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

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Background

- Hepatocellular carcinoma (HCC) is a growing cause of cancer death among people living with HIV (PLWH)
- PLWH have a fourfold higher risk of HCC than uninfected persons
- It remains unclear if HIV-related factors contribute to development of HCC

Specific Aim

- Evaluate impact of HIV-related and traditional factors on risk of HCC in PLWH, accounting for baseline cirrhosis status.

Methods

- **Study Design/Patients**:
  - Retrospective cohort study of 35,659 U.S. Veterans with HIV in the Veterans Aging Cohort Study between 1999-2015
    - Inclusion: HIV RNA, CD4+, CD8+ with ≥180 days follow-up
    - Exclusion: patients with HCC prior to start of follow-up.
- **Outcome**:
  - Incident HCC defined by VA Cancer Registry and ICD-9 codes
- **Data Collection/Definitions** :
  - Demographic, clinical, laboratory data from VA Electronic Health Record
  - Baseline defined by 180 days prior to start of follow-up
  - Cirrhosis defined by validated ICD-9 codes
- **Statistical Analysis**:
  - Evaluated characteristics at baseline, HCC diagnosis
  - Cox regression: Hazard ratios (HRs) of HCC by baseline cirrhosis
    - Lagged HIV RNA, CD4+ percentage by 180 days
    - Time-updated diabetes, HIV RNA, CD4+ percentage
  - Model #1: per 1.0 log10 copies/mL HIV RNA
  - Model #2: consecutive months of HIV viremia ≥500 copies/mL
  - Results stratified by baseline cirrhosis status, as cirrhosis is in the causal pathway (**Figure 1**)

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Figure 1. Pathway to Development of Hepatocellular Carcinoma

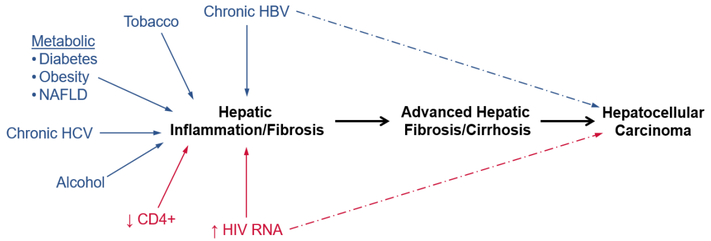

Table 1. Baseline Patient Characteristics

	Baseline no cirrhosis (n=34,886)	Baseline cirrhosis (n=773)
Median age (IQR), years	46 (39-53)	49 (44-55)
Male sex	97.6%	98.3%
Black race	48.0%	41.3%
BMI ≥30 kg/m²	14.6%	15.1%
Diabetes mellitus	9.0%	20.4%
Alcohol abuse/dependence	28.8%	61.3%
Tobacco abuse	69.2%	71.0%
HCV coinfection		
HCV RNA+	31.4%	58.5%
HCV antibody+/RNA-	2.9%	4.5%
HCV antibody-	60.9%	29.1%
Unknown	4.8%	7.9%
HBV surface antigen+	5.4%	14.0%
HIV RNA		
Median (IQR), log_{10} cells/mm³	3.2 (1.7-4.6)	3.0 (1.7-4.6)
≥500 copies/mL	56.7%	55.0%
CD4+ cell percentage		
Median (IQR)	22 (14-31)	22 (14-31)
<14%	23.9%	22.8%
Median baseline FIB-4	1.17 (0.81-1.74)	3.00 (1.58-5.82)

Abbreviations: BMI: body mass index; FIB-4: Fibrosis-4 Index; HBV: hepatitis B virus; HCV: hepatitis C virus; IQR: interquartile range; RNA: ribonucleic acid

Table 2. Factors Associated with Incident Hepatocellular Carcinoma, by Cirrhosis Status

	Baseline no cirrhosis		Baseline cirrhosis
	Model 1* Adjusted HR (95% CI)	Model 2* Adjusted HR (95% CI)	Model 3† Unadjusted HR (95% CI)
Age, per 10 years	1.48 (1.26-1.73)	1.44 (1.23-1.69)	1.10 (0.74-1.65)
Diabetes mellitus	1.46 (1.12-1.91)	1.45 (1.11-1.90)	0.71 (0.32-1.58)
Alcohol abuse/dependence	1.45 (1.11-1.89)	1.46 (1.12-1.90)	0.76 (0.38-1.54)
Tobacco abuse	1.65 (1.14-2.38)	1.66 (1.15-2.39)	2.08 (0.73-5.94)
HCV RNA+	7.65 (5.35-10.94)	7.68 (5.36-10.98)	9.01 (2.15-37.76)
HBV surface antigen+	3.92 (2.87-5.35)	3.91 (2.86-5.34)	1.95 (0.84-4.54)
HIV RNA per log_{10} copies/mL	1.25 (1.11-1.89)	--	1.21 (0.89-1.64)
HIV RNA			
1-11 months ≥500 copies/mL	--	1.46 (0.94-2.26)	1.52 (0.45-5.07)
12+ months ≥500 copies/mL		1.47 (1.02-2.11)	1.57 (0.59-4.14)
CD4+ <14%	0.97 (0.66-1.43)	1.12 (0.78-1.62)	0.24 (0.03-1.83)

*Models additionally adjusted for: sex, race/ethnicity, BMI. †Small sample size precluded multivariable adjustment. Abbreviation: CI: confidence interval; HBV: hepatitis B virus; HCV: hepatitis C virus; HR: hazard ratio; IQR: interquartile range; RNA: ribonucleic acid

Results

- 302 HCC diagnoses identified over 281,441 person-years (p-y) (IR: 107.3/100,000 p-y)
  - Among PLWH with HCC, 32.8% did not have cirrhosis at time of HCC diagnosis
- Determinants of HCC in PLWH without baseline cirrhosis, included higher and prolonged HIV viremia, HBV, HCV, older age, diabetes, alcohol or tobacco abuse
- Among PLWH with baseline cirrhosis, only HCV coinfection was associated with increased risk of HCC

Conclusion

- Higher HIV RNA and longer duration of HIV viremia, in addition to viral hepatitis coinfection, increase risk of HCC among PLWH without baseline cirrhosis
- HIV-related immunosuppression was not associated with increased risk of HCC
- Strongest evidence to date that HIV viremia contributes to risk of HCC