ABSTRACT

Hepatocellular carcinoma (HCC), is increasingly common among those aging with HIV (HIV+). Compared with uninfected persons, HIV+ patients have a 4-fold increased risk of HCC. As HIV+ patients continue to age, HCC-related mortality is expected to increase over time.

Despite the increasing impact of HCC on mortality in HIV, the factors associated with the development of this malignancy in aging HIV+ patients remain unknown. Studies of HCC in HIV+ patients have been limited by small numbers of HCC cases, short follow-up, inclusion of demographically different uninfected comparators, lack of inclusion of traditional risk factors for HCC, and concerns about generalizability to HIV+ patients. This proposal will address these knowledge gaps and existing limitations by merging over 15 years of electronic medical record data from HIV+ and demographically similar uninfected patients in the Veterans Aging Cohort Study (VACS), the largest HIV cohort in North America, with HCC tissue specimens from these individuals.

HCC represents an ideal model with which to explore Provocative Question 4 of this RFA and gain generalizable insights into the “interplay between long-term HIV infection in the context of ART, general pathological processes of aging, and incident cancer. In this application, we will use the unique data of the VACS to conduct a series of epidemiologic and pathologic analyses to discover how factors specific to aging with HIV infection (e.g., immune deficiency/activation, chronic HIV-1 RNA exposure, hepatotoxic antiretrovirals) interact with conditions associated with liver injury in the general population (e.g., polypharmacy, obesity, diabetes, alcohol use, viral hepatitis) to promote development of HCC. We will characterize the extent to which associations with HCC are mediated exclusively through advanced fibrosis/cirrhosis or have direct associations with HCC. We will also determine important pathologic differences in HCC tumor and parenchymal tissue between HIV+ and uninfected patients with HCC.

Aim 1 will evaluate the risk of HCC associated with polypharmacy and current/cumulative use of antiretroviral drugs with known hepatotoxic potential among HIV+ patients on ART and determine how these alter HCC histology. Aim 2 will examine if cumulative exposure to immune deficiency, immune activation, and HIV viremia increase risk of HCC or alter HCC histology among HIV+ patients on ART, after accounting for traditional HCC risk factors (e.g., viral hepatitis, alcohol). Finally, in Aim 3, we will evaluate both HIV+ and uninfected persons to determine if obesity and diabetes mellitus, which can each promote hepatic steatosis, inflammation, and fibrosis, have a differential association with risk of HCC or alter HCC histology differently. The completion of these Aims will provide valuable information on how the biology of aging and HIV interact to promote HCC. These results will also inform future interventions to decrease the incidence of liver cancer.