

SPECIFIC AIMS

Hepatocellular carcinoma (HCC), a devastating disease with few effective treatments, is increasingly common among those aging with HIV (HIV+).¹⁻⁴ For those without HIV (uninfected), HCC is a disease of aging (median, 64 years), occurring in the context of cumulative liver injury from multiple chronic conditions (multimorbidity).⁵⁻⁷ Among uninfected patients, multimorbidity associated with HCC includes chronic hepatitis B and C virus (HBV, HCV) infections,⁵⁻⁸ heavy alcohol use,⁹ obesity,¹⁰⁻¹³ and diabetes mellitus.^{14,15} Further, 90% of uninfected with HCC have advanced liver fibrosis/cirrhosis.^{5-7,16,17} Less is known about HCC among HIV+.¹⁻⁴ Compared with uninfected, HIV+ have a 2-4-fold increased risk of HCC,^{1,18} and HIV+/HCV+ coinfection doubles the risk of HCC over HCV+.^{2,18,19} However, many cases of HCC in HIV+ occur without HCV.²⁰⁻²⁵ The extent to which this represents silent HBV infection or less understood mechanisms of injury is unclear.⁵⁻⁷ Moreover, incident HCC is increasing at a higher rate in HIV+ than uninfected, particularly in those over 65 years of age.²⁶ Consequently, HCC mortality is expected to increase dramatically with time among HIV+ patients.²⁷

The Veterans Aging Cohort Study (VACS) is well characterized with national longitudinal access to electronic medical records (EMR).^{28,29} It includes 47,700 HIV+ patients demographically matched to 95,400 uninfected persons with 576 confirmed cases of HCC as of 2012 (270 in HIV+) and an additional 411 HCC cases (208 in HIV+) are expected to develop over our observation period.^{18,28-30} Of confirmed diagnoses, 60% are based on liver biopsy results in the Veterans Health Administration (VA). Among HIV+ with HCC in VACS, 58% are HCV+ (18% known HCV-), 27% are HBV+, 21% have a diagnosis of alcohol dependence, and 6% have diabetes.³⁰ FIB-4, a composite biomarker comprising age, liver aminotransferases, and platelet count is predictive of HCC in HIV+³⁰ and uninfected persons,³¹ and is associated with liver fibrosis and inflammation.³² Among HIV+ patients with HCC in VACS, 37% had no evidence of advanced hepatic fibrosis/cirrhosis.³⁰ Interestingly, 58% of HIV+/HCV- with HCC presented without cirrhosis.³⁰ In contrast, 33% of HCC cases among HIV+/HCV+ patients and 20% among HIV-/HCV+ patients occurred without cirrhosis.³⁰

Thus, early data suggests that, controlling for HCV, HIV alters the pathogenesis of HCC, including its association with liver fibrosis/cirrhosis. This intriguing finding may be due to a number of unexplored mechanisms that are asymmetric among HIV+ and uninfected. These include medication toxicity from hepatotoxic antiretroviral therapy (ART), general polypharmacy (which occurs 10 years earlier among HIV+ on ART³³⁻³⁵), prolonged immune activation in the context of immune dysfunction, and/or a differential response to obesity and diabetes.

Provocative Question 4 asks, "How do the biology of aging and HIV infection interact in the development of various cancers?" We propose to enhance 15 years of longitudinal, EMR data from the VACS by adding an additional 5 years of observation linked to HCC pathological specimen collection and blinded, standardized, readings by experienced pathologists to study the interplay between HIV and ART, polypharmacy, multimorbidity (in the setting of immune activation and dysfunction), and incident HCC, and, where possible, to contrast these effects in demographically similar uninfected individuals. Our Specific Aims are:

Aim 1: Determine if cumulative exposure to hepatotoxic antiretroviral drugs (ARVs) or polypharmacy differentially increase risk of HCC or alter HCC histology. Hypotheses:

- 1a. Among HIV+, hepatotoxic ARVs will increase the risk of HCC.
- 1b. Polypharmacy will increase HCC risk, but more so among HIV+ than uninfected.
- 1c. Among HIV+, HCC tumor and parenchymal histology will differ by exposure to hepatotoxic ARVs.
- 1d. Among HIV+ and uninfected, HCC tumor and parenchymal histology will differ by HIV status and exposure to polypharmacy.

Aim 2: Among HIV+ patients on ART, determine if cumulative exposure to immune activation and dysfunction and HIV-1 RNA increase risk of HCC after adjustment for known risk factors (HCV, HBV, alcohol, obesity, and diabetes) or alter HCC histology. Hypotheses:

- 2a. Cumulative exposure to low CD4 and low CD4/CD8 ratio will increase risk for HCC.
- 2b. Cumulative exposure to HIV-1 RNA will increase risk for HCC.
- 2c. HCC tumor and parenchymal histology will differ by level of CD4, CD4/CD8 ratio, and HIV-1 RNA.

Aim 3: Among HIV+ compared with uninfected, determine if obesity or diabetes have a differential association with risk of HCC (after controlling for known risk factors for HCC) or alter HCC histology.

Hypotheses:

- 3a. Obesity will be an independent risk factor for HCC among uninfected, but not among HIV+.
- 3b. Diabetes will be an independent risk factor for HCC among both HIV+ and uninfected.
- 3c. Among HCV+ without HBV or heavy alcohol use, HCC tumor histology will differ by HIV status and obesity.