, studies evaluating the factors associated with HCC must account for baseline cirrhosis status.

We evaluated HIV-related and traditional risk factors for HCC among HIV-infected patients. We hypothesized that higher HIV RNA levels, longer duration of HIV viremia, and lower CD4+ cell percentage, which is not affected by liver disease progression,[13] were significant determinants of HCC. We also examined the risk of HCC with traditional risk factors in the general population, including older age, black race, overweight/obesity, diabetes mellitus, alcohol dependence/abuse, tobacco use, and HBV and HCV coinfection.[16] To account for the role of cirrhosis in the development of HCC and the possibility that risk factors for HCC might vary by presence of cirrhosis, we stratified our analysis by baseline cirrhosis status.

METHODS

Study Design and Data Source

We conducted a retrospective cohort study among HIV-infected individuals in the Veterans Aging Cohort Study (VACS) between October 1, 1999 and September 30, 2015.[17] The VACS consists of electronic medical record data from HIV-infected patients receiving care at Veterans Health Administration (VA) facilities across the United States (US). Data include demographics, hospital and outpatient diagnoses (recorded using International Classification of Diseases, Ninth Revision [ICD-9] codes), procedures, laboratory results, and dispensed medications. Death date was determined from the VA Vital Status File. The study was approved by the Institutional Review Boards of the University of Pennsylvania, Corporal Michael Crescenz VA

Medical Center in Philadelphia, VA Connecticut Healthcare System, and Yale University.

Study Patients

HIV-infected patients were included if they had: 1) HIV RNA, CD4+, and CD8+ count/percentage simultaneously assessed (which occurs routinely as part of HIV care in the VA system) between October 1, 1999 and September 30, 2015, and 2) at least 180 days of observation after determination of these laboratory results. We defined the start of follow-up as 180 days after the date that HIV RNA, CD4+, and CD8+ results were assessed. The 180 days prior to start of follow-up represented the baseline period, during which baseline comorbidities and laboratory results were collected. Patients were excluded if they had HCC diagnosed prior to start of follow-up. Follow-up continued until HCC, death, or last VA visit before September 30, 2015.

Main Study Outcomes

The primary outcome was incident HCC diagnosis. HCC diagnoses were determined from the VA national cancer registry by topography code C22.0 (liver) and morphology codes 8170-8180 (HCC) from the International Classification of Diseases for Oncology, Third Edition (ICD-O-3),[18] consistent with Surveillance, Epidemiology, and End Results coding algorithms.[19] The VA cancer registry records cancers diagnosed and/or treated within the VA.[7] ICD-O-3 codes validly identify cancer diagnoses, including HCC.[20] To account for lags in reporting diagnoses in the cancer registry and minimize the likelihood of missing HCC events, we supplemented HCC case finding with ICD-9 diagnoses for HCC (155.0, 155.1, and 155.2) recorded in the VA electronic medical record. Prior research has shown that use of both VA cancer registry records

and ICD-9 diagnoses have 90% sensitivity for incident cancer diagnosis when compared to chart review; however, positive predictive value varied (96% for VA cancer registry; 63% for ICD-9 diagnosis).[20,21] Consequently, HCC diagnoses from the registry and claims were confirmed by medical record review by trained adjudicators. For all confirmed HCC cases, we determined the presence of cirrhosis by review of medical records within one year prior to HCC diagnosis. Details on cirrhosis adjudication appear in **Appendix 1**.

Data Collection

Baseline data included: age; sex; race/ethnicity; body mass index (BMI); diabetes (defined by random glucose ≥200 mg/dL, hemoglobin A1c ≥6.5%, or anti-diabetic drug use[22]); alcohol dependence/abuse; injection/non-injection drug use; tobacco use (ever); HBV coinfection (ever positive HBV surface antigen); HCV coinfection (ever detectable HCV RNA or genotype); cirrhosis; HIV RNA; absolute CD4+ and CD8+ counts and percentages; and antiretroviral therapy (ART) use. Cirrhosis was defined by a hospital discharge diagnosis or outpatient diagnosis for cirrhosis or hepatic decompensation (**Appendix 2**). Prior studies validated this determination within the VA system, with ≥90% of these diagnoses confirmed by medical records.[23,24] Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and platelet count were collected from dates closest, but within 360 days prior, to start of follow-up. FIB-4, a non-invasive measure of hepatic fibrosis, was calculated by: (age [years] x AST [U/L])/(platelet count [10^9/L]) x (ALT [U/L])$^{1/2}$).[25]

Time-varying variables were assessed on a monthly basis and included HIV RNA, CD4+ and CD8+ counts/percentages, and diabetes. When multiple results of the same test were measured within a month, in order to be most conservative, we used

the highest HIV RNA and CD8+ result, and lowest CD4+ result. When a test was not updated during a month, we carried forward the value from the previous month until the next available result. HIV RNA, CD4+, and CD8+ results were updated at the beginning of each 30-day interval from baseline but were lagged by 180 days (approximate mean doubling time of HCC tumors <5 centimeters in length[26]) to reduce the possibility that the presence of HCC influenced these variables (i.e., reverse causality).

Statistical Analysis

We determined unadjusted incidence rates (IR) of HCC (events/100,000 person-years), overall and by HBV and HCV status. We used multivariable Cox regression to determine adjusted hazard ratios (HR [95% confidence interval]) of HCC for risk factors of interest. HIV-related factors included higher time-updated HIV RNA level, longer duration of detectable HIV (≥500 copies/mL), and lower time-updated CD4+ percentage. Traditional HCC risk factors examined included older age, black race, overweight/obesity, diabetes, alcohol dependence/abuse, ever use of tobacco, HBV coinfection, and HCV coinfection.[16] Given the importance of cirrhosis on development of HCC, analyses were stratified by baseline cirrhosis status.

To evaluate the effects of HIV viremia on HCC risk, we created four separate models that examined HIV as a time-updated: 1) continuous variable by 1.0 $\log_{10}$ increments (model #1), 2) categorical variable defined by detectable HIV (≥500 copies/mL; model #2), 3) categorical variable classified by increasing categories of HIV RNA (<500 copies/mL; 500-9,999 copies/mL; ≥10,000 copies/mL; model #3), and 4) categorical variable classified by increasing consecutive months of detectable HIV (compared to those with undetectable HIV; model #4). For model

#4, detectable HIV was evaluated as a monthly time-updated variable. Once a patient was classified with HIV viremia, consecutive months were counted until a viral load <500 copies/mL was identified. If detectable HIV recurred, the count of consecutive months of viremia was restarted at one month. We determined HRs of HCC associated with increasing consecutive months of detectable HIV (1-11 months; ≥12 months) compared to persons whose HIV RNA was suppressed throughout follow-up, adjusting for all other risk factors.

We performed five sensitivity analyses to assess the robustness of our results. First, we repeated the analysis accounting for competing risk of death.[27] Second, we repeated analyses, lagging HIV RNA and CD4+ cell percentages by 360 and 540 days. Third, we evaluated risk factors for HCC separately among persons with HBV coinfection, HCV coinfection, and without viral hepatitis. Fourth, to explore the potential impact of hepatic steatosis on HCC risk, we classified patients with possible fatty liver disease prior to start of follow-up based on the presence of both obesity (BMI ≥30 kg/m^2) and diabetes mellitus, since these act synergistically to promote steatosis,[28] and examined associations with HCC. Fifth, since duration of HIV-related immunosuppression might affect HCC risk, we determined whether longer consecutive months with CD4+ percentage <14% increased risk of HCC. Finally, in an exploratory analysis, we examined the risk of HCC with lower time-updated CD4+/CD8+ ratio, which indicates dysfunctional immune activation,[29] by cirrhosis status.

Proportionality of hazards was assessed by log-log plots and Schoenfeld residuals.[30] To address the potential bias of missing data among covariates, we implemented multiple imputation using chained equations by means of 10 imputations using all variables in **Table 1**.[31] Results across the 10 datasets were

combined to arrive at confidence intervals that accounted for within- and across-dataset variances. Data were analyzed using SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Patient Characteristics

We identified 37,946 HIV-infected individuals in the VACS who had HIV RNA, CD4+, and CD8+ results measured simultaneously between October 1, 1999 and September 30, 2015. After exclusions, 35,659 remained in the final sample.

Patients in the cohort had a median age of 46 years at baseline and were predominantly male, black, and overweight/obese (**Table 1**). Tobacco use, alcohol dependence/abuse, and injection/non-injection drug use were common. At the start of follow-up, 56.7% had HIV RNA ≥500 copies/mL, 23.9% had CD4+ percentage <14%, and 88.5% had a CD4+/CD8+ ratio <1.0. A total of 31.9% had HCV coinfection, and 5.6% were HBV-coinfected. Only 11.9% of HCV-coinfected persons received anti-HCV therapy at baseline or during follow-up.

Overall, 68.7% received ART during the baseline period. ART regimens prescribed reflected the antiretrovirals used at the time of study entry (**Table 1**). Among 1,981 HBV-coinfected individuals, 1,211 (61.1%) were on ART at baseline. Of these, 689 (56.9%) received HBV-active ART with lamivudine or emtricitabine alone, 374 (30.9%) with tenofovir plus emtricitabine or lamivudine, and 27 (2.2%) with tenofovir alone; 121 (10.0%) were on ART without an HBV-active antiretroviral. By the end of follow-up, 1,840 (92.9%) received HBV-active ART.

A total of 773 (2.2%) patients had a baseline diagnosis of cirrhosis. These patients were older and more commonly had diabetes, alcohol dependence/abuse, and HCV or HBV coinfection compared to those without cirrhosis (**Table 1**).

Incidence Rates of HCC

Overall, 302 medical record-confirmed HCC diagnoses were identified over 281,441 person-years (IR, 107.3/100,000 person-years) with median duration of follow-up of 7.4 (interquartile range, 3.3-12.8) years. Rates were particularly high among the 11,981 HBV-coinfected (IR, 350.4/100,000 person-years) and 11,392 HCV-coinfected (IR, 224.6/100,000 person-years) individuals.

Patients diagnosed with HCC had a high prevalence of HCV coinfection (82.8%), alcohol dependence/abuse (63.2%), overweight/obesity (47.7%), and HBV coinfection (18.9%; **Table 2**). Notably, 99 (32.8%) did not have cirrhosis at HCC diagnosis (**Table 2**).

Determinants of HCC, by Baseline Cirrhosis Status

Among individuals without baseline cirrhosis, higher HIV RNA in model #1 (1.25 [1.12-1.40] per 1.0 $\log_{10}$ copies/mL increase), detectable HIV in model #2 (1.46 [1.07-1.99]), HIV RNA ≥10,000 copies/mL in model #3 (1.63 [1.11-2.40]), and ≥12 months of detectable HIV viremia in model #4 (1.47 [1.02-2.11]) increased the risk of HCC (**Table 3**). Absolute CD4+ counts <200 cells/mm^3 increased HCC risk (**Appendix 3**); however, lower CD4+ percentage was not associated with an increased risk of HCC (**Table 3**). Additionally, in all models, older age, diabetes, HBV coinfection, HCV coinfection, history of alcohol dependence/abuse, and ever use of tobacco increased the risk of HCC (**Table 3**). Among individuals with baseline cirrhosis, only HBV and HCV coinfection were associated with HCC (**Appendix 4**).

Results were similar in analyses accounting for the competing risk of death (data not shown) and using 360-day and 540-day lags for HIV RNA and CD4+ cell percentage (**Appendix 5**). Similar findings were observed when analyses were restricted to HBV-coinfected (**Appendix 6**) and HCV-coinfected (**Appendix 7**)

individuals, though results for some risk factors did not achieve statistical significance given the smaller sample sizes in these groups. There were too few HCC events (n=17) among HIV-infected patients without viral hepatitis to permit analysis. When possible fatty liver disease was evaluated, patients who had both baseline obesity and diabetes had a higher risk of HCC than those who did not (2.32 [1.19-4.52]; **Appendix 8**). Longer consecutive months with CD4+ percentage <14% did not increase HCC risk (≥12 months: 1.02 [0.69-1.51]; 1-11 months: 1.15 [0.65-2.05]) compared to those with ≥14% throughout follow-up.

In exploratory analyses, after adjustment for HIV RNA and traditional risk factors, the risk of HCC was not increased with lower time-updated CD4+/CD8+ ratio among either individuals with baseline cirrhosis (1.000 [0.999-1.001] per 0.1 unit decrease) or without cirrhosis (0.991 [0.981-1.002] per 0.1 unit decrease).

DISCUSSION

To our knowledge, this is the largest study to evaluate HIV-related and traditional risk factors for HCC among HIV-infected patients, and the first to examine such determinants by baseline cirrhosis status. We stratified our analyses by baseline cirrhosis status to account for the possibility that risk factors for HCC might vary by the presence of cirrhosis. Among patients without baseline cirrhosis, time-updated detectable HIV (≥500 copies/mL), higher HIV RNA (particularly ≥10,000 copies/mL), and ≥12 months of detectable HIV increased risk of HCC, independent of traditional risk factors. Older age, HBV, HCV, diabetes, alcohol dependence/abuse, and tobacco use, which are traditional risk factors for HCC, also increased HCC risk in this group. The risk of HCC was particularly high in those with both obesity and diabetes. Among patients with baseline cirrhosis, only HBV and HCV coinfection remained associated with HCC. Notably, lower CD4+ cell

percentage was not associated with increased risk of HCC regardless of cirrhosis status.

Our study is the first to find that higher level and longer duration of HIV viremia contribute to HCC risk. HIV viremia could contribute to HCC by accelerating hepatic fibrosis progression to cirrhosis or by directly promoting hepatocarcinogenesis via immune dysregulation, oxidative stress, hepatocyte apoptosis, and/or depletion of CD4+ cells in the gastrointestinal tract with resultant microbial translocation.[32-34] We have previously shown that suppression of HIV viremia can delay onset of cirrhosis.[21] Our findings suggest that achieving and maintaining HIV suppression could mitigate the risk of HCC.

Three prior studies found no association between HIV RNA and risk of HCC, but none stratified analyses by baseline cirrhosis status. One study of 31,576 HIV-infected patients in the VA HIV Clinical Case Registry from 1985-2010 found that longer percentage of time with undetectable HIV RNA (<500 copies/mL) did not decrease HCC risk.[5] A follow-up study among 8,563 HIV/HCV-coinfected patients in this registry similarly found no association between duration of undetectable HIV RNA and HCC.[6] However, both analyses included cirrhosis as a covariate in multivariable models. Since cirrhosis is in the causal pathway to HCC, controlling for cirrhosis could have adjusted away associations between HIV suppression and HCC. A third study among 42,441 HIV-infected patients in the VACS from 1999-2015 found that neither early (≤2 years) nor long-term (>2 years) HIV suppression decreased rates of HCC compared to 104,712 demographically similar uninfected persons.[7] However, this analysis did not stratify results by baseline cirrhosis status.

Contrary to previous studies,[6,8-12] we found that HIV-related immunosuppression, as measured by CD4+ cell percentage, was not associated

with an increased risk of HCC. Notably, those prior studies evaluated the risk of HCC associated with lower absolute CD4+ count. Indeed, when we evaluated associations between absolute CD4+ count and HCC in our cohort, CD4+ counts <200 cells/mm^3 increased HCC risk. However, absolute CD4+ count may decrease during cirrhosis as a result of portal hypertension-induced splenic sequestration, but CD4+ percentage remains unchanged during cirrhosis.[13] Our results suggest that HIV-related immunosuppression is not an important contributor to HCC risk and that the findings of prior analyses likely reflected the effect of liver fibrosis progression on absolute CD4+ count.

Interestingly, 32.8% of patients with HCC in our study did not have evidence of cirrhosis based on review of medical records within one year prior to cancer diagnosis. HCC can develop in the absence of advanced hepatic fibrosis in chronic HBV infection or non-alcoholic fatty liver disease.[35,36] Further research is needed to determine how frequently HCC occurs in the absence of cirrhosis in HIV and if this differs from uninfected persons.

The study has several potential limitations. First, we might have underestimated cirrhosis, since this condition is clinically silent. However, cirrhosis was identified using validated diagnoses, and the negative predictive value of this definition exceeded 99%.[23,24] Second, we were unable to determine fatty liver disease, since this diagnosis requires liver imaging or biopsy to confirm. We classified possible fatty liver disease by baseline presence of both obesity and diabetes. Future studies should evaluate the effect of fatty liver disease on HCC in HIV. Third, we did not evaluate the risk of HCC with antiretroviral drugs, particularly those associated with hepatotoxicity,[37] or viral hepatitis treatments. Additional research should evaluate the effects of these medications on incidence of HCC. Finally, our sample

345was predominantly comprised of male US Veterans, but the study included 867 HIV-
346infected women.

347 In conclusion, among HIV-infected patients without cirrhosis, higher HIV RNA
348and longer duration of HIV viremia, in addition to HBV and HCV coinfection, were
349important determinants of HCC, independent of traditional risk factors. HIV-related
350immunosuppression, determined by CD4+ cell percentage, was not associated with
351increased risk of HCC. This study provides the strongest evidence to date that HIV
352viremia contributes to the risk of HCC in this group.

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Figure 1. Pathway to development of hepatocellular carcinoma (HCC). The figure shows the contributions of the key modifiable determinants of HCC, including traditional risk factors (blue) and the hypothesized HIV-related determinants in this study (red). Both chronic hepatitis B virus (HBV) infection and HIV viremia could increase the risk of HCC by inducing hepatic fibrosis and cirrhosis or by directly promoting development of HCC outside of the liver fibrosis pathway.

494 **Table 1**. Baseline characteristics of study patients, stratified by cirrhosis diagnosis.

Characteristic*	Overall (n=35,659)	Baseline No Cirrhosis† (n=34,886)	Baseline Cirrhosis† (n=773)
Median age (years, IQR)	46 (39-53)	46 (39-53)	49 (44-55)
Male sex	34,792 (97.6)	34,032 (97.6)	760 (98.3)
Race/ethnicity			
Black	17,069 (47.9)	16,750 (48.0)	319 (41.3)
Caucasian	13,859 (38.9)	13,522 (38.8)	337 (43.6)
Hispanic	2,720 (7.6)	2,632 (7.5)	88 (11.4)
Other/Unknown	2,011 (5.6)	1,982 (5.7)	29 (3.8)
Body mass index			
Underweight (<18.50 kg/m^2)	837 (2.3)	819 (2.3)	18 (2.3)
Normal (18.50-24.99 kg/m^2)	14,083 (39.5)	13,768 (39.5)	315 (40.8)
Overweight (25.00-29.99 kg/m^2)	11,415 (32.0)	11,184 (32.1)	231 (29.9)
Obesity (30.00-34.99 kg/m^2)	3,882 (10.9)	3,789 (10.9)	93 (12.0)
Morbid obesity (≥35.00 kg/m^2)	1,323 (3.7)	1,299 (3.7)	24 (3.1)
Missing weight and/or height	4,119 (11.6)	4,027 (11.5)	92 (11.9)
Diabetes mellitus	3,308 (9.3)	3,150 (9.0)	158 (20.4)
History of alcohol dependence/abuse	10,538 (29.6)	10,064 (28.8)	474 (61.3)
History of injection/non-injection drug use	16,235 (45.5)	15,781 (45.2)	454 (58.7)
Tobacco use			
Never	9,533 (26.7)	9,393 (26.9)	140 (18.1)
Ever‡	24,707 (69.3)	24,158 (69.2)	549 (71.0)
Unknown	1,419 (4.0)	1,335 (3.8)	84 (10.9)
Hepatitis C virus coinfection§			
Detectable HCV RNA or genotype	11,392 (31.9)	10,940 (31.4)	452 (58.5)
Ever treated with HCV antiviral	*1,354 (11.9)*	*1,304 (11.9)*	*50 (11.1)*
HCV antibody+/HCV RNA-	1,055 (3.0)	1,020 (2.9)	35 (4.5)
HCV antibody-	21,472 (60.2)	21,247 (60.9)	225 (29.1)
Never tested	1,740 (4.9)	1,679 (4.8)	61 (7.9)
Hepatitis B virus coinfection‖			
HBsAg+	1,981 (5.6)	1,873 (5.4)	108 (14.0)
Ever treated with HBV-active antiretroviral	*1,840 (92.9)*	*1,748 (93.3)*	*92 (85.2)*
HBsAg-	31,712 (88.9)	31,096 (89.1)	616 (79.7)
Never tested	1,966 (5.5)	1,917 (5.5)	49 (6.3)
HIV RNA			
Median (log_{10} cells/mm^3, IQR)	3.2 (1.7-4.6)	3.2 (1.7-4.6)	3.0 (1.7-4.6)
≥500 copies/mL	20,216 (56.7)	19,791 (56.7)	425 (55.0)
CD4+ cell percentage			
Median (%, IQR)	22 (14-31)	22 (14-31)	22 (14-31)
≥28%	11,776 (33.0)	11,530 (33.1)	246 (31.8)
14-27.99%	14,798 (41.5)	14,456 (41.4)	342 (44.2)
<14%	8,513 (23.9)	8,337 (23.9)	176 (22.8)
Unknown	572 (1.6)	563 (1.6)	9 (1.2)
CD4+/CD8+ ratio			
Median (IQR)	0.40 (0.21-0.69)	0.40 (0.21-0.69)	0.42 (0.21-0.70)
<1.0	31,553 (88.5)	30,879 (88.5)	674 (87.2)
Median alanine aminotransferase (U/L)	31 (21-47)	30 (21-47)	41 (27-71)
Not assessed at baseline	2,362 (6.6)	2,338 (6.7)	24 (3.1)
Median aspartate aminotransferase (U/L)	30 (23-44)	29 (22-43)	55 (32-94)

Characteristic*	Overall (n=35,659)	Baseline No Cirrhosis† (n=34,886)	Baseline Cirrhosis† (n=773)
Not assessed at baseline	1,987 (5.6)	1,964 (5.6)	23 (3.0)
Platelet count (x 10^6/L)			
≥150,000	30,570 (85.7)	30,194 (86.6)	376 (48.6)
<150,000	4,812 (13.5)	4,420 (12.7)	392 (50.7)
Not assessed at baseline	277 (0.8)	272 (0.8)	5 (0.6)
Median baseline FIB-4 (IQR)	1.18 (0.81-1.78)	1.17 (0.81-1.74)	3.00 (1.58-5.82)
Unable to be calculated at baseline	3,325 (9.3)	3,290 (9.4)	35 (4.5)
On antiretroviral therapy	24,506 (68.7)	23,980 (68.7)	526 (68.0)
Most common baseline antiretroviral regimens¶			
Efavirenz/tenofovir/emtricitabine	3,639 (14.8)	3,565 (14.9)	74 (14.1)
Efavirenz/zidovudine/lamivudine	1,764 (7.2)	1,738 (7.2)	26 (4.9)
Nelfinavir/zidovudine/lamivudine	1,177 (4.8)	1,156 (4.8)	21 (4.0)
Indinavir/zidovudine/lamivudine	1,033 (4.2)	1,015 (4.2)	18 (3.4)
Atazanavir/tenofovir/emtricitabine	965 (3.9)	950 (4.0)	15 (2.9)
Nelfinavir/stavudine/lamivudine	888 (3.6)	863 (3.6)	25 (4.8)
Indinavir/stavudine/lamivudine	725 (3.0)	708 (3.0)	17 (3.2)
Nevirapine/zidovudine/lamivudine	663 (2.7)	652 (2.7)	11 (2.1)
Efavirenz/stavudine/lamivudine	611 (2.5)	590 (2.5)	21 (4.0)

Abbreviations: HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IQR=interquartile range; RNA=ribonucleic acid

* Results reported as n (%) unless otherwise specified.

† Cirrhosis defined as any diagnosis of compensated or decompensated cirrhosis prior to the start of follow-up.

‡ Ever tobacco use includes current and prior tobacco use.

§ Hepatitis C virus coinfection defined as positive quantitative HCV RNA (absolute value determinable or not), positive qualitative HCV RNA, or quantifiable HCV genotype at baseline or during follow-up.

|| Hepatitis B virus coinfection defined as positive HBV surface antigen at baseline or during follow-up.

¶ Percentages represent proportion of antiretroviral use among patients prescribed therapy.

506**Table 2**. Characteristics of patients with incident hepatocellular carcinoma, stratified by

507cirrhosis as determined by review of medical records within one year prior to diagnosis.

Characteristic*	Overall Incident HCC (n=302)	No Evidence of Cirrhosis (n=99)	Evidence of Cirrhosis (n=203)
Median age at diagnosis (years, IQR)	56.4 (51.3-61.1)	57.5 (51.3-61.8)	56.0 (51.3-60.9)
Median time to diagnosis (years, IQR)	7.2 (3.9-10.6)	6.3 (3.5-10.3)	7.4 (4.2-11.1)
Male sex	299 (99.0)	99 (100.0)	200 (98.5)
Race/ethnicity			
Black	159 (52.6)	62 (62.6)	97 (47.8)
Caucasian	97 (32.1)	24 (24.2)	73 (36.0)
Hispanic	37 (12.3)	10 (10.1)	27 (13.3)
Other/Unknown	9 (3.0)	3 (3.0)	6 (3.0)
Body mass index			
Underweight (<18.50 kg/m^2)	25 (8.3)	16 (16.2)	9 (4.4)
Normal (18.50-24.99 kg/m^2)	128 (42.4)	47 (47.5)	81 (39.9)
Overweight (25.00-29.99 kg/m^2)	102 (33.8)	25 (25.3)	77 (37.9)
Obesity (30.00-34.99 kg/m^2)	34 (11.3)	9 (9.1)	25 (12.3)
Morbid obesity (≥35.00 kg/m^2)	8 (2.6)	2 (2.0)	6 (3.0)
Missing weight and/or height	5 (1.7)	0 (0.0)	5 (2.5)
Diabetes mellitus	94 (31.1)	24 (24.2)	70 (34.5)
History of alcohol dependence/abuse	191 (63.2)	61 (61.6)	130 (64.0)
History of injection/non-injection drug use	246 (81.5)	81 (81.8)	165 (81.3)
Tobacco use			
Never	40 (13.2)	10 (10.1)	30 (14.8)
Ever†	262 (86.8)	89 (89.9)	173 (85.2)
Hepatitis C virus coinfection‡			
Detectable HCV RNA or genotype	250 (82.8)	79 (79.8)	171 (84.2)
HCV antibody+/HCV RNA-	5 (1.7)	1 (1.0)	4 (2.0)
HCV antibody-	39 (12.9)	15 (15.2)	24 (11.8)
Never tested	8 (2.6)	4 (4.0)	4 (2.0)
Hepatitis B virus coinfection§			
HBsAg+	57 (18.9)	17 (17.2)	40 (19.7)
HBsAg-	236 (78.1)	79 (79.8)	157 (77.3)
Never tested	9 (3.0)	3 (3.0)	6 (3.0)
Median HIV RNA (log_{10} copies/mL, IQR)	1.7 (1.7-2.6)	1.7 (1.7-2.6)	1.7 (1.7-2.7)
CD4 percentage			
Median (%, IQR)	26 (17-35)	26 (14-35)	26 (18-35)
≥28%	135 (44.7)	42 (42.4)	93 (45.8)
14-27.99%	120 (39.7)	35 (35.4)	85 (41.9)
<14%	47 (15.6)	22 (22.2)	25 (12.3)
CD4:CD8 ratio			
Median (IQR)	0.57 (0.31-0.93)	0.52 (0.26-0.98)	0.59 (0.33-0.91)
<1.0	239 (79.1)	77 (77.8)	162 (79.8)
Median alanine aminotransferase (U/L, IQR)	54 (36-79)	52 (35-74)	57 (36-79)
Not assessed within 360 days prior to HCC diagnosis	2 (0.7)	0 (0.0)	2 (1.0)
Median aspartate aminotransferase (U/L, IQR)	68 (44-101)	61 (38-95)	73 (47-104)
Not assessed within 360 days prior to HCC diagnosis	1 (0.3)	0 (0.0)	1 (0.5)
Platelet count <150,000 x 10^6/L	172 (57.0)	42 (42.4)	130 (64.0)

Characteristic*	Overall Incident HCC (n=302)	No Evidence of Cirrhosis (n=99)	Evidence of Cirrhosis (n=203)
FIB-4‖			
<1.45	27 (8.9)	18 (18.2)	9 (4.4)
1.45-3.25	99 (32.8)	39 (39.4)	60 (29.6)
>3.25	173 (57.3)	42 (42.4)	131 (64.5)
Insufficient data to calculate FIB-4	3 (1.0)	0 (0.0)	3 (1.5)
On antiretroviral therapy	229 (75.8)	77 (77.8)	152 (74.9)
Ever dideoxynucleoside analogue use¶	207 (68.5)	74 (74.7)	133 (65.5)

Abbreviations: HBsAg=hepatitis B surface antigen; HCC=hepatocellular carcinoma; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IQR=interquartile range; NRTI=nucleoside reverse transcriptase inhibitors; RNA=ribonucleic acid

* Results reported as n (%) unless otherwise specified.
† Ever tobacco use includes current and prior tobacco use.
‡ Hepatitis C virus coinfection defined as positive quantitative HCV RNA (absolute value determinable or not), positive qualitative HCV RNA, or quantifiable HCV genotype at baseline or during follow-up.
§ Hepatitis B virus coinfection defined as positive HBV surface antigen at baseline or during follow-up.
‖ FIB-4 was calculated using current age and most recent alanine aminotransferase, aspartate aminotransferase, and platelet count within 360 days prior to HCC diagnosis.
¶ Included didanosine, stavudine, zalcitabine, and zidovudine.

Table 3. Factors associated with incident hepatocellular carcinoma among HIV-infected patients in the Veterans Aging Cohort Study (October 1, 1999-September 30, 2015) without a baseline diagnosis of cirrhosis (n=34,886; 270 hepatocellular carcinoma events).

Characteristic	Unadjusted HR (95% CI)	Model #1* Adj. HR (95% CI)	Model #2† Adj. HR (95% CI)	Model #3‡ Adj. HR (95% CI)	Model #4§ Adj. HR (95% CI)
Age (per 10 years)	**1.33 (1.17-1.51)**	**1.48 (1.26-1.73)**	**1.44 (1.23-1.69)**	**1.45 (1.23-1.70)**	**1.44 (1.23-1.69)**
Male sex	2.30 (0.74-7.19)	1.38 (0.44-4.31)	1.37 (0.44-4.30)	1.37 (0.44-4.29)	1.37 (0.44-4.30)
Race					
White	Reference	Reference	Reference	Reference	Reference
Black	**1.50 (1.15-1.97)**	0.97 (0.73-1.28)	0.97 (0.74-1.29)	0.97 (0.74-1.29)	0.97 (0.74-1.29)
Hispanic	**1.77 (1.17-2.68)**	1.24 (0.82-1.89)	1.23 (0.81-1.87)	1.23 (0.81-1.88)	1.23 (0.81-1.87)
Other	1.40 (0.68-2.89)	1.72 (0.83-3.58)	1.72 (0.83-3.56)	1.71 (0.83-3.55)	1.72 (0.83-3.56)
Baseline body mass index					
Underweight (<18.50 kg/m^2)	0.63 (0.18-2.15)	0.59 (0.17-2.08)	0.59 (0.17-2.09)	0.59 (0.17-2.09)	0.59 (0.17-2.09)
Normal (18.50-24.99 kg/m^2)	Reference	Reference	Reference	Reference	Reference
Overweight (25.00-29.9 kg/m^2)	0.88 (0.67-1.17)	0.96 (0.72-1.27)	0.96 (0.72-1.27)	0.96 (0.72-1.27)	0.96 (0.72-1.27)
Obesity (30.00-34.9 kg/m^2)	0.92 (0.61-1.40)	1.01 (0.65-1.56)	1.01 (0.65-1.56)	1.01 (0.65-1.56)	1.01 (0.65-1.56)
Morbid obesity (≥35.00 kg/m^2)	0.84 (0.39-1.80)	0.98 (0.45-2.14)	0.98 (0.45-2.13)	0.98 (0.45-2.13)	0.98 (0.45-2.13)
Time-updated diabetes mellitus	**1.70 (1.32-2.20)**	**1.46 (1.12-1.91)**	**1.45 (1.11-1.90)**	**1.45 (1.11-1.90)**	**1.45 (1.11-1.90)**
Hepatitis B virus coinfection					
HBsAg-	Reference	Reference	Reference	Reference	Reference
HBsAg+	**3.65 (2.68-4.97)**	**3.92 (2.87-5.35)**	**3.91 (2.86-5.34)**	**3.91 (2.86-5.35)**	**3.91 (2.86-5.34)**
Never tested	1.01 (0.48-2.15)	1.12 (0.52-2.42)	1.13 (0.52-2.44)	1.13 (0.52-2.44)	1.13 (0.52-2.44)
Hepatitis C virus coinfection					
HCV antibody-	Reference	Reference	Reference	Reference	Reference
Detectable HCV RNA or genotype	**9.25 (6.53-13.11)**	**7.65 (5.35-10.94)**	**7.68 (5.36-10.98)**	**7.68 (5.37-11.00)**	**7.68 (5.36-10.98)**
HCV antibody+/HCV RNA-	**4.83 (1.90-12.28)**	**3.73 (1.46-9.52)**	**3.81 (1.49-9.72)**	**3.80 (1.49-9.71)**	**3.81 (1.49-9.72)**

Characteristic	Unadjusted HR (95% CI)	Model #1* Adj. HR (95% CI)	Model #2† Adj. HR (95% CI)	Model #3‡ Adj. HR (95% CI)	Model #4§ Adj. HR (95% CI)
Never tested	**4.85 (2.16-10.88)**	**4.64 (2.04-10.55)**	**4.68 (2.06-10.65)**	**4.68 (2.06-10.64)**	**4.68 (2.06-10.65)**
Time-updated CD4+ cell percentage	Reference	Reference	Reference	Reference	Reference
≥28%	1.05 (0.81-1.37)	0.86 (0.66-1.12)	0.89 (0.68-1.16)	0.88 (0.68-1.16)	0.89 (0.68-1.16)
14%-27.99%	**1.52 (1.08-2.14)**	0.97 (0.66-1.43)	1.12 (0.78-1.62)	1.09 (0.75-1.59)	1.12 (0.78-1.62)
<14%					
History of alcohol abuse	**2.38 (1.85-3.05)**	**1.45 (1.11-1.89)**	**1.46 (1.12-1.90)**	**1.46 (1.12-1.90)**	**1.46 (1.12-1.90)**
Tobacco use					
Never	Reference	Reference	Reference	Reference	Reference
Ever‖	**2.58 (1.81-3.67)**	**1.65 (1.14-2.38)**	**1.66 (1.15-2.39)**	**1.66 (1.15-2.40)**	**1.66 (1.15-2.39)**
Time-updated HIV RNA (per 1.0 log_{10} copies/mL)	**1.26 (1.14-1.39)**	**1.25 (1.12-1.40)**	-	-	-
Current HIV RNA ≥500 copies/mL	**1.58 (1.19-2.10)**	-	**1.46 (1.07-1.99)**	-	
Current HIV RNA categories					
<500 copies/mL	Reference			Reference	
500-9,999 copies/mL	1.41 (0.94-2.11)	-		1.31 (0.87-1.97)¶	-
10,000+ copies/mL	**1.73 (1.22-2.47)**	-	-		-
Consecutive months of HIV RNA ≥500 copies/mL			-	**1.63 (1.11-2.40)¶**	
HIV RNA always <500 copies/mL	Reference	-	-		Reference
1-11 months of HIV RNA ≥500 copies/mL	**1.63 (1.07-2.49)**	-	-		1.46 (0.94-2.26)
≥12 months of HIV RNA ≥500 copies/mL	**1.55 (1.10-2.18)**	-	-		**1.47 (1.02-2.11)**

522Abbreviations: CI=confidence interval; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human
523immunodeficiency virus; HR=hazard ratio; RNA=ribonucleic acid
524* Model #1 includes continuous values of HIV RNA as log_{10} copies/mL
525† Model #2 includes current HIV RNA ≥500 copies/mL
526‡ Model #3 includes current categories of HIV RNA ≥500 copies/mL
527§ Model #4 includes consecutive months of HIV RNA ≥500 copies/mL
528‖ Ever tobacco use includes current and prior tobacco use
529¶ p for trend=0.01.