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Role of Hepatitis C Coinfection in HIV Prognosis: Data from the HIV Atlanta VA Cohort Study (HAVACS)

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ABSTRACT

Title: Role of Hepatitis C Coinfection in HIV Prognosis: Data from the HIV Atlanta VA Cohort Study (HAVACS)

By Lauren Buehler, MD/MPH Candidate

Background: This study compared survival and progression to AIDS among patients coinfected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) to that of patients infected with HIV alone.

Methods: This analysis used data from the prospective HIV Atlanta Veterans Affairs Cohort Study (HAVACS), which includes HIV-positive patients who received care at the Infectious Disease Clinic at the Atlanta Veterans Affairs (VA) Medical Center between January 1997 to April 2014, (n= 3,236). Kaplan Meier curves and adjusted proportional hazard (PH) regression models compared survival of HCV/HIV coinfected and HIV monoinfected patients for the following time-to-event outcomes: 1) from HIV-diagnosis to death, 2) from HIV diagnosis to AIDS diagnosis, and 3) from AIDS diagnosis to death. The analysis for the first outcome was conducted separately for patients with low (< 200 cells/mm^3) and high CD4 count (≥200 cells/mm^3) due to a statistical interaction between CD4 count and HCV coinfection.

Results: A total of 3,236 patients from the HAVACS dataset were eligible for inclusion in this study, and HCV coinfection was present in 21% (n=693) of participants. Twenty-seven percent (n=890) of all study participants died during the follow-up period. Adjusted PH models showed HCV coinfection was not associated decreased survival among HIV patients with low CD4 count (hazard ratio [HR]=0.95, 95% confidence interval [CI]: 0.76-1.19); however, patients with HCV experienced shorter survival time after HIV diagnosis in the group with higher CD4 counts (HR=1.66, 95% CI: 1.27-2.17). HCV coinfection was also associated with higher rates of death among AIDS patients (HR=1.33; 95% 1.03-1.72). There was no significant difference in time between diagnoses of HIV and AIDS by HCV coinfection status (HR=0.87, 95% CI: 0.72-1.10).

Conclusion: HCV coinfection among HIV-positive individuals in the HAART era is associated with decreased length of survival after HIV diagnosis in patients with higher CD4 counts (≥200 cells/mm^3). HCV infection is also associated with shorter survival time after AIDS diagnosis. HCV infection does not appear to significantly impact the length of time between HIV diagnosis and progression to AIDS.

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CHAPTER I: LITERATURE REVIEW

Hepatitis C virus: Background Information

Hepatitis C virus (HCV) is an enveloped positive-stranded ribonucleic acid (RNA) flavivirus with six main genotypes.[1] HCV was first recognized in the 1970's as a clinical entity referred to as "non-A non-B hepatitis;"[2] however, the virus was not isolated and identified until 1989. Today, HCV infection affects an estimated 180 million people worldwide and is the leading cause for liver transplantation in North America and Western Europe.[3-5] According to the Centers for Disease Control and Prevention (CDC) estimates, there are over 3.2 million people living with chronic hepatitis C infection in the United States.[1] Annually there are over 17,000 new HCV cases and 15,000 deaths related to HCV in the United States alone.[1,3] There is currently no vaccine for the prevention of HCV infection.[1]

HCV infection can cause acute and chronic hepatic inflammation, cirrhosis, and hepatocellular carcinoma.[1] Only around 20-30% of patients infected with HCV develop an acute phase of hepatitis marked by fever, fatigue, jaundice, and abdominal pain. About 75-85% of infected patients go on to develop chronic hepatitis.[1,6] An estimated 15% to 30% of chronic hepatitis C patients later develop liver cirrhosis within 30 years after diagnosis, and 1-5% of those infected eventually die from resulting hepatocellular carcinoma or cirrhosis.[1,4,6]

Risk factors for HCV infection include intravenous drug use (IVDU), a high number of lifetime sexual partners, receipt of blood products prior to 1992, working in the healthcare field, chronic hemodialysis, and human immunodeficiency virus (HIV) infection. However, up to 30% of patients with chronic HCV report no history of exposure to an identifiable risk factor. HCV

infection can be acquired via IVDU, blood transfusions, hemodialysis, healthcare-associated needlesticks, vertical transmission (from mother to child), and sexual contact. IVDU is the leading cause of hepatitis C infection in the United States.[1,2,4] The prevalence of HCV among persons who have used IV drugs for greater than five years is estimated to be as high as 90%.[2,7] The importance of sexual contact as a route of transmission for HCV remains debatable; however, it is well known that HCV is not as readily transmitted during sex as HIV or hepatitis B virus.[2] Studies of monogamous HCV-discordant heterosexual couples show very low rates of transmission.[7,8] Within the last decade there have been several reported outbreaks of HCV infection among HIV-positive men who have sex with men (MSM), demonstrating that HCV can be effectively transmitted by sex in this sub-population.[8,9] Following the introduction of routine HCV screening of blood products in 1992, the chances of acquiring HCV through blood transfusion have decreased to 1-2 per million transfusions.[1]

Preliminary diagnosis of HCV infection is made based on elevation in liver transaminases and serological enzyme immunoassay (EIA) for anti-HCV antibodies. Confirmatory testing requires detection of HCV RNA present in the serum. For staging and prognostic purposes, the gold-standard is liver biopsy and histopathologic evaluation.[10] Newer, less invasive tests, including the aminotransferase:platelet ratio index (APRI) and biomarker assays are also used to estimate the extent of liver fibrosis in the presence of HCV infection.[4] Since 2012, the CDC has recommended a one-time screening for anti-HCV antibodies using EIA for all persons born between the years of 1945 and 1965. In addition,

the CDC recommends that all patients with known risk factors undergo periodic screening for HCV.[10]

Until recent advances, the treatment of choice for chronic hepatitis C infection was a combination of pegylated interferon, ribavirin, and protease inhibitors administered over a course of 24 to 48 weeks. This regimen resulted in sustained virologic response (SVR) in 50-80% of patients. SVR is defined as undetectable HCV RNA for greater than 24 weeks after completion of treatment.[1,4] In 2013, several new direct acting antiviral drugs were approved for the treatment of HCV infection. These drugs have a shorter duration of treatment (12-24 weeks), are associated with an improved side effect profile, and result in SVR in 80-95% of patients.[1]

Hepatitis C and Human Immunodeficiency Virus (HIV) Coinfection

HIV-positive patients are known to have a high rate of HCV coinfection. The estimated prevalence of HCV infection in HIV-positive patients in Western Europe and North America is 25-30% (compared to a prevalence of only 3-4% among the general population in these regions). Due to the high prevalence of HCV/HIV coinfection, the US Public Health Service (USPHS) and the Infectious Diseases Society of America (IDSA) Prevention of Opportunistic Infections Working Group recommend that all HIV-positive patients should undergo HCV screening with an anti-HCV antibody test upon entry into HIV care.[7,11]

The high prevalence of coinfection of HIV with HCV may have several explanations. First, it may be due to shared routes of viral transmission, as both viruses are efficiently transmitted through parenteral routes.[9,12-21] In the sub-

population of patients who acquired HIV through IVDU or blood transfusion, the proportion with HCV coinfection is as high as 75-80%.[9,12-15,17,19,22,23] A second explanation for the high rate of coinfection with HCV is a behavior called 'serosorting,' a term describing unprotected sex among HIV-positive MSM with the same HIV genotype. Serosorting results in the concentration of HCV infection among HIV-positive MSM, thus contributing to the prevalence of coinfection.[7] Third, HIV-positive patients are more likely to transmit HCV during sex compared to their HIV-negative counterparts. Patients with HIV have elevated HCV viral loads and lower rates of spontaneous viral clearance, both of which increase the likelihood of sexual transmission.[7] Furthermore, Briat et al. found that HIV/HCV coinfected men are more likely to shed HCV in their semen than HCV mono-infected men.[24] Recent data also show that re-infection with HCV after previous SVR is common among HIV-positive individuals who abuse IV drugs or who are MSM with multiple partners.[17,25]

Mortality in HCV/HIV Coinfected Population

Most studies conducted prior to the introduction of highly active antiretroviral therapy (HAART) in mid-1996 found no difference in HIV survival by HCV coinfection status.[6,21] For example, an observational study on over 1,800 HIV-positive veterans showed no impact of HCV infection on HIV disease progression or survival. In contrast, the majority of studies examining patients in the HAART era show that HCV coinfection is associated with decreased survival primarily due to an increase in the number of liver-related deaths in this population.[6,11,18,22,26-28] A large meta-analysis of 37 studies conducted in both the

pre-HAART and HAART eras showed that the risk ratio for all-cause mortality after the introduction of HAART was increased by 35% in coinfected individuals compared to HIV mono-infected patients.[21] In a separate analysis limited to patients with a diagnosis of acquired immunodeficiency syndrome (AIDS) in the HAART era, Branch et al. reported that HCV coinfection was associated with a 50% increased risk for death. Lastly, study of HIV-positive U.S. veterans after 1997 found that the presence of HCV coinfection was associated with a shorter survival both from the time of HIV diagnosis and from the time of AIDS diagnosis.[15]

There are several hypothesized reasons for the observed differences in survival among HCV/HIV coinfected individuals when comparing the pre- and post-HAART eras. First, the introduction of HAART therapy extended survival of HIV-positive patients and decreased the number of AIDS-related deaths.[11,18,26] The resulting increase in survival time after HIV diagnosis allowed for a greater likelihood of competing causes of death, such as HCV-induced liver disease.[12,21,29] Liver disease has become one of the most common causes of hospitalization and death among HIV-positive patients in the HAART era, and several studies show that HCV coinfected patients have a higher risk of liver-related death than HIV-monoinfected patients.[9,12,15,17,28,30] A large observational study found that 9% of deaths among HIV-positive patients are due to liver-related causes.[25,31] The high rate of liver-related causes of death in coinfected patients may be worsened by hepatotoxicity of HAART regimens.[7,32]

Aside from liver-related causes of death, the reason for the observed increase in all-cause mortality among HCV coinfected compared to HIV mono-infected

individuals is not completely understood. Some hypothesize that it may be due to potentiation of immune activation by HCV leading to chronic inflammation.[27] Others suggest that HCV causes direct damage to T-lymphocytes, as it is known to undergo viral replication within lymphatic tissue and bone marrow of HIV-positive patients.[20] Studies have also shown that HIV-positive individuals who are infected with HCV have a higher rate of certain extrahepatic comorbidities, such as type 2 diabetes, cardiovascular disease, hypertension, renal disease, psychiatric conditions, and dementia.[1,9,17,27,33,34] HCV may also increase the risk for lymphoma and other malignancies, as some evidence shows that HCV promotes lymphoproliferation in HIV-positive patients.[29] The HCV coinfected population is also more likely to experience socioeconomic problems such as substance abuse, unemployment, and homelessness, which can have negative effects on healthcare access, treatment compliance, and mortality.[9,17]

HIV accelerates HCV disease progression

Several studies have demonstrated that the presence of coinfection with HIV accelerates the progression of liver disease in HCV-infected patients compared to those who are infected with HCV alone.[7,9,12,14,16,18-20,25,35-37] Coinfected patients have an increased HCV viral load, higher rates of acute hepatic decompensation, lower likelihood of spontaneous viral clearance, and faster progression to liver fibrosis, end-stage liver disease, and hepatocellular carcinoma.[7,11,14,19,20,23] It is hypothesized that the acceleration in HCV disease progression is due to HIV-related T-lymphocyte dysfunction, direct damage by HIV to hepatocytes,

hepatotoxicity of HAART therapy, and lack of treatment with anti-HCV drugs.[9,12,15]

Although combination therapy for the treatment of HCV in HIV/HCV coinfected patients has been approved by US Food and Drug Administration (FDA) since 2005, studies show that HIV-positive patients with HCV are less likely to receive and respond to treatment for their hepatitis C infection[9,11,19]. A large number of coinfected patients are ineligible for treatment with ribavirin and pegylated interferon due to social and/or psychiatric conditions that affect access and compliance, such as substance abuse, homelessness, and incarceration.[9] However, data show that even among eligible patients, only about 10% to 20% receive treatment for HCV.[11] When coinfected patients do receive treatment for HCV, they are less likely to achieve a sustained virologic response (SVR) and are more likely to experience significant side effects than HCV mono-infected patients.[19] Coinfected patients are also more likely to have extra-hepatic comorbidities and potential drug-drug interactions that complicate treatment for HCV.[9] A combination of these factors results in fewer coinfected individuals being effectively treated for HCV compared to HCV mono-infected patients, which likely contributes to the acceleration of HCV-related disease progression in these patients.

Effect of HCV coinfection on HIV disease progression

Although it is well known that the presence of HIV accelerates disease progression in HCV-infected individuals, there is conflicting evidence as to whether HCV affects the progression of HIV infection.[15,19,21,29] Several studies

have shown that the time from diagnosis of HIV to diagnosis of AIDS is shorter in HCV coinfected individuals and that the risk of developing AIDS is several-fold higher among coinfected patients.[15,29] Other studies have shown that there is a higher risk for bacterial and mycotic AIDS-defining illnesses (ADIs) and HIV-related diseases, such as wasting syndrome and HIV-dementia among HCV coinfected patients.[29] In contrast, a large meta-analysis by Chen et al. showed no association between HCV coinfection and risk for ADIs or acceleration of HIV disease progression.[21]

Several researchers have hypothesized that HCV infection may accelerate HIV disease progression due to its effect on immune cell function. Some studies indicate that HCV impairs dendritic cell and CD4 T-lymphocyte function and that this effect may be more prominent in patients with HIV.[17,29] Another explanation is that HCV may alter CD4 recovery in response to HAART; however, this point is also controversial. There is some evidence that HCV blunts CD4 response to antiretrovirals, while others show no such effect.[15,17,20,29] Lastly, a study on a large dataset of veterans with HIV showed that HCV coinfected individuals are also less likely to receive HAART therapy, which may result in faster progression to AIDS or death in this group.[15] Further investigation is needed to clarify the effect of HCV coinfection on HIV disease progression and response to antiretroviral therapy.

CHAPTER II: MANUSCRIPT

INTRODUCTION

Hepatitis C (HCV) coinfection is common among individuals infected with human immunodeficiency virus (HIV). The Centers for Disease Control and Prevention (CDC) estimates that the prevalence of HCV infection among HIV-positive patients is 25-30% compared to only 3-4% in the general population.[1,3] High rates of coinfection are thought to be attributable to shared means of viral transmission, including parenteral and sexual routes. [9,12-21] Among patients who acquired HIV through intravenous drug use (IVDU) or transfusion of contaminated blood products, the prevalence of HCV coinfection is 75-80%.[9,12-15,17,19,22,23]

The clinical impact of HCV coinfection on HIV-positive patients has been studied in a variety of patient populations. The majority of studies using data collected after the introduction of highly active antiretroviral therapy (HAART) in 1996 show that HIV/HCV coinfected individuals have higher all-cause mortality rates than those infected with HIV alone.[6,11,18,22,26-28] Notably, liver disease is one of the most common causes of hospitalization and death among HIV-positive patients in the HAART era.[20,27,38] One large observational study estimated that 9% of deaths among HIV-positive patients are due to liver-related causes.[25,31]

Although liver disease is an important cause of death among HCV/HIV coinfected individuals, it does not completely explain the observed increase in all-cause mortality in this population. Some hypothesize that HCV increases mortality by promoting chronic inflammation and by compromising immune cell function in HIV-positive patients. Studies have also shown that HIV-positive

individuals who are infected with HCV have a higher rate of certain extrahepatic comorbidities and socioeconomic problems that may contribute to higher mortality in this population.[1,9,17,27,33,34]

Although it is well known that the presence of HIV accelerates the progression of HCV-related liver disease, there is conflicting evidence as to whether HCV infection affects the progression of HIV to AIDS.[15,19,21,29] Several observational studies have shown that HCV coinfected individuals have a higher prevalence of opportunistic infections (OIs) and experience a more rapid progression to AIDS from the time of HIV diagnosis.[15,29] In contrast, a large meta-analysis by Chen et al. showed no association between HCV coinfection and risk for OIs or rate of progression to AIDS.[21]

The present analysis is an extension of two prior reports that were based on the HIV Atlanta VA Cohort Study (HAVACS), a computerized dataset of prospectively gathered information on HIV-positive patients who received care at the Infectious Disease Clinic at the Atlanta Veterans Affairs (VA) Medical Center between January 1982 and April 2014.[6,15] The first study, conducted in the pre-HAART era, showed no increase in mortality among HCV coinfected patients when compared to those who were infected with HIV alone, which is consistent with other studies from this period.[6] The second study analyzed data collected after the introduction of HAART and found that HCV coinfection status was associated with decreased intervals from time of HIV and AIDS diagnoses to death.[15]

The primary aim of the present study is to evaluate the effect of HCV coinfection \ on all-cause mortality and HIV progression to AIDS among patients

in the HAVACS cohort with the addition of new data collected since 2001. This study also expands on prior HAVACS analyses through the application of new modeling strategies such as formal assessment of statistical interaction among covariates, and re-evaluation of the proportional hazards regression (PHR) model assumptions in view of the extended follow up.

METHODS

Study Population and Variables

The HAVACS data used in the present analysis covered the interval from January 1997 through April 2014. Patients who were seen prior to 1997 were excluded to limit the analysis to the post-HAART period. After exclusions, 3,236 patients remained in the analysis. The primary study outcomes were all-cause mortality and AIDS diagnosis. The independent variable of interest was coinfection with HCV. Covariates that were assessed as potential confounding factors or effect modifiers included age at diagnoses of HIV and AIDS (categorized as older vs. younger than age 40 at time of diagnosis), race, history of ARV use, history of infection with hepatitis B (HBV) virus, CD4 cell count at time of HCV testing, and primary risk factor for acquisition of HIV.

HIV status was determined using serological enzyme immunoassay (EIA) and was confirmed by Western blot testing. Presence of HCV infection was established using EIA for anti-HCV antibodies. A small number of patients who were diagnosed with acute HCV, but who never developed chronic HCV, were not included in the coinfected group. History of HBV infection was determined by serologic testing for HBV surface antigen and anti-HBV core antibodies. With

respect to race, participants were categorized as: White (including Hispanic Whites) or Other (including Blacks, Hispanic Blacks, and Asians). Patients' primary risk factors for HIV acquisition were assigned into one of three groups: history of IVDU, MSM, and other/unknown. The latter category included persons with risk factors other than IVDU or MSM (e. g., work in healthcare or history of blood transfusion), patients with no identifiable risk factors, and those whose risk factor status was unknown. Risk factors for HIV were self-reported by patients. Date of AIDS diagnosis was defined as the day on which the patient met either the 1987 or the 1993 CDC definition of AIDS.[39] CD4 count was measured at the time of HCV testing and was divided into two categories (<200 cells/mm^3 and ≥200 cells/mm^3).

Statistical Analyses

Descriptive statistics were used to examine baseline demographic and clinical characteristics of the study population. Analyses of variance (ANOVA) and chi-square tests were used to compare the distribution of continuous and categorical variables, respectively, among patients with and without HCV coinfection. Kaplan Meier curves and adjusted proportional hazard (PH) regression models were used to compare survival of HCV/HIV coinfected and HIV monoinfected patients for the following time-to-event outcomes: 1) from HIV-diagnosis to death, 2) from HIV diagnosis to AIDS diagnosis, and 3) from AIDS diagnosis to death. Observations were censored at the date of last follow up at the Atlanta VA Medical Center or on April 1, 2014, whichever occurred first. For all three multivariate models, PH assumptions were tested by inspecting the

log-log curves. For co-variates that did not satisfy PH assumptions, stratified analyses were performed, and no hazard ratios were generated. Kaplan-Meier curves were accompanied by log-rank tests. The results of survival analyses were expressed as hazard ratios (HR) and the corresponding 95% confidence intervals (CI). All models were assessed for interactions. In the presence of interaction, separate stratum specific analyses were performed to more fully assess effect modification. Two sided p-values of <0.05 were considered statistically significant. All analyses were performed using Statistical Analysis Software (SAS) version 9.3.

RESULTS

Cohort Characteristics

A total of 3,236 patients from the HAVACS dataset were eligible for inclusion in this study. HCV coinfection was present in 21% (n=693) of the total study participants. The mean age of participants at the time of HIV diagnosis was 37.3 years with a standard deviation (SD) of 11.0 years. The cohort was predominantly male (98%), and over three-quarters of participants (77%) were African Americans. Over a quarter of patients in the cohort (n=844) received a diagnosis of AIDS before the end of the follow-up period. Greater than 90% (n=2,922) of patients reported a history of antiretroviral use in the past. The most common risk factor for HIV was a history of male-to-male sexual contact, which was reported in 50% of patients. Twenty-seven percent (n=890) of all study participants died during the follow-up period (Table 1). Nearly a third of

patients died from AIDS-related causes (25%, n=251), and 7% (n=63) died from liver-related causes (Figure 1).

Bivariate analyses

Compared to the HIV monoinfected group, HCV coinfected patients were older at the time of HIV diagnosis (mean age: 40 vs. 37 years, $p<0.001$) and were more likely to be African American (85% vs. 25%, $p<0.001$). A history of AIDS diagnosis was more common in the HCV coinfected sub-cohort (29% vs. 25%, $p=0.03$). The most common primary risk factor for HIV among HCV-positive patients was a history of IVDU, while MSM was the most common reported risk factor among HIV monoinfected patients ($p<0.001$). Prevalence of past ARV use did not differ significantly by HCV coinfection status ($p=0.233$). A greater percentage of HCV-positive patients relative to HCV-negative patients (45% vs. 23%, $p<0.001$) died during the follow up period (Table 1).

Survival Analyses

For the first survival analysis (assessing time from HIV diagnosis to death), a significant interaction was observed between HCV coinfection status and CD4 count at the time of testing for HCV. To address this issue, the cohort was divided into two groups: patients with AIDS-defining CD4 counts (< 200 cells/mm^3) and patients with higher CD4 counts (≥200 cells/mm^3). Separate KM curves and hazards ratios were generated for each group. Among patients with low CD4 counts (Figure 2a), the presence of HCV coinfection was not significantly associated with survival from time of HIV diagnosis (log-rank p-

value = 0.122). In contrast, among patients with a CD4 count ≥200 cells/mm^3 (Figure 2b) HCV coinfected participants had lower survival after HIV diagnosis ($p<0.001$). The corresponding multivariable PHR models (Table 2) showed that HCV coinfection was not associated decreased survival among patients with low CD4 count (HR=0.95, 95% CI: 0.76-1.19); however, patients with HCV experienced shorter survival time after HIV diagnosis in the group with higher CD4 counts (HR=1.66, 95% CI: 1.27-2.17).

In the analyses assessing survival following AIDS diagnosis, presence of HCV infection was associated with higher mortality (log-rank p-value <0.001), as evidenced in the KM curves (Figure 3). In the PHR models adjusting for additional covariates (Table 3), the HR estimate reflecting the association between HCV and post-AIDS survival was 1.33 (95% CI: 1.03-1.72). Other factors independently and significantly associated with survival in this model, included ARV use (HR=0.29), history of IVDU as primary risk factor (HR=1.41), and CD4 count ≥200 cells/mm^3 (HR=0.034) at time of HCV testing.

KM curves for the interval between HIV and AIDS diagnoses (Figure 4) showed no difference between HCV infected and non-infected cohorts members (log-rank p-value =0.397). As shown in Table 4, the result remained statistically non-significant after adjusting for covariates (HR=0.87, 95% CI=0.72-1.10). It is important to note that this third model was limited because there were multiple covariates that failed to meet the PH assumptions. A stratified analysis was performed for each of these variables, which included history of ARV treatment, history of hepatitis B infection, and primary risk factor for HIV, and no hazards ratios were generated. The only other variable that was significantly associated

with transition from HIV to AIDS was CD4 count. Using 200 cells/mm^3 as the cutoff, those with high CD4 count at the time of HIV diagnosis had a roughly 86% lower incidence rate of AIDS (HR=0.14, 95% CI=0.11-0.17) than those with lower CD4 concentrations.

DISCUSSION

The aim of the present study was to evaluate the role of HCV coinfection in all-cause mortality and progression to AIDS among HIV-positive veterans in the post-HAART era. We found that HCV coinfection was not associated with survival after HIV diagnosis among patients with low CD4 cell count (< 200 cells/mm^3). In contrast, in patients with higher CD4 counts (≥200 cells/mm^3), HCV infection was associated with decreased survival after HIV diagnosis. We also analyzed survival after AIDS diagnosis and found that patients who were infected with HCV and those with lower CD4 counts had a shorter length of survival compared to HIV monoinfected patients and subjects with higher CD4 concentrations. Lastly, our results showed while HCV infection was not significantly associated with progression from HIV diagnosis to AIDS, CD4 count remained an important predictor of this outcome.

Our findings regarding survival following HIV and AIDS diagnoses reaffirm those of the 2004 HAVACS publication, which conducted a similar analysis using data collected between 1997 and 2001.[15] The 2004 HAVACS study found that HCV coinfection was associated with decreased length of survival after both HIV diagnosis (HR= 2.47; 95% CI: 1.26–4.82) and AIDS diagnosis (HR 1.84; 95% CI: 1.09–3.10). This study found no difference in length of time from

HIV to AIDS diagnoses between HCV coinfected patients compared to HIV monoinfected patients. In comparison, the first HAVACS report, which analyzed data collected in the pre-HAART between 1992-1997,[6] showed no effect of HCV coinfection on survival from time of HIV (HR=1.11) and AIDS diagnoses (HR=1.07) to death and no difference in length of time to AIDS progression (HR=0.98).

The trends in mortality among HCV/HIV coinfected patients in the HAVACS cohort are in agreement with similar findings from other study populations. Evidence from previous studies conducted in the pre-HAART era shows no impact of HCV coinfection on mortality or progression to AIDS, while data collected and analyzed following introduction of the HAART indicate that HCV infection is associated with decreased survival among HIV-positive patients.[6,11,18,22,26-28] A meta-analysis of 27 studies from the pre- and post-HAART eras reported that HCV coinfection was associated with lower mortality among HIV-positive patients (odds ratio [OR]=0.68, 95% CI=0.53–0.87) in the pre-HAART era, but the association changed direction (OR=1.35, 95% CI= 1.11–1.63) in the post-HAART era.[21]

There are several hypothesized reasons for the observed differences in survival of HCV/HIV coinfected patients when comparing the pre- and post-HAART eras. First, after the introduction of HAART in 1996, HIV-positive patients experienced longer survival times after HIV diagnosis and fewer AIDS-related deaths. Among HCV coinfected patients, longer lifespans following HIV diagnosis allowed for greater chance of developing liver disease related to their HCV, which has become one of the most common causes of hospitalization and

death among coinfected patients in the HAART era.[9,11,12,18,21,25,26,29,31] Studies have also shown that HIV-positive individuals who are infected with hepatitis C have a higher prevalence of extrahepatic comorbidities, such as type 2 diabetes, cardiovascular disease, hypertension, renal disease, psychiatric conditions, dementia, lymphoma, and other malignancies that may contribute to decreased survival in this group.[1,9,17,27,33,3429] HCV coinfected patients have also been shown to be affected by substance abuse, unemployment, and homelessness, all of which can impact healthcare access, treatment compliance, and mortality.[9,17]

The literature is less consistent in determining the effect of HCV coinfection on HIV progression to AIDS in the HAART era. [15,19,21,29] Several prior survival analyses have shown that time from diagnosis of HIV to diagnosis of AIDS is shorter in HCV coinfected individuals. [15,29] Other studies have shown that there is a higher risk for bacterial and mycotic AIDS-defining illnesses (ADIs) and HIV-related diseases, such as wasting syndrome and HIV-dementia among coinfected patients.[29] In contrast, a large meta-analysis by Chen et al. showed no association between HCV coinfection and risk for ADIs or acceleration of HIV disease progression.[21]

There are several limitations to this study. First, the generalizability of our findings may be limited given the demographics of the study population (the participants included in the HAVACS cohort are 97.3% percent male and 76.8% African American). Also, we used multivariate analyses which controlled for several potentially confounding variables; however, there are likely other unknown or unmeasured covariates (e.g., HCV genotype, aminotransferase levels) which were not included that may have affected our results. Lastly, risk

factors for HIV acquisition (i.e., IVDU, MSM) were self-reported, and may be inaccurate.

Despite the aforementioned limitations, this study has several notable strengths, including a large number of study participants (n=3,326) and a long period of follow-up (>16 years). Also, loss to follow up was minimal because veterans receive free care within the VA medical system and therefore are not likely to leave this system to seek care elsewhere. Under the current V.A. family benefit structure, patients' families have a financial incentive to report a patients' death to the V.A. health system; therefore, lack of data on date and cause of death is minimal in this population.

The analysis is notable for systematic and formal assessment of PH assumptions and interactions. This feature identified a number of issues that were considered in the analyses and affected the results and conclusions. Lack of testing for assumptions and interactions in survival analyses is a well-documented shortcoming of many clinical studies. For example, Tetrault et al., reported that only 45% of studies in the medical literature performed testing for interactions, and only 21% of survival analyses assessed PH assumptions.

CONCLUSION

Hepatitis C coinfection among HIV positive individuals in the HAART era is associated with decreased length of survival after HIV diagnosis in patients with higher CD4 counts (≥200 cells/mm^3). Coinfection is also associated with increased mortality after AIDS diagnosis among all patients. However, HCV infection does not appear to significantly impact the length of time between HIV

diagnosis and progression to AIDS. Additional research is warranted to further evaluate the physiologic and/or socioeconomic mechanisms by which HCV impacts survival in HIV-positive patients. Future studies also need to explore the time-dependent effects of variables that did not meet the PH assumptions.

REFERENCES:

1. Hepatitis C FAQs for Health Professionals. . July 17, 2014 2014 (accessed August 20 2014).
2. Alter MJ. HCV routes of transmission: what goes around comes around. *Semin Liver Dis* 2011; **31**(4): 340-6.
3. Ly KN XJ, Klevens RM, Jiles RB, Ward JW, Holmberg SD. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. *Ann Intern Med* 2012; **156**(4): 271-8.
4. HR R. Chronic hepatitis C infection. *N Engl J Med* 2011; **364**(25): 2429-38.
5. Norton BL PL, McGrath LJ, Proeschold Bell RJ, Muir AJ, Naggie S. Health care utilization in HIV-infected patients: assessing the burden of hepatitis C virus coinfection. *AIDS Patient Care STD* 2012; **26**(9): 541-5.
6. C. T. Staples J, D. Rimland, and D. Dudas. Hepatitis C in the HIV (Human Immunodeficiency Virus) Atlanta V.A. (Veterans Affairs Medical Center) Cohort Study (HAVACS): The Effect of Coinfection on Survival. *Clin Infect Dis* 1999 **29**(1): 150-4.
7. Taylor LE ST, Mayer KH. HIV coinfection with hepatitis C virus: evolving epidemiology and treatment paradigms. *Clin Infect Dis* 2012; **55**(Suppl 1): S33-42.
8. Urbanus AT vdLT, Stolte IG, Schinkel J, Heijman T, Coutinho RA, Prins M. Hepatitis C virus infections among HIV-infected men who have sex with men: an expanding epidemic. *AIDS* 2009; **23**(12): F1-7.
9. Soriano V VE, Fernandez-Montero JV, Labarga P, Barreiro P. Update on HIV/HCV coinfection. *Curr HIV/AIDS Rep* 2013; **10**(3): 226-34.
10. Mukherjee R, Burns A, Rodden D, et al. Diagnosis and Management of Hepatitis C Virus Infection. *Journal of laboratory automation* 2015.
11. Vellozzi C, Buchacz K, Baker R, et al. Treatment of hepatitis C virus (HCV) infection in patients coinfected with HIV in the HIV Outpatient Study (HOPS), 1999-2007. *J Viral Hepat* 2011; **18**(5): 316-24.
12. van der Helm J GR, Sabin C, Meyer L, Del Amo J, Chêne G, Dorrucci M,, Muga R PK, Prins M; CASCADE Collaboration in EuroCoord. Effect of HCV infection on cause-specific mortality after HIV seroconversion, before and after. *Gastroenterology* 2013; **144**(4): 751-60.
13. Linas BP WB, Smurzynski M, Losina E, Bosch RJ, Schackman BR, Rong J, Sax , PE WR, Schouten J, Freedberg KA. The impact of HIV/HCV co-infection on health care utilization and disability: results of the ACTG Longitudinal Linked Randomized Trials (ALLRT) Cohort. *J Viral Hepat* 2011; **18**(7): 506-12.
14. Ambrosioni J, Negro F, Calmy A. [The challenges of HIV-HCV co-infection]. *Rev Med Suisse* 2012; **8**(338): 905-10.
15. Anderson KB, Guest JL, Rimland D. Hepatitis C virus coinfection increases mortality in HIV-infected patients in the highly active antiretroviral therapy era: data from the HIV Atlanta VA Cohort Study. *Clin Infect Dis* 2004; **39**(10): 1507-13.
16. Limketkai BN MS, Sutcliffe CG, Higgins YM, Torbenson MS, Brinkley SC,, Moore RD TD, Sulkowski MS. Relationship of liver disease stage and antiviral

therapy with liver-related events and death in adults coinfected with HIV/HCV. *JAMA* 2012; **308**(4): 370-8.
17. Branch AD VNM, Vachon ML, Dieterich DT, Meinert CL, Jabs DA. Studies of the Ocular Complications of AIDS Research Group. Mortality in hepatitis C virus-infected patients with a diagnosis of AIDS in the era of combination antiretroviral therapy. *Clin Infect Dis* 2012; **55**(1): 137-44.
18. Hernando V P-CS, Lewden C, Gonzalez J, Segura F, Oteo JA, Rubio, R DD, Moreno S, Amo JD. All-cause and liver-related mortality in HIV positive subjects compared to the general population: differences by HCV co-infection. *J Hepatol* 2012; **57**(4): 743-51.
19. Bakaj G VT, Prabhukhot R, Siraj D. Evaluation and treatment of hepatitis C in patients with human immunodeficiency virus. *South Med J* 2012; **105**(10): 500-3.
20. Greub G, Ledergerber B, Battegay M, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. *Lancet* 2000; **356**(9244): 1800-5.
21. Chen TY, Ding EL, Seage Iii GR, Kim AY. Meta-analysis: increased mortality associated with hepatitis C in HIV-infected persons is unrelated to HIV disease progression. *Clin Infect Dis* 2009; **49**(10): 1605-15.
22. Martín-Carbonero L S-SM, García-Samaniego J, Núñez MJ, Valencia ME, González-Lahoz J, Soriano V. Reduction in liver-related hospital admissions and deaths in HIV-infected patients since the year 2002. *J Viral Hepat* 2006; **13**(12): 851-7.
23. Lo Re V, 3rd, Kallan MJ, Tate JP, et al. Hepatic decompensation in antiretroviral-treated patients co-infected with HIV and hepatitis C virus compared with hepatitis C virus-monoinfected patients: a cohort study. *Ann Intern Med* 2014; **160**(6): 369-79.
24. Briat A, Dulioust E, Galimand J, et al. Hepatitis C virus in the semen of men coinfected with HIV-1: prevalence and origin. *AIDS* 2005; **19**(16): 1827-35.
25. Garcia-Samaniego J, Rodriguez M, Berenguer J, et al. Hepatocellular carcinoma in HIV-infected patients with chronic hepatitis C. *Am J Gastroenterol* 2001; **96**(1): 179-83.
26. Rosenthal E S-CD, Lewden C, Bouteloup V, Pialoux G, Bonnet F,, Karmochkine M MT, François M, Burty C, Jougla E, Costagliola D, Morlat P,, Chêne G CP. Liver-related deaths in HIV-infected patients between 1995 and 2005 in the French GERMIVIC Joint Study Group Network (Mortavic 2005 Study in collaboration with the Mortalite´ 2005 survey, ANRS EN19)*. *HIV Med* 2009; **10**(5): 282-9.
27. Fuster D1 CD, Quinn EK, Nunes D, Saitz R, Samet JH, Tsui JI. Chronic hepatitis C virus infection is associated with all-cause and liver-related mortality in a cohort of HIV-infected patients with alcohol problems. *Addiction* 2014; **109**(1): 62-70.
28. McDonald SA, Hutchinson SJ, Bird SM, et al. A population-based record linkage study of mortality in hepatitis C-diagnosed persons with or without HIV coinfection in Scotland. *Stat Methods Med Res* 2009; **18**(3): 271-83.

29. d'Arminio Monforte A, Cozzi-Lepri A, Castagna A, et al. Risk of developing specific AIDS-defining illnesses in patients coinfected with HIV and hepatitis C virus with or without liver cirrhosis. *Clin Infect Dis* 2009; **49**(4): 612-22.
30. Rockstroh JK, Peters L, Grint D, et al. Does hepatitis C viremia or genotype predict the risk of mortality in individuals co-infected with HIV? *J Hepatol* 2013; **59**(2): 213-20.
31. Puoti M, Moioli MC, Travi G, Rossotti R. The burden of liver disease in human immunodeficiency virus-infected patients. *Semin Liver Dis* 2012; **32**(2): 103-13.
32. Sulkowski MS, Thomas DL, Mehta SH, Chaisson RE, Moore RD. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology* 2002; **35**(1): 182-9.
33. R Bedimo AOW, M Mugavero, H Drechsler, N Khanna, and M Saag. Hepatitis C virus coinfection and the risk of cardiovascular disease among HIV-infected patients. *HIV Medicine* 2010; **11**: 462–8.
34. Fischer MJ, Wyatt CM, Gordon K, et al. Hepatitis C and the risk of kidney disease and mortality in veterans with HIV. *J Acquir Immune Defic Syndr* 2010; **53**(2): 222-6.
35. Bonacini M, Puoti M. Hepatitis C in patients with human immunodeficiency virus infection: diagnosis, natural history, meta-analysis of sexual and vertical transmission, and therapeutic issues. *Arch Intern Med* 2000; **160**(22): 3365-73.
36. Di Martino V, Rufat P, Boyer N, et al. The influence of human immunodeficiency virus coinfection on chronic hepatitis C in injection drug users: a long-term retrospective cohort study. *Hepatology* 2001; **34**(6): 1193-9.
37. Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis* 2001; **33**(4): 562-9.
39. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. Council of State and Territorial Epidemiologists; AIDS Program, Center for Infectious Diseases. *MMWR Morbidity and mortality weekly report* 1987; **36 Suppl 1**: 1s-15s.

TABLES AND FIGURES

TABLE 1: Characteristics of study population and relationship of covariates to HCV infection status				
	All Patients	**HCV Negative**	**HCV Positive**	**P-value**
	(n=3236)	**(n=2543)**	**(n=693)**	
Age at HIV diagnosis (mean ± STD), years	37.3 ± 11.0	36.5 ± 11.2	40.4 ± 9.6	<0.001
Age at AIDS Diagnosis (mean ± STD), years	42.5 ± 10.3	41.5 ± 10.6	45.3 ± 8.7	<0.001
Sex, n (%)				
Male	3146 (97.3)	2464 (96.9)	682 (98.4)	0.035
Female	89 (2.8)	78 (3.1)	11 (1.6)	
Race, n (%)				<0.001
Black	2469 (76.8)	630 (25.0)	588 (85.0)	
White	731 (22.7)	1881 (74.5)	101 (14.6)	
Other	15 (0.5)	12 (0.5)	3 (0.4)	
AIDS diagnosis, n (%)	844 (26.1)	641 (25.2)	203 (29.3)	0.030
CD4 Count at HCV testing (cells/mm^3), n (%)				<0.001
<200	806 (25.6)	560 (23.1)	237 (34.6)	
≥200	2340 (74.4)	1892 (76.9)	448 (65.4)	
Primary Risk Factor Group, n (%)				<0.001
MSM	1613 (49.9)	1425 (56.0)	188 (27.1)	
Injection Drug User	507 (15.7)	149 (5.9)	358 (51.7)	
Other	211 (6.5)	186 (7.3)	25 (3.6)	
Unknown	905 (28.0)	783 (30.8)	122 (17.6)	
History of ARV use, n (%)	2922 (90.3)	2288 (90.0)	634 (91.5)	0.233
History of Hepatitis B Infection, n (%)	282 (8.7)	231 (9.1)	51 (7.4)	0.154
Patient Outcome, n (%)				<0.001
Survival	1572 (48.6)	1326 (52.1)	246 (35.5)	
Death	890 (27.5)	577 (22.7)	313 (45.2)	
Lost to Follow up	774 (23.9)	640 (25.2)	134 (19.3)	

KEY
AIDS defined as CD4 < 200 cells/microliter or presence of AIDS-defining illness
IVDU: Intravenous drug use
MSM: Men who have sex with men
ART: Antiretroviral

Table 2: Multivariable survival analysis for time from HIV diagnosis to death, stratified by CD4 cell count

	CD4 count < 200 cells/mm³			CD4 count ≥ 200 cells/mm³		
	Hazard Ratio	**95% Confidence Interval**	**P-value**	**Hazard Ratio**	**95% Confidence Interval**	**P-value**
Hepatitis C Infection	0.95	(0.76, 1.19)	0.667	1.66	(1.27, 2.17)	<0.001
Age > 40 at HIV Diagnosis	1.99	(1.64, 2.42)	<0.001	2.844	(2.298, 3.619)	<0.001
Primary Risk factor						
MSM	Ref	Ref	Ref	Ref	Ref	Ref
IVDU	1.38	(1.06, 1.78)	0.015	2.02	(1.45, 2.80)	<0.001
Other/Unknown	1.33	(1.06, 1.67)	0.014	1.76	(1.35, 2.30)	<0.001
History of ARV use	--	--	--	2.88	(0.31, 0.60)	<0.001
Hepatitis B Infection	1.16	(0.90, 1.51)	0.261	1.75	(1.22, 2.50)	0.002
Race	1.05	(0.85, 1.31)	0.652	0.77	(0.60, 1.00)	0.048

-- Did not satisfy PH assumptions and was used in the model as a stratifying variable. No hazard ratios were generated for this variable.

Table 3: Multivariable survival analysis for time from AIDS diagnosis to death

	Hazard Ratio	95% Confidence Interval	P-value
Hepatitis C Infection	1.33	(1.03, 1.72)	0.031
Age > 40 at HIV Diagnosis	1.18	(0.95, 1.46)	0.136
Primary Risk factor			
MSM	Ref	Ref	Ref
IVDU	1.41	(1.05, 1.90)	0.022
Other/Unknown	1.15	(0.88, 1.49)	0.293
History of ARV use	0.29	(0.20, 0.42)	<0.001
CD4 Count			
< 200 cells/mm3	Ref	Ref	Ref
≥200 cells/mm3	0.16	(0.12, 0.21)	<0.001
History of Hepatitis B Infection	--	--	--
Race	0.85	(0.66, 1.09)	0.197

-- Did not satisfy PH assumptions and was used in the model as a stratifying variable. No hazard ratio was generated for this variable.

Table 4: Multivariable survival analysis for time from HIV diagnosis to AIDS diagnosis

	Hazard Ratio	95% Confidence Interval	P-value
Hepatitis C Infection	0.87	(0.72, 1.06)	0.155
Age > 40 at HIV Diagnosis	--	--	--
Primary Risk factor*			
MSM	--	--	--
IVDU	--	--	--
Other/Unknown	--	--	--
History of ARV use	--	--	--
CD4 Count			
< 200 cells/mm3	Ref	Ref	Ref
≥200 cells/mm3	0.26	(0.22, 0.29)	<0.001
History of Hepatitis B Infection*	--	--	--
Race	0.90	(0.76, 1.06)	0.212

-- Did not satisfy PH assumptions and were used in the model as stratifying variables. No hazard ratios were generated for these variables.

Figure 1: Causes of Death, total study population

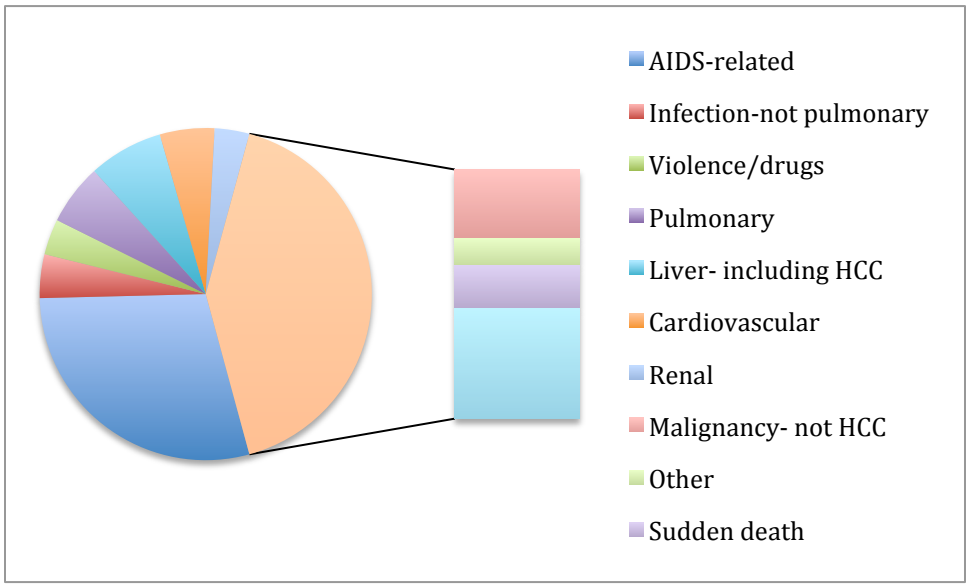

FIGURE 2a: Kaplan Meier analysis comparing length of survival from time of HIV diagnosis to death (patients with CD4 count < 200 at the time of HCV diagnosis) (p=0.1218)

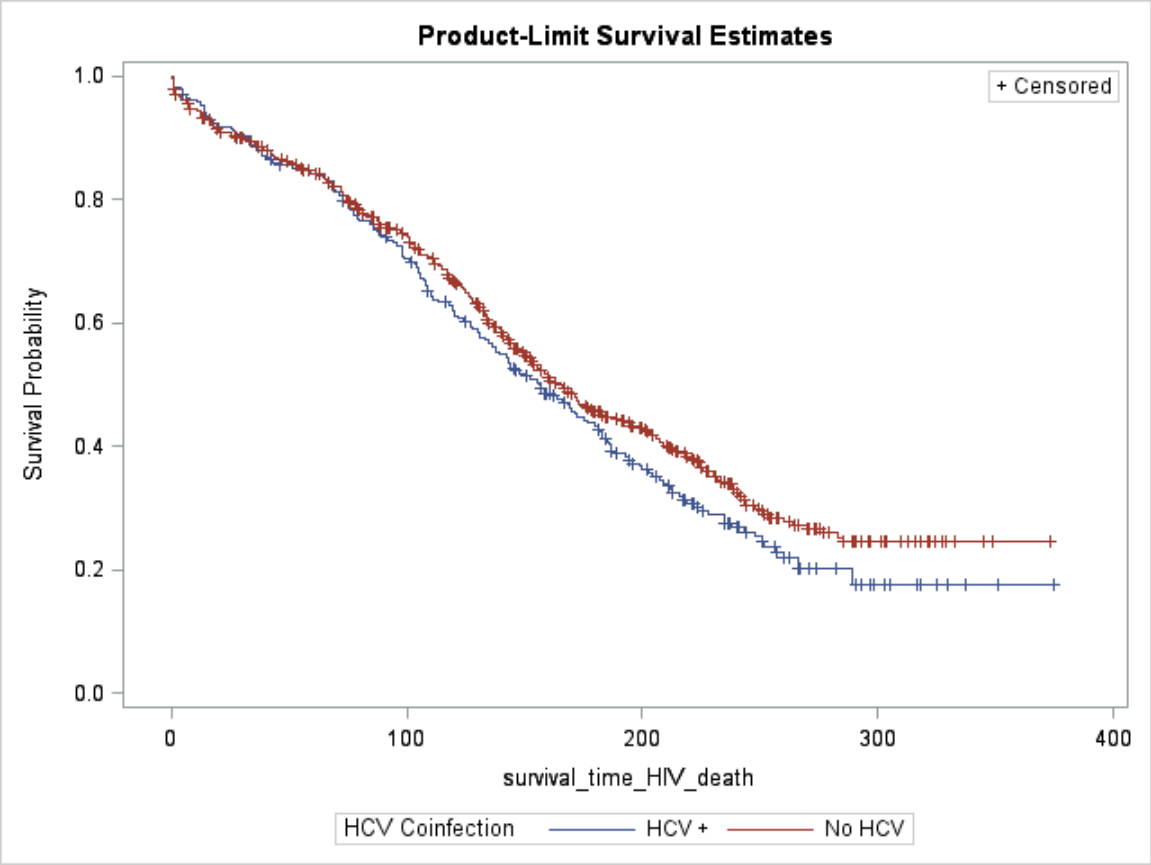

FIGURE 2b: Kaplan Meier analysis comparing length of survival from time of HIV diagnosis to death (patients with CD4 count ≥200 at the time of HCV diagnosis) (p<0.0001)

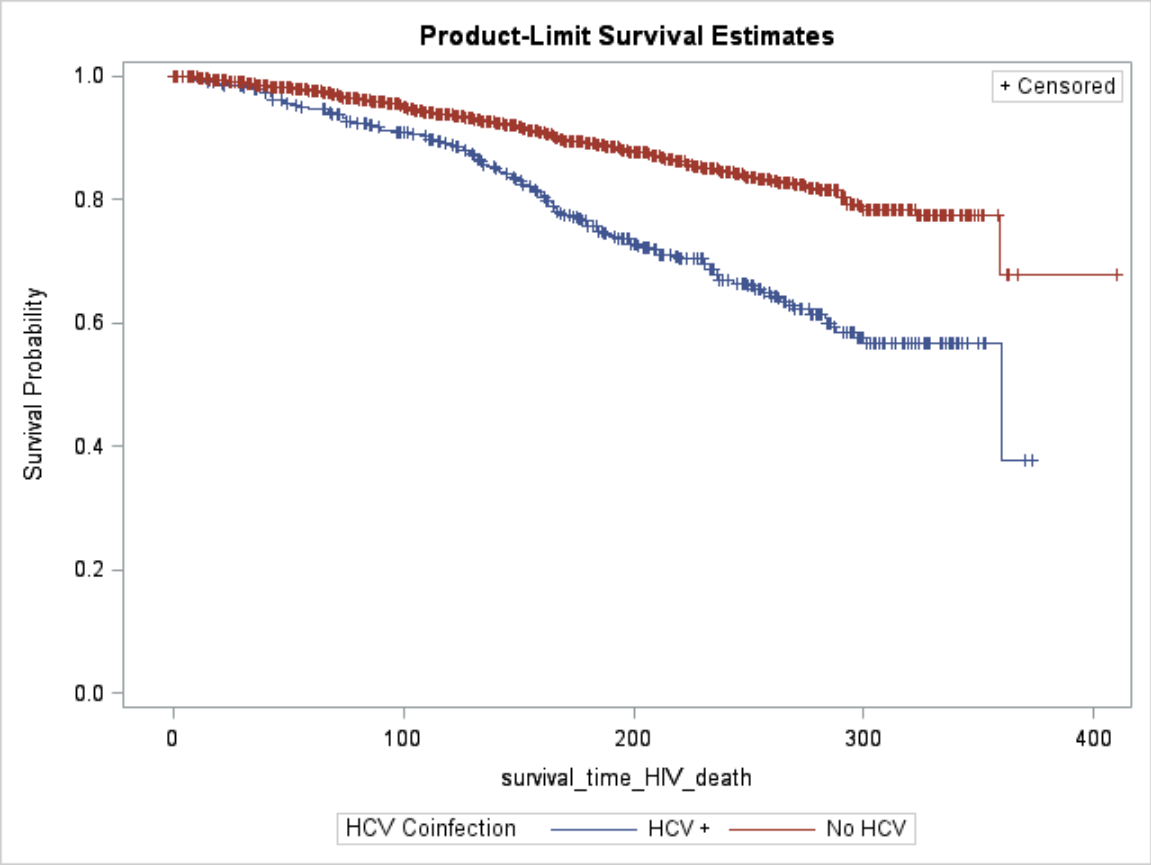

FIGURE 3: Kaplan Meier analysis comparing length of survival from time of AIDS diagnosis to death (p=0.0006)

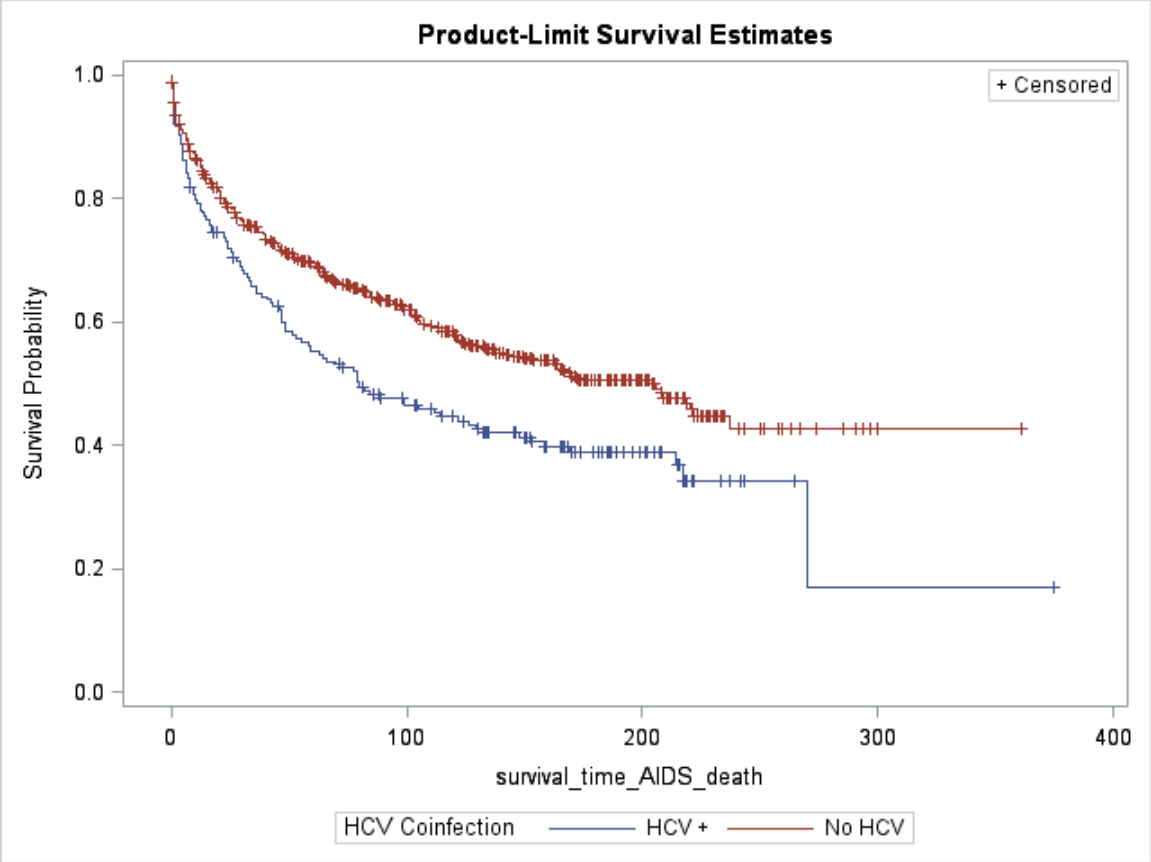

FIGURE 4: Kaplan Meier analysis comparing length of survival from time of HIV to AIDS diagnosis (p=0.3964)