LIVER-RELATED MORTALITY DURING THE HAART ERA IN MACS AND WIHS

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ABSTRACT

It is not clear how the risk of liver-related mortality (LRM) among people infected with HIV has changed during the 20 years since the introduction of HAART; Thus, this study was designed to 1) characterize changes in all-cause mortality and LRM rates since the introduction of HAART in 1996, and 2) examine the effect of HIV/viral hepatitis co-infection on LRM among those infected with HBV or HCV.

Methods: This observational cohort study included all participants with known HBV and HCV status being followed in the Multicenter Center AIDS Cohort Study (MACS) and Women's Interagency HIV Study (WIHS) between 1996 and 2013. Poisson and Cox regression methods were used to examine the rate of and risk factors for the study outcomes of all-cause mortality and LRM.

Results: The overall all-cause mortality and LRM rates during the study period were 15.2 and 2.3 per 1000 person-years, respectively. Following adjustment, all-cause mortality decreased significantly by 3.6% (95% CI: 2.2% - 5.1%) while LRM did not (decreased by 2.2% (95% CI: -1.7% - 5.8%) annually). Importantly, both all-cause mortality and LRM decreased over time among those with CH-B and increased among those with CH-C. Adjusted for age, race, education, income, and blood pressure, CH-B, CH-C and HIV infection were independently associated with a higher LRM (HRs of 9.09 (95% CI, 5.35 – 15.43), 11.63 (95% CI, 7.52 – 17.98), and 1.84 (95% CI, 0.99 – 3.42), respectively), and HAART use was significantly associated with a lower LRM risk (HR, 0.61; 95% CI, 0.42 – 0.88).

Conclusions: During the 20 years since HAART was introduced, liver disease has become an increasingly important cause of death among people infected with HIV. Although CH-B was associated with higher LRM during the early HAART era, LRM has been higher among those with CH-C in recent years; a shift that might be related to our findings that HARRT was associated with lower LRM. Collectively, the findings from our study suggest that there is an urgent need to increase the awareness of hepatitis among people infected with HIV, and that effective strategies to prevent, detect, and treat hepatitis infections are important in this population.

PREFACE AND AKNOWLEDGEMENTS

The data analyzed in this thesis are from the Multicenter AIDS Cohort Study (MACS) and Women's Interagency HIV Study (WIHS). For the analyses presented in this thesis, I have submitted a project proposal to the MACS and WIHS committee. After receiving approval, I performed all statistical analyses, and prepared manuscript for the thesis.

This thesis tries to address the issue of increasing importance of non-AIDS related diseases, specifically viral hepatitis infection caused by hepatitis B virus and hepatitis C virus among the HIV-infected people since the introduction of Highly Active Antiretroviral Therapy (HAART) 20 years ago. I had seen the increasing epidemic of HCV infection among the HIV-infected population when I was conducting a summer project as a medical student in China three years ago. That experience had led me to the field of public health research in graduate school. I believe that there is a major change in the situation of HIV epidemics, since HAART has been successful in treating HIV infection. My thesis tries to show a comprehensive picture of the current situation of hepatitis/HIV co-infection. I think a better understanding of the issue is the first step and the key to solve the problem.

I am grateful for the education and experience I had during my master degree training. I especially thank all the people who helped me in the process of learning and conducting the project. First, I would like to thank to my supervisor Dr. Eric Seaberg, for his humor, patience, and all the guidance that leaded me through this project. I would also like to express my gratitude to my advisor Dr. Maria Wawer, for her kindness, invaluable

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INTRODUCTION

The survival among HIV infected individuals has increased dramatically since the introduction of Highly Active Antiretroviral Therapy (HAART) in the mid-1990s, a direct result of the improved HIV viral suppression achieved through combination treatment. Nevertheless, HIV-related mortality is still the primary cause of death in this population. Furthermore, as people live longer with HIV-infection, death due to chronic diseases like liver disease, cardiovascular disease, and cancer which were not previously considered to be AIDS-related have become more common among HIV-infected people. [1, 2] Liver disease is now the second leading non-HIV cause of death among HIV-infected individuals, following non-AIDS cancer (15%), and followed by cardiovascular disease (11%). [1, 2]

Investigators from the Concerted Action on Sero-Conversion to AIDS and Death in Europe (CASCADE) collaboration studied a large cohort of 16534 individuals in Europe, Australia, and Canada and reported that the excess mortality rate of HIV infection before the introduction of HAART was 40.8 per 1000 person-years (PYs). [3] In 1986, the first clinical trial of antiretroviral therapy (ART) was conducted, and during the next decade dual therapy became well established. However, HIV treatment during the first decade of ART is viewed as unsuccessful. [4] The 11th International Conference on AIDS on July 7 – 16, 1996 is considered to be the beginning of the HAART era. During the conference, the need for HIV antiviral treatment was brought into sharp focus for the first time. Though this seems

obvious now, at that time, the issue was not well recognized. [5, 6] Following the conference, the concept of the triple-drug therapy was being incorporated into clinical practice. Since then, the first ten years has seen an impressive benefit of the rapid decline in rates of AIDS and mortality. The CASCADE collaboration reported that the excess mortality rate decreased dramatically to 6.1 per 1000 PYs in 2004 – 2006. [3] Other studies in the US also showed decreased mortality among HIV infected individuals in the HAART era. A clinical cohort in Baltimore, United States followed 6366 patients from 1995 to 2010 and reported mortality rates of 2.1 per 100 PYs, which was approaching the overall mortality rate in the general population in Baltimore (0.7 – 0.9 per 100 PYs). [7, 8]

HIV was known to be associated with AIDS-defining malignancies, i.e. Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer. HAART has led to reductions in the incidence of Kaposi sarcoma and non-Hodgkin lymphoma, however, it did not change the incidence of cervical cancer. Since 1996, non-AIDS-defining cancers, comprised about 30% of cancers before 1996, and elevated to 58% in 1996 to 2002. [9] Currently, non-AIDS-related cancers have become one of the major causes of death among the HIV-infected individuals. Aside from malignancies, a significant portion of non-AIDS related deaths is due to cardiovascular disease (CVD). Some studies have reported CVD as the leading cause of mortality and morbidity in HIV positive patients. [10] Other studies reported liver disease, non-AIDS related infections, pulmonary disease are also among the most frequent causes of death. In Women's Interagency HIV Study (WIHS), liver-related disease is the most common cause of non-AIDS related death (11.2%), followed by homicides, suicides and accidents (9.0%). [11]

Both the CASCADE Collaboration and a large Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) cohort found that liver disease was one of the most common non-AIDS causes of death. [2, 12, 13] Viral hepatitis such as hepatitis B and hepatitis C has assumed great contribution to liver-related deaths. [2] Co-infection with HIV and HBV or HCV is common in this population due to transmission modes being shared with HIV, including intravenous drug use (IVDu), unprotected sex with an infected partner, and transfusion of blood or blood products.

Liver disease is mainly caused by viral hepatitis infection and alcohol abuse. Hepatitis B and C are the two major virus infection among the HIV-infected individuals. Approximately 10% of HIV-infected patients worldwide are co-infected with hepatitis B. [14] Particularly in developed countries, co-infection of HIV/HBV is more common in men who have sex with men (MSM) and injection drug users than the general population. [15] Most of the risk factor studies for HIV/HBV co-infection were performed during the first couple decades of the HIV epidemics before the advent of tolerable and effect ART. Co-infection with HIV/HBV was primarily related with unsafe sexual behaviors, i.e. anal intercourse, history of gonorrhea, rectal douching, sexual activity with a person who developed AIDS, etc. [16]

Approximately 25 - 30% of HIV-infected people were co-infected with hepatitis C Virus (HCV) in the United States, according to a study published in 2005. [17] However, the prevalence of co-infection varies among risk groups, ranging from 73% in high-risk group

like intravenous drug users and people with hemophilia to about 4% in other low-risk groups. Researchers have found that age, race, lifestyle, high level of HIV viral load, reported smoking, reported cocaine use, current infection with hepatitis B are associated with HCV infection. [18, 19]

The effect of hepatitis on HIV/AIDS progression remains controversial. One study has found HCV-infected women were more likely to have AIDS when their HCV RNA level was over 2.3 million IU/mL ($p < 0.001$), and were more likely to have AIDS-related death when HCV RNA level was over 13.98 million IU/mL ($p = 0.03$). They also reported that among patients who never had a CD4 less than 200 cells/μL, AIDS was more likely to occur on HCV-infected people, and such risk increased with time. This is also true among ART-naïve patients. The author also reported an association between HCV status and immune activation, both in unadjusted and adjusted models. [20] Another study, conducted during the same period among HIV clinic patients, reported no difference in the risk of AIDS development or death among HCV-infected and HCV-uninfected patients. After stratifying by HAART, baseline CD4 cell count and the control status of HIV replication, the data still showed no significant difference. Similarly, AIDS-related death was found not to be associated with HCV infection. [21] Similarly, whether chronic hepatitis B affects the progression of HIV/AIDS is also unclear. On one hand, some studies have shown association between HBV and AIDS progression, while others reported no association. [22, 23]

Though the effect of hepatitis on HIV/AIDS progression remains unclear, many studies have seen the negative effect of HIV on liver disease. HBV/HIV co-infection is associated with increased risk of cirrhosis, steatosis, hepatic decompensation, end-stage liver disease, and hepatocellular carcinoma (HCC). [24-26] Liver-related mortality rates were 14.2 versus 0.8 per 1000 person-years among HIV/HBV co-infected patients versus those with only HBsAg. HBV DNA levels are higher among HIV infected patients than among HBV mono-infected patients; co-infection with HIV/HBV is associated with increased risk of reinfection, and slower spontaneous clearance rate of the antibodies. [27, 28] Co-infection of HIV and HCV leads to more rapid fibrosis progression, high risk of hepatocellular carcinoma (HCC) and a high risk of hepatic compensation. [13, 29-31] A study of 3990 HIV-infected people from Denmark from 1995 to 2005 reported a mortality rate of 59 per 1000 person-years in persons with HIV/HCV co-infection, compared to 39 per 1000 person-years in those with HIV alone. [32]

Because HIV alters the natural progression of liver disease, the treatment for viral hepatitis infection among the co-infected patients is highly important. The approach to treat hepatitis B in HIV infected patients differs much from that which is used for HBV mono-infected patients. Because some drugs are used to treat both HBV and HIV, it is recommended to initiate antiretroviral therapy for both viruses concurrently, regardless of CD4 cell count. [33] Particularly, because some drugs for HBV and HIV treatment share the same agents, HAART for HIV/HBV co-infected patients that has agents against hepatitis B virus can be

characterized as HBV-active HAART. Early initiation of HAART is also recommended among the co-infected patients. Ongoing concerns exist regarding the risk of drug-associated hepatotoxicity of ART. One cohort study in South Africa found that the risk of hepatotoxicity had a strong association with a high baseline serum HBV DNA level. [34]

For HCV antiviral treatment, the introduction of multiple direct-acting antivirals (DAAs) in recent years has offered a highly effective treatment option for HCV infected patients with mild side effects. [35] These new treatments are very effective in curing HCV infections and are likely to translate into substantially increase life expectancies for HCV infected people. [36, 37] In 2004, several DAAs drugs have been approved by the Food and Drug Administration (FDA). Despite the undeniable benefits of the new treatment, the associated cost is unfortunately high. Even after the discount of some healthcare programs, each pill still costs about $ 1,000 USD, and a standard course of treatment requires the pill to be taken daily for 12 weeks. [38] This creates significant barriers to the cure, leaving a large pool of patients who are willing yet unable to be treated. Notably, substance abuse and psychiatric health issues exist commonly among HIV/HCV co-infected patients. Many patients are homeless or live in poor living conditions. Thus, decisions about which patients to treat are made which considering a patient's ability to adhere to medications, return for follow-up, and limit the risk for reinfection. Unlike hepatitis B, HAART treatment was not found to be effective against hepatitis C virus. However, some researchers did find that HAART was effective in HIV/hepatitis co-infected people, and might even lead to decreased liver disease progression among HIV/HCV co-infected patients. In one study among 638 patients with

HIV-monoinfection or HIV/HCV co-infection, current ART exposure was associated with a decreased risk of liver-related events (incidence RR, 0.34; 95% CI, 0.18 – 0.66), including end-stage liver disease, hepatocellular carcinoma, or liver-related death, after adjusting for other variables. While this study suggests that ART is associated with slower liver disease progression, other researchers pointed out that achieving HIV viral suppression while taking ART is also an important factor. [32, 39, 40] The relationship of ART and other negative events as hepatic decompensation, and end-stage liver disease were also investigated. A veteran cohort study between 1996 and 2010 found that ART reduced the rate of hepatic decompensation by 28% - 41%. [41] Moreover, early initiation of ART is important to achieve a beneficial effect on liver disease progression, particularly when HCV antiviral therapy uptake is low or when patients do not respond to HCV therapy. [42]

While both HBV and HCV co-infection are associated with adverse outcomes and poorer survival, the outcome for those with triple infection can be even worse. About 3 to 5 percent of the HIV-infected patients were found to be infected with both HBV and HCV. [43] These patients have more severe liver disease, and in most of the cases, one virus outcompetes the other virus due to viral interference. The approach to treat the triple infected patients is critical since there are concerns that the suppression of the predominant virus will cause the other to rebound. [44]

In summary, the issue of HIV/hepatitis co-infection among people living with HIV requires close attention. Due to the success of HAART, mortality from traditional AIDS-related diseases has decreased, leaving liver disease the opportunity to become a major cause of morbidity and mortality. Characteristically, HIV has been recognized to be associated with liver fibrosis and malignancies in HBV and HCV infections. The treatment for hepatitis B and C can be challenging, and HAART therapy can also be more difficult in co-infected individuals.

The majority of the current literature related to hepatitis/HIV co-infection focused only on the pre- and early-HAART eras. Now that 20 years have passed since the introduction of HAART, it is necessary to have more updated information. Most of the previous studies only looked at either HIV/HBV co-infection or HIV/HCV co-infection; and some of the studies have compared two co-infections. However, a more comprehensive analysis that also examined the effect of hepatitis treatment and HAART is needed to better assess the situation.

STUDY AIM AND HYPOTHESIS

The primary aims of our study are 1) to characterize changes in liver-related mortality rates in MACS and WIHS since the introduction of Highly Active Antiretroviral Therapy (HAART) in 1996, and 2) to examine the effect of HIV/viral hepatitis co-infection on liver-related mortality (LRM) separately for those with chronic hepatitis B and hepatitis C during

this period. Our hypotheses are as follows: H1. The LRM rate has decreased between 1996 and 2015 in MACS and WIHS, and the decrease has been larger among HBV infected participants than among HCV infected participants in both cohorts; H2. The LRM hazard is elevated among hepatitis-infected participants, and is highest among HIV/hepatitis co-infected participants; H3. Among HIV/hepatitis co-infected participants, HAART reduced the risk of LRM among those infected with HBV more than among those infected with HCV.

METHODS

Study Population

This study was performed using data from the Multicenter AIDS Cohort Study (MACS) and the Women's Interagency HIV Study (WIHS). The MACS is a prospective cohort study of men who have sex with men (MSM) that was initiated in 1984 and continues today. The MACS was initially designed to identify the cause of, risk factors of, and course of AIDS. Today, the primary objective of the MACS is to describe the burden and outcomes of the many chronic diseases experienced by HIV-infected MSM in the era of effective HIV treatment. The details about the enrollment and the descriptions of the characteristics of MACS cohort have been published elsewhere. [45] The WIHS study was initially established to investigate the impact of HIV infection on women in the United States. It continues to investigate the new trend in the HIV epidemic among women accounting for the effectiveness and consequences of HAART. More information about the recruitment and characteristics of the WIHS study has been reported elsewhere. [46]

In MACS, men with or at risk for HIV-infection were enrolled into the study at four sites located across the US (Baltimore/Washington DC, Chicago, Pittsburgh and Los Angeles) to study the history of HIV infection. During the first three enrollment periods, 6972 men entered the cohort. Among those participants, 4954 were enrolled from April 1984 through March 1985, 668 were enrolled from April 1987 through September 1991, and the last 1350 were enrolled from October 2001 through August 2003. A fourth enrollment period started in year 2010 and continues today. After baseline assessment, follow-up visits were conducted every 6 months. The semiannual questionnaires include questions about the medical history, use of health services, behaviors, and medication history of the participants. Demographics data were collected. HIV RNA, HBV and HCV serology testing were performed. Other information also included physical examination and psychosocial evaluation. Assessed clinical outcomes included AIDS diagnosis and non-AIDS diagnoses included cardiovascular disease, cerebrovascular disease, kidney disease, liver disease, lung infection, etc. Occasionally, phone calls would be made if the participants missed the follow-up visits, and partial information was collected. Participants were followed until death, or loss to follow-up, whichever occurred first. [47]

The initial enrollment period for WIHS was from October 1994 through November 1995, the second enrollment period was in 2001 to 2002, and the most recent period was from 2011 to 2012. In the year 2013, the WIHS added four new sites from the South. However, because of the few amount of participants enrolled, the new enrollment was excluded from

our current study. Participants were asked to complete a detailed interview on socio-demographic, substance use, sexual behaviors, medical, obstetric, gynecological, contraceptive history. The WIHS study collects medical history including detailed medication inventory to include new therapies. Physical and gynecologic examinations, and laboratory testing were also performed at baseline and in every study visit. In addition, biological samples were also being collected and stored. Participants in WIHS also have follow-up visits every six months. [48]

Because the goal of our study was to examine and describe LRM during the HAART era, our study population included all participants in MACS and WIHS from 1996 to 2015 who had been tested for both HBV and HCV infection. The baseline was established at the first study visit that had results for HIV, hepatitis B, and hepatitis C, on or after January 1st, 1996, and continued through death, loss to follow-up or cessation due to right-truncation in 2015. Participants were excluded if they only attended the baseline study visit and had no follow-up information recorded in the study databases. Occasionally a participant would miss multiple study visits and then return to follow-up at a later time. If these gaps in follow-up time exceeded 2 years, then we censored the follow-up time for the given interval at 2 years, and then the participant follow-up time resumed later when he/she resumed regular study visits.

Study Exposures

Our primary exposures were chronic HBV (CH-B) infection and chronic HCV (CH-C) infection. In MACS, a participant had HBV infection if the Hepatitis B surface antigen (HBsAg) was positive and had HCV infection if the HCV antibody and HCV RNA were positive. Both CH-B and CH-C infection was determined using longitudinal information. Tests to determine viral hepatitis infection status were performed on stored serum sample. HBsAg and HCV antibody testings were determined by enzyme immunoassay (Abbott Laboratories, ADVIA Centura HCV assay, respectively). HCV RNA levels were determined with COBAS AmpliPrep TaqMan HCV Assay. [49] In WIHS, CH-B infection status was carried forward through the remaining follow up time from the HBsAg result obtained at study entry. Longitudinal results were used in the analyses for CH-C infection, i.e. determined as infected if he/she had detectable HCV RNA and HCV antibody. HBV and HCV serologies were performed using standard commercial assays (Abbott Laboratories, EIA 3.0 Ortho-Clinical Diagnostics, respectively). HCV RNA levels were determined with COBAS Amplicor Monitor 2.0 assay or COBAS Taqman. [11]

We also included a number of potential confounding factors in our analyses. Information was collected on demographic characteristics, socioeconomic status (SES), clinical characteristics, and behavioral characteristics. Birth date of participants, race, and education status were obtained at baseline. SES measures such as employment status was defined as being employed if participants either working full time, part-time, as student, or retired, self-employment and people who have disability but still currently under employment are also considered as being employed. Income levels were categorized in two ways during the

MACS study period, most of our baseline income information was collected using the original nine categories, which later became ten categories because of the relative high income level in MACS cohort. We used a cutoff point of 10,000 USD per year for MACS, anyone who has an annual income lower than 10, 000 were considered as low income. For WIHS, 12,000 USD per year was the cutoff point. For participants who didn't provide income status in one visit, information was obtained from the nearest visits. High blood pressure was defined if SBP >= 140 mmHg or DBP >= 90 mmHg or if the person was diagnosed with hypertension and used anti-hypertension medications. Also if blood pressure status was not available for one study visit, information would be obtained from the nearest study visits. This method also applies to diabetes status, which was defined as blood glucose transporter 2 >= 126 or if the person was diagnosed with diabetes and used anti-diabetic medications. Depression status was defined using CESD scale over or equals to 16. Behavioral characteristics include smoking, alcohol drinking and drug use. Non-injection drugs included hash/marijuana, poppers (chemical class called alkyl nitrites that are inhaled for recreational purposes), cocaine, uppers (stimulants that affect basic body processes), downers (inhibitors that affect basic body processes), sexual performance enhancing drugs, ecstasy, heroin, Phencyclidine (PCP), ethyl chloride, Gamma Hydroxybutyrate (GHB) and other unspecified drugs. Information was also available for treatment against viral hepatitis and HIV infection. All covariates except race and sex were examined as time-varying covariates.

Study Outcomes

Our primary outcome was mortality related to liver disease, but we also examined mortality due to any cause to provide a frame of reference when examining liver-related mortality. Deaths were ascertained in both cohorts via death registry matching and death certificates coded per the International Classification of Diseases (ICD), in some cases supplemental information was obtained from medical record review, communication with the primary clinician, or patient families. [11, 49]

We then examined the cause of death (COD) information to determine which of the deaths were documented as being due to or carried an underlying or contributing cause that was related to liver disease. In MACS, all the underlying and contributing causes of death are coded using ICD9 or ICD10 codes. We considered any death for which the underlying or any contributing cause included one or more of the causes listed in the following codes was classified as being related to liver disease.

ICD-9	
Viral hepatitis	070, 070.0 – 070.9
Malignant neoplasm of liver	155, 155.0 – 155.2
Acute hepatic failure	570, 570.0
Chronic liver disease/cirrhosis	571, 571.0 – 571.9
Liver abscess/other sequelae of chronic liver disease	572, 572.0 – 572.8
Other liver disorders	573, 573.0 – 573.9
ICD-10	
Viral hepatitis	B15 – B19
Malignant neoplasm of liver	C22

Disease of Liver	K70 – K76

In WIHS, death information is stored in the master database using text descriptions that are based on ICD9 and ICD10 codes as well as textual narratives from the source documents. For this study, we reviewed all of the cause of death (COD) text data and then classified any death where a COD text description included one of the following text strings as being related to liver disease: "hepatitis", "liver", "cirrhosis", "hepatic", "hepb", "hepc", "hepato", or "hcc".

Statistical Methods

For this prospective time-to-event analysis, the follow up time origin was defined as the date of the first study visit on or after January 1st, 1996, and follow-up time continued until death or censoring at the last study visit, whichever came first. We excluded observations after September 30th, 2013 for both MACS and WIHS, because the mortality data were likely to be incomplete for 2014 due to reporting delays.

A person-years analysis was used to estimate and compare LRM rates for hypothesis one that the LRM rate has decreased during the study period, and the decrease has been larger among HBV infected participants than among HCV infected participants. The overall and

stratum-specific LRM rates were estimated as the number of LR deaths divided by the cumulative number of person-years of follow up accrued by all participants in the strata defined by HIV, CHB and CHC. We used a Poisson regression to compare the LRM rates across strata (i.e. between exposure groups of interest) and over time (by calendar year) while accounting for important cofactors and potential confounders. The adjusted covariates were either considered as important confounders or showed as important risk factors for LRM in Cox proportional hazard models. For hypothesis one, we tested the trend of annual change in liver-related mortality and all-cause mortality; we compared the differences of trend between hepatitis B infection and hepatitis C infection.

We also used Kaplan-Meier curves to plot the survival probability of death and cumulative incidence of liver-related mortality. As there were few observations in the HBV mono-infection group, HBV and HCV co-infected group and triple-infection group, those groups were excluded in the Kaplan-Meier analysis. We plotted the Kaplan-Meier curves across all other combinations of HIV, HBV and HCV infection groups.

Finally, we fit unadjusted and adjusted Cox proportional hazard regression models to examine the effect of the primary exposures on LR mortality. To generate the adjusted Cox models, we manually implemented a stepwise selection process to choose the best model. For hypothesis two, in order to examine whether the LRM is elevated among HIV/hepatitis coinfected participants, we also tested for interactions between HIV infection and hepatitis

infection, and also for HIV with hepatitis B infection and hepatitis C infection separately. We then also included hepatitis B and hepatitis C treatment information to examine the treatment effect on liver-related mortality. A subgroup analysis was performed to examine the effect of HAART on LRM among the HIV infected individuals, and then to evaluate the effect of the use of HAART according to whether or not HBV infection was active. Finally, we did a sensitivity analysis by using Fine and Gray competing risk method. [50] Selected models we used for hypothesis two and three were performed to validate our results.

All statistical analysis was done with STATA (version 13). A p-value of 0.05 or less was judged to indicate statistical significance.

RESULTS

Our study population consisted of 3148 men participating in the MACS study cohort and 3571 women from WIHS study cohort between Jan. 1st, 1996 and Sep. 30th, 2013. At baseline, age of participants ranged from 17 to 76, with a median age of 39 years. The total amount of accrued follow up time was 67717.6 person-years with a maximum of 18.0 years (median: 6.4 years, IQR, 2.9 – 10.1 years). During our follow-up period, 1028 (15.3%) participants died (275 (8.7%) in MACS and 753 (21.1%) in WIHS), 153 (14.9%) of them died of a liver-related cause; 42 (15.3%) in MACS and 111(14.7%) in WIHS.

Among the 3148 men in MACS, most were white, had higher than high school education, were employed, and had a yearly income above 10,000 USD (Table 1). In addition, about two thirds had a history of smoking or were smoking at baseline visit, about 9% consumed 14 or more alcohol-containing drinks per week, more than 80% of men had used or were using non-injection drugs while 11.3% had a history of using injection drugs, nearly one-third had hypertension, about one-quarter had been diagnosed with depression, and 3.0% were diabetic at baseline visit. Among the 1577 (50.1%) of men who were infected with HIV prior to the baseline visit, 10% had previously been diagnosed with AIDS and nearly one-third had initiated HAART. Chronic hepatitis infection (hepatitis B or hepatitis C) was detected in 11.5% of the participants at baseline; 4.2% with chronic HBV (CH-B) and 7.7% with chronic HCV (CH-C). Among the men with CH-B, 43% were taking an anti-HBV treatment whereas only 2.5% of men with CH-C were taking an anti-HCV treatment.

Among the 3751 women in WIHS, most of them were Black, had high school education or lower, were unemployed, and had a yearly income of less than 12,000 USD. (Table 1) In addition, about half of the individuals were current smokers at the baseline visit, 8% consumed 14 or more alcohol-containing drinks per week, 70% had used or were using non-injection drugs while 28% had a history of using injection drugs. Similar to MACS cohort, nearly one-third in WIHS had hypertension, about one-quarter had been diagnosed with depression, and 4.7% were diabetic at baseline visit. Among the 2637 (73.8%) of women who were infected with HIV prior to the baseline visit, 25.7% had previously been

diagnosed with AIDS, and 46.2% had initiated HAART. Chronic hepatitis infection (hepatitis B or hepatitis C) was detected in 23.1% of the participants at baseline; 1.9% with chronic HBV (CH-B), and 21.6% with chronic HCV (CH-C). Among the women with CH-B, 4.4% were taking an anti-HBV treatment whereas only 0.1% of women with CH-C were taking an anti-HCV treatment.

Overall, the participants from MACS and WIHS differed significantly for each characteristic in Table 1. For example, the mean age was higher in MACS than in WIHS (mean: 49.3 and 42.0, respectively). The majority in MACS were white, had higher than high school education, were employed, and had high income, while the the majority in WIHS were Black, had high school education or lower, were unemployed, and had low income. A higher proportion of injection drug users and current smokers were found in WIHS than in MACS. A higher proportion of men had hypertension and diabetes in MACS than the women in WIHS. The two cohorts were similar on diabetes status. A higher proportion of women in WIHS had been previously diagnosed with HIV than the men in MACS, and a higher proportion of the HIV-infected women had initiated HAART than the men in MACS. A lower proportion of women had CH-B than the men in MACS, however, a much higher proportion of women had CH-C than the men in MACS.

We also examined co-infection with HIV and/or HBV and/or HCV at baseline. Overall, 33.4% were negative for all three viruses. HIV mono-infection was present in 47.3% of the

study participants while 0.5% had HBV mono-infection and 3.0% had HCV mono-infection. Regarding viral co-infection, HIV/HCV co-infection was the most commonly observed (11.7%) followed by HIV/HBV (2.1%) and the HBV/HCV (n=1). Triple infection with all three viruses was documented in 23 people (0.3). Finally, 115 (1.7%) participants had missing HBV and/or HCV information baseline visit.

Overall, the all-cause mortality observed during the entire study period from January, 1996 to September, 2013 was 15.18 (95% CI, 14.28 – 16.14) per 1000 person-years. During the same time frame, the liver-related mortality was 2.26 (95% CI, 1.93 – 2.65) per 1000 person-years. We examined the overall all-cause mortality and liver-related mortality rates by infection status. As shown in Table 2, all-cause mortality has increased among HIV, HBV and HCV infected individuals, and was the highest among HCV infected individuals. Liver-related mortality was increased among HBV and HCV infected, however, it was not notably increased much among HIV infected individuals. In the adjusted Poisson regression models, neither all-cause mortality nor liver-related mortality rates were significantly different between HBV infection and HCV infection, though HBV infected individuals had slightly higher mortality rates than HCV infected individuals (data not shown).

During the study period, the all-cause mortality rate decreased in both cohorts, though this trend was more obvious in WIHS than in MACS (Figure 1). We then plotted separately for HIV, HBV, and HCV infection groups (Figure 2). The all-cause mortality among HCV

infected individuals stayed flat over the years, all-cause mortality rates among HIV infected and HBV infected individuals declined over time. For liver-related mortality rates shown in Figure 3, though there was variation over time, the overall trend tended to be more flat for both the MACS and WIHS studies. We also plotted LRM separately for HIV, HBV, and HCV (Figure 4). Liver-related mortality rates seemed to be flat for HIV infected. Except for a bump among the HBV infected from year 2006 to year 2007, liver-related mortality rates among HBV-infected participants had a declining trend while the liver-related mortality rates among HCV-infected increased over time.

After adjusting for important covariates and potential confounders, we found that the all-cause mortality rate had a statistically significant decline of about 3.6% (95% CI: 2.2% - 5.1%) per year, and individuals with HBV infection had the steepest decline. The liver-related mortality rate declined by 2.2% (95% CI: -1.7% - 5.8%) annually, but the change was not statistically significant. We then compared these to rates of changes and found that the annual declines among HBV infected participants and HCV infected participants were not significantly different.

Figure 5 and Figure 6 show the Kaplan-Meier survival curves for all-cause mortality and liver-related mortality. For all-cause mortality, the 18-year survival probability was highest among the uninfected individuals (93.2%), followed by HIV mono-infected and HCV mono-infected individuals. HIV mono-infected and HCV mono-infected individuals had

almost identical survival curves during the first ten years after baseline, but they diverged after 10 years with the 18-years survival among HCV mono-infected individuals being lower than that among HIV mono-infected individuals (78.4% and 63.8%, respectively). Co-infected individuals had lower survival than mono-infected individuals with the 18-year survival among HIV/HCV co-infected individuals being lower than that among HIV/HBV co-infected individuals (42.8% and 58.4%, respectively). For liver-related mortality, the 18-year cumulative incidence was lowest among the uninfected and HIV mono-infected individuals (0.4% and 1.1%, respectively), followed by HCV mono-infected (8.3%), and then followed by the co-infected individuals, with the 18-year cumulative incidence among HIV/HBV co-infected individuals being slightly lower than that among HIV/HCV co-infected individuals (18.0% and 20.1%, respectively).

There were 30 individuals who were infected with HIV, CH-B, and CH-C at baseline and throughout follow-up. 11 of them died, 6 of them died of liver-related disease. The shortest follow-up period was 0.25 years and the longest follow-up period was 17.9 years. Due to the small number of participants with triple infection, this group was not included in the Kaplan Meier curves.

Results from the univariate and multivariate Cox regression analysis are shown in Table 3 for all-cause mortality. While the mortality hazard was 2.44 (95% CI: 2.12 – 2.80) times higher among WIHS versus MACS participants, the difference disappeared (adjusted HR (aHR):

1.16; 95% CI: 0.95 – 1.43) following adjustment for important demographic and clinical characteristic differences between the two cohorts. As expected, the mortality hazard increased with age in the adjusted model. Race and education were not significantly associated with all-cause mortality in the adjusted analysis. Other characteristics found to be significantly ($p<0.05$) associated with an increased mortality hazard in the adjusted analysis include low income, history of cigarette smoking, and the presence of hypertension or depression. In addition, HIV-infected participants had 2.1 (95% CI, 1.68 – 2.64) times higher mortality hazard than HIV-uninfected participants; and among those infected with HIV, participants who had been diagnosed with AIDS had 2.7 times more likely to die compared to those without a prior AIDS diagnosis. Finally, both CH-B (aHR: 2.38; 95% CI, 1.76 – 3.22) and CH-C (aHR: 2.04; 95% CI, 1.75 – 2.37) were found to be independently associated with a higher mortality hazard following adjustment for the other factors included in the adjusted model.

Results from the univariate and multivariate Cox regression analysis are shown in Table 4 for liver-related mortality. The mortality hazard was 2.32 (95%CI: 1.63 – 3.31) times higher among WIHS vs. MACS participants, the difference disappeared (aHR: 1.06; 95% CI: 0.63 – 1.78) following adjustment for important demographic and clinical characteristic differences between the two cohorts. Though not statistically significant, as expected, the mortality hazard increased with age in the adjusted models. Characteristics found to be significantly ($p<0.05$) associated with an increased mortality hazard in the adjusted analysis include white race, low education, low income, and the presence of hypertension. In addition, HIV-

infected participants had 1.84 (95% CI, 0.99 – 3.42) times higher LR mortality hazard than HIV-uninfected participants; and among those infected with HIV, individuals who had been diagnosed with AIDS had 2.30 (95% CI, 1.56 – 3.41) times higher LR mortality than those without AIDS diagnosis. Any hepatitis infection, i.e. infection with either hepatitis B or hepatitis C, was associated with 17.53 (95% CI, 10.66 – 28.82) times higher LR mortality hazard. Specifically, individuals with CH-B had 9.09 (95% CI, 5.35 – 15.43) times higher LR mortality hazard than those without CH-B while individuals with CH-C had 11.63 (95% CI, 7.52 – 17.98) times higher LR mortality hazard than those without CH-C.

Next, we examined the effect of HIV/viral hepatitis co-infection on LR mortality by testing for interactions between HIV and hepatitis, HIV and HBV, and HIV and HCV, and found that none of the interaction terms that we added to the model were statistically significant (p-values, 0.79, 0.12, and 0.95, respectively). We also tested the effect of hepatitis treatment, and found that hepatitis B treatment was significantly associated with a lower LRM hazard (aHR: 0.67, 95% CI, 0.44 – 1.03, p=0.06) while hepatitis C treatment was not (aHR = 1.00; 95% CI, 0.24 – 4.11).

We then restricted our analysis to the subgroup of HIV-infected individuals to explore the effect of HAART treatment on LRM. (Table 5) As shown in Model 3, taking HAART was associated with 0.61 (95% CI, 0.42 – 0.88, p=0.009) times lower hazard of LRM than those who were not taking HAART. We then included interaction terms in the model to test for

the effect of HAART among those co-infected with CH-B or CH-C, and found that neither interaction term was statistically significant (p=0.308 and 0.860, respectively). We also partitioned HAART into HBV-active HAART and non HBV-active HAART (Model 4), and found that both classes of HAART were effective at improving LR survival (aHR1=0.65, 95% CI, 0.41 – 1.04 and aHR2=0.58, 95% CI, 0.37 – 0.90, respectively).

Finally, we performed several sensitivity analyses to account for the possibility that competing risks due to HIV-related deaths might have affected the results from our analyses of liver-related deaths. The results from four separate competing risks models (data not shown) were very consistent with the results reported above, which demonstrates that these liver-related survival analyses that restricted follow-up time to the HAART era were not adversely affected by competing HIV-related mortality.

DISCUSSION

Our study is one of the first to compare and contrast overall mortality and liver-related mortality among people with or at risk for HIV infection since the introduction of HAART in the mid-1990s. In the MACS and WIHS cohorts, we observed a statistically significant decline in the overall mortality rate of approximately 3.5% per year between 1996 and 2013. In contrast, the liver-related mortality rate declined by only about 2% which was not a statistically significant decline. Interestingly, both overall mortality and LRM were higher

among those with CH-B compared to those with CH-C during the first five years of the study period, but during the last five years the outcomes were reversed with both mortality rates being higher among those with CH-C compared to those with CH-B. We then compared the effects of CH-B and CH-C on mortality and found them to be independently and similarly associated with an increased hazard of both overall and LR mortality, and in neither case did we observe a significant effect of HIV/hepatitis co-infection. However, we did find that HBV treatment was significantly associated with reduced LR mortality while HCV treatment was not. Finally, we examined the subgroup of HIV-infected participants to test the effect of HAART on LR mortality and found that effective HIV treatment was associated with a significantly lower risk of dying from liver disease. Although we expected to find that HAART would be more beneficial for those with CH-B than for those with CH-C, our results indicate that the beneficial effect of HAART was essentially the same for both hepatitis groups and did not depend on whether or not the HAART regimen included HBV-active medications. Taken together, the results from our study indicate that the contribution of liver disease to mortality among men and women with or at risk for HIV infection has increased since the introduction of HAART in the mid-1990's, and that the excess mortality risk due to viral hepatitis infection that has been reported to be higher among those with CH-B [49] may now be higher among those with CH-C.

In a previous MACS study among participants followed between 1984 and 1999, the all-cause mortality rate was 29.9 per 1000 PYs, and 62 (3.8%) of the individuals died of liver-related death, resulting in a LR mortality rate of 1.1 per 1000 PYs. [26] In the current study,

the all-cause mortality rate had decreased almost 50% compared to the previous study (Mortality Rate = 15.18 per 1000 PYs). Furthermore, 14.9% died of liver-related diseases and the LR mortality rate was 2.3 per 1000 PYs, which is more than double the rate reported in the previous study.

The results from the current study about the change in overall and LR mortality provide one possible explanation for the differences between the current study and the prior MACS study. [26] Specifically, the overall mortality rate declined between 1996 and 2013 in both the MACS and WIHS while the LR mortality rate remained largely unchanged. These trends indicate that liver disease now contributes to a larger proportion of deaths compared to during the pre-HAART era which support our hypothesis that liver-related mortality has assumed increasing importance during the 20 years since the introduction of HAART. Moreover, the all-cause mortality rate tended to be decreasing for HBV while increasing for HCV. This is most likely a result of HIV treatments also being active against HBV but not against HCV. All-cause mortality rate declined among the HIV-infected individuals, which further confirmed the effectiveness of HAART.

Not surprisingly, HIV, CH-B, and CH-C were associated with significantly higher all-cause mortality hazard, with or without adjusting for confounders. We observed a higher all-cause mortality rate among the hepatitis infected individuals than the HIV infected individuals, especially since the mortality rate among HCV infected patients was twice as high as that

among HIV infected patients. We did not find a significant interaction due to co-infection with HIV and either hepatitis viruses. These results also suggest that in the HAART era, more attention is needed for the prevention and treatment of hepatitis infection.

As expected, for liver-related deaths, the mortality rates among hepatitis infected individuals was about four times higher than that among HIV infected patients. In a previous study, which followed participants with either CH-B or CH-C from study entry to year 2010, a higher liver-related mortality was found among the HBV-infected individuals than the HIV and HCV-infected individuals. [49] In our study, however, we found that LR mortality rate was higher among HCV-infected participants compared to HBV-infected participants. This may seem to be inconsistent at first glance, but the previous study reported that the comparative risk of liver-related mortality between HBV and HCV decreased from pre-HAART era to early HAART era and to current HAART era, with incidence rate ratio (IRR) dropping from 2.1 to 1.2. After adjusting for confounders and important covariates in the current study, the hazard ratio associated with CH-C (aHR: 9.09) remained higher than that associated with CH-B (aHR: 11.63), though the difference was not statistically significant. So our study indicates that compared to hepatitis B infection, hepatitis C infection has worse outcomes. The biological basis for the different severity of liver disease caused by hepatitis B infection versus hepatitis C infection is not apparent. One possible explanation is that infection with HIV accelerates the progression of HCV disease to cirrhosis by increasing hepatitis C viremia. However, this effect was also observed among HIV and HBV co-infected individuals, so it is not likely to explain the difference of mortality between the CH-

B and CH-C. [13] Another possible explanation is that while HCV infection has a negative effect on HIV, which reduces the effectiveness of HAART; no such effect occurs in HBV infection. [40, 51] Our study demonstrated that CH-B was more important during the early HAART era while CH-C is more important during recent years, and these temporal changes in the relative effects of CH-C and CH-B might be confounding the results. Therefore, further research is required to examine these changes over time to see if biological explanation about the possible differential effects of CH-B and CH-C on LR mortality can be uncovered.

HIV infection was associated with 80% higher liver-related mortality hazard, and we had expected to observe this association since HIV was found to have a negative effect on liver disease progression in several studies. [24, 26, 29, 31] However, we did not find an significant interaction between HIV and hepatitis for LRM, i.e. neither HIV nor hepatitis infection seemed to worsen the effect of the other infection among the co-infected individuals.

Our findings showed that HBV treatment was associated with decreased liver-related mortality. This is plausible since HBV treatment has been proved to be effective against viral hepatitis B infection. Though liver-related mortality hazard associated with HBV seemed to have decreased, CH-B remained one of the most important risk factors for LR mortality. Continuing effort on HBV prevention and treatment among HIV-infected patients are

necessary. On the other hand, HCV treatment was not associated with liver-related mortality. We had also expected such result since the effective treatment drugs were not available until late in the study. Very few participants were on HCV treatment during our study period which severely limited our power to examine this question. This might have contributed to our finding that CH-B had the higher LR mortality rate during the early HAART period while CH-C had the higher LR mortality rate in recent years. Though highly effective treatment for hepatitis C infection has been available since 2004, the hepatitis C infected patients are still poorly treated. One of the reasons is that anti-hepatitis C treatments cost too much, patients with low income are not able to afford the treatment. Another reason is the lack of awareness of hepatitis C infection. Because CH-C infection can have no symptoms for a long time, some patients may know that they are infected with CH-C, yet do not seek treatment until it has progressed to an advanced stage. Our study suggests that awareness and education for hepatitis C infection needs to be increased, and that more affordable drugs should be made available for these patients. Our study also showed a nearly 40% decreased liver-related mortality hazard among HIV-infected individuals who were treated with HAART, and that the protective effect of HAART was similar for both CH-B and CH-C infected individuals. This is in consistent with another study that found HAART to be associated with a lower probability of developing adverse liver-related events among the HIV/HCV co-infected patients. [39] For CH-B, some of the HAART drugs are active against hepatitis B virus, which likely contributed to the lower risk of LR mortality. Thus, the findings from our study suggest that HAART should be offered to anyone who is co-infected with viral hepatitis, and that more specific guidelines for HAART initiation may be helpful for these individuals.

Interestingly, we also found that though Caucasian race was not associated with all-cause mortality, it was associated with a more than doubling of the risk of liver-related mortality. A prior WIHS study reported that liver-related mortality was lower among African-American women than among Caucasian and Hispanic women. [11] The authors speculated that a genetic factor may play a role in the liver-related mortality, but in a subsequent study they demonstrated that polymorphism in the IFN-lambda region did not explain the race difference. [52] Other plausible explanations for the race difference include cultural or behavioral differences that were not measured or otherwise not included in our study. Lower education attainment and low income were also found to be risk factors for liver-related disease in our study which emphasizes the need to increase education and address SES related problems. High blood pressure is associated with more than twice higher of the liver-related mortality hazard. It is not clear what this finding means, but this might stem from reverse causality where advanced liver-disease fibrosis may have contributed to high blood pressure. However, this remains to be explored further.

There are several other limitations in our study. Firstly, our study combined the data in MACS and WIHS cohort to examine the liver-related mortality. The two cohorts are fundamentally different from each other in terms of gender, race, or socio-economic status, etc., so it was questionable whether meaningful inferences could be obtained from the combined data. However, we have performed the same analysis on both cohorts and did not find major difference in the results for liver-related mortality, so it was reasonable to

combine the observations in order to increase our power. Secondly, one significant limitation is that while HCV testing has been rigorously performed in MACS, the HCV testing in WIHS and the HBV testing in MACS has been less rigorous, and the HBV testing in WIHS was performed only at baseline. Thus, we may have misclassified participants according to HBV and/or HCV status. If this is true, then our results would most likely be biased toward the null, which in turn suggests that the findings from this study might be even stronger than the results we observed. Thirdly, more precise evaluation of liver disease progression can be achieved if we have information of the liver histology instead of liver-disease mortality. Finally, for many participants who died the determination of whether the death was liver-related was based on information recorded on death certificates. While likely to have resulted in the misclassification of some deaths, this would most likely have resulted in a bias toward the null for reasons analogous to those given above about the impact of misclassifying hepatitis status.

IMPLICATIONS

Our study is one of the first to examine all-cause and liver-related mortality rates during the HAART era. We demonstrated that the overall mortality rate has declined more than the LR mortality rate during the HAART era which helps to explain why liver disease has become a major cause of morbidity and mortality in recent years. We also observed that CH-B was the primary cause of liver-related deaths 20 years ago while CH-C is the primary cause today.

Importantly, HBV treatment is associated with a reduced LR mortality risk overall, and HAART is associated with a similar reduction among those infected with HIV. Collectively, our findings indicate an urgent need to increase the awareness of hepatitis and HIV co-infection, especially CH-C and HIV co-infection. Prevention, detection, treatment, and management are needed to address the issue. Also, further studies are needed to better examine hepatitis and HIV co-infection in the post-HAART era. HAART and HBV treatment has shown great importance in the HIV epidemic. Future public health studies should focus more on hepatitis treatment, especially the effectiveness and impact of hepatitis C treatment.

Table 1. Baseline Characteristics

	Overall		MACS		WIHS		p-value
	N	% *	N	% *	N	% *	
Total	6719	100	3148	100	3571	100	
Age							0.000
< 45 years	4914	73.1	1940	61.6	2974	83.3	
45 – 54 years	1380	20.5	868	27.6	512	14.3	
55 – 64 years	382	5.7	301	9.6	81	2.3	
>= 65 years	43	0.6	39	1.2	4	0.1	
Race							0.000
White	2951	43.9	2168	68.9	783	21.9	
Black	2931	43.6	781	24.8	2150	60.2	
Other	825	12.3	196	6.2	629	17.6	
Education							0.000
High school and lower	3062	45.6	667	21.2	2395	67.1	
College or some college	2646	39.4	1566	49.8	1080	30.2	
Graduate	990	14.7	912	29.0	78	2.2	
Income level per year **							0.000
<10,000	2719	42.4	729	23.8	1990	59.3	
>=10,000	3696	57.6	2331	76.2	1365	40.7	
Current Employment							0.000
No	2859	42.6	331	11.0	2528	71.1	
Yes	3718	55.3	2690	89.0	1028	28.9	
Smoking status							0.000
Never	2048	30.5	942	29.9	1106	31.0	
Former	1664	24.8	1055	33.5	609	17.1	
Current	2971	44.2	1127	35.8	1844	51.6	
Drinking Status							0.000
No drink	2380	35.9	521	16.7	1859	52.9	
1-3 drinks per week	2457	37.1	1378	44.3	1079	30.7	
4-13 drinks per week	1245	18.8	941	30.2	304	8.6	
>13 drinks per week	548	8.3	273	8.8	275	7.8	
Non-injection drug use status							0.000
Never	1454	21.6	551	17.9	903	25.4	
Former	2372	35.7	858	27.8	1514	42.6	
Current	2814	42.4	1678	54.4	1136	32.0	
Injection drug use							0.000
Never	5281	79.5	2729	88.4	2552	71.8	
Former	966	14.5	154	5.0	812	22.9	
Current	396	6.0	206	6.7	190	5.4	
Hypertension							0.000
No	4534	69.2	1784	59.7	2750	77.1	
Yes	2022	30.8	1203	40.3	819	23.0	
Diabetes							0.026
No	4829	94.3	1427	93.8	3402	95.3	
Yes	264	5.2	95	6.2	169	4.7	
Depression							0.000
No	4157	61.9	2263	71.9	1894	53.0	
Yes	2562	38.1	885	28.1	1677	47.0	

Table 1. Baseline Characteristics (continued)

	Overall		MACS		WIHS		p-value
	N	**%**	**N**	**%**	**N**	**%**	
HIV-infection							0.000
Negative	2505	37.3	1571	49.9	934	26.2	
Positive	4214	62.7	1577	50.1	2637	73.8	
Prior diagnose with AIDS (HIV+)							0.000
No	3379	80.2	1419	90.0	1960	74.3	
Yes	835	19.8	158	10.0	677	25.7	
HAART treatment (HIV+)							0.000
No	2482	58.9	1063	67.4	1419	53.8	
Yes	1728	41.0	511	32.4	1217	46.2	
Any hepatitis infection							0.000
No	5419	82.0	2787	88.5	2632	76.1	
Yes	1186	18.0	361	11.5	825	23.9	
Hepatitis B infection							0.000
Negative	6484	97.0	3017	95.8	3467	98.1	
Positive	199	3.0	131	4.2	68	1.9	
HBV treatment (HBsAg+)							0.000
No	140	70.4	75	57.3	65	95.6	
Yes	59	29.7	56	42.8	3	4.4	
Hepatitis C infection							0.000
Negative	5596	84.7	2907	92.3	2689	77.7	
Positive	1011	15.3	241	7.7	770	22.3	
HCV treatment (CH-C+)							0.000
No	1004	99.3	235	97.5	769	99.9	
Yes	7	0.7	6	2.5	1	0.1	

*The cutoff point for low income is 10,000 USD per year for MACS, and 12,000 USD per year for WIHS

Table 2. Cumulative Incidence Rates of all-cause mortality and LRM by infection status

	Total Person Years	Number of all-cause death	All-cause mortality per 1000 PYs	95% CI	Number of Liver-related death	Liver-related mortality per 1000 PYs	95% CI
Overall	67718	1028	15.18	14.28 – 16.14	153	2.26	1.93 – 2.65
HIV infected	42380	902	21.28	19.94 – 22.72	138	3.26	2.76 – 3.85
HBV infected	1569	52	33.14	25.25 – 43.49	19	12.11	7.72 – 18.99
HCV infected	10065	432	42.92	39.06 – 47.17	113	11.23	9.34 – 13.50

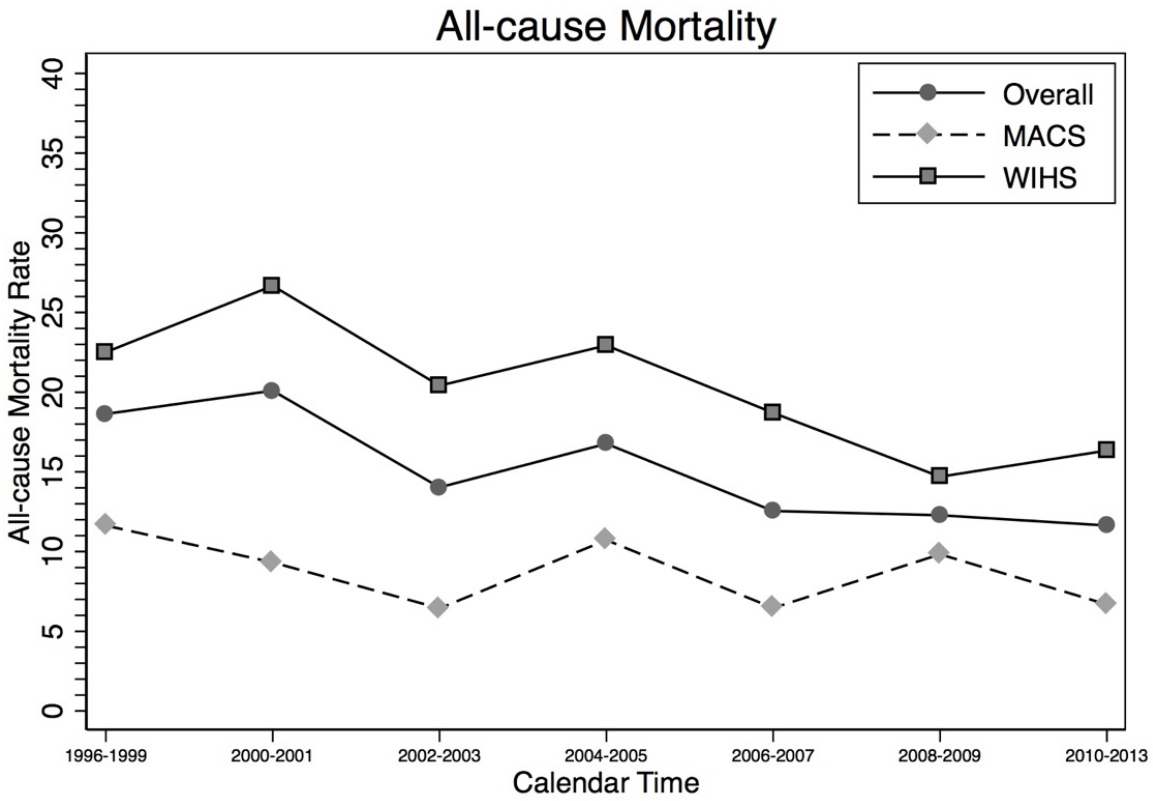

Figure 1. All-cause Mortality Rates per 1000 PYs by Calendar Year

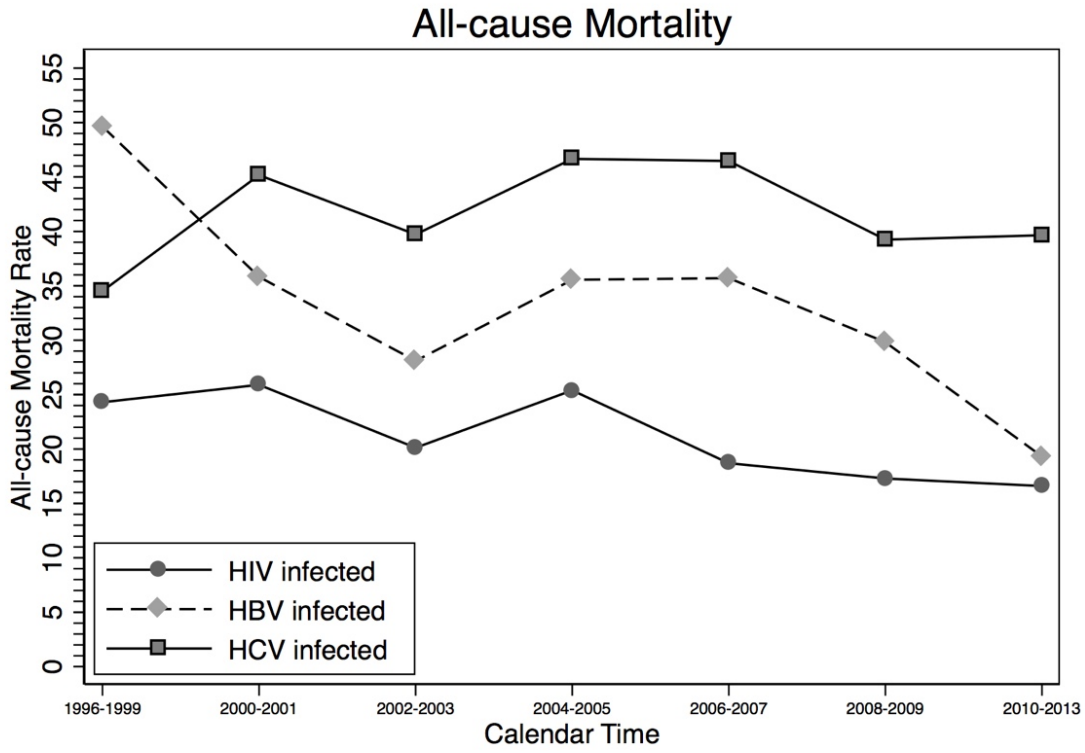

Figure 2. All-cause Mortality rate per 1000 PYs by Calendar Years and Infectious Status

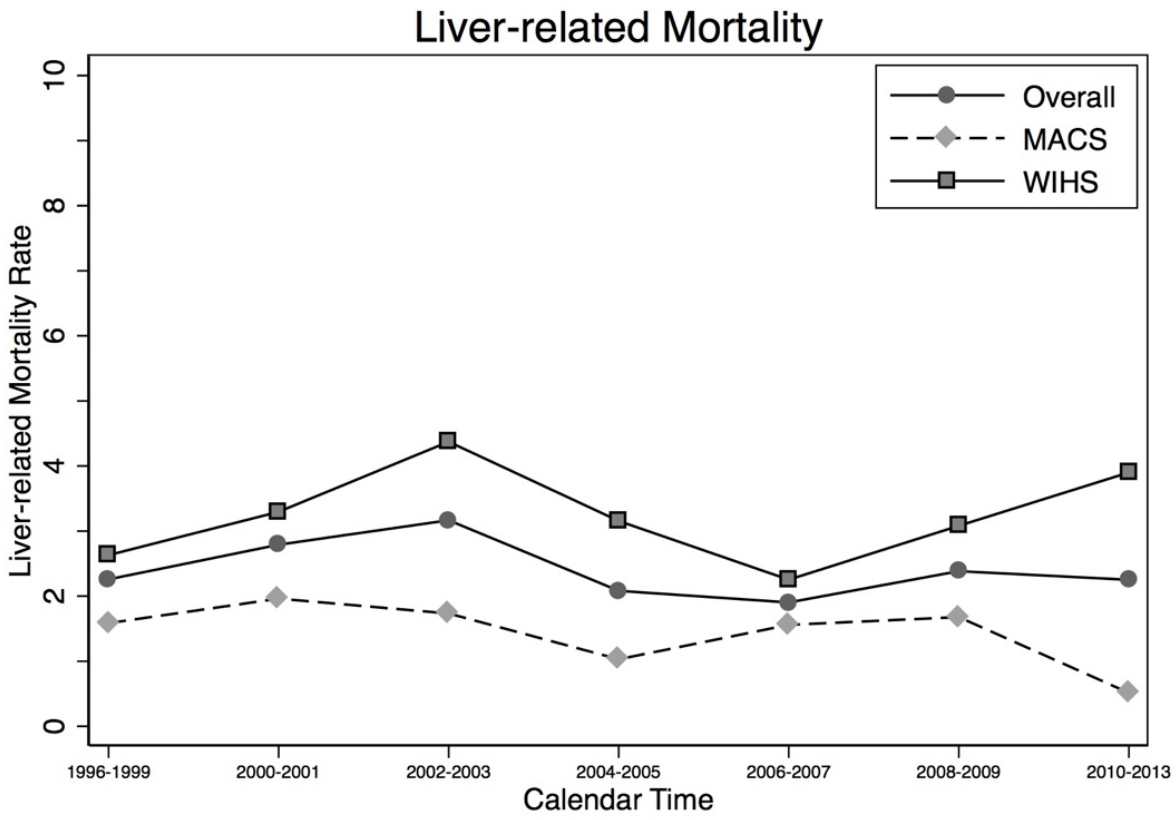

Figure 3. Liver-related Mortality Rates per 1000 PYs by Calendar Year

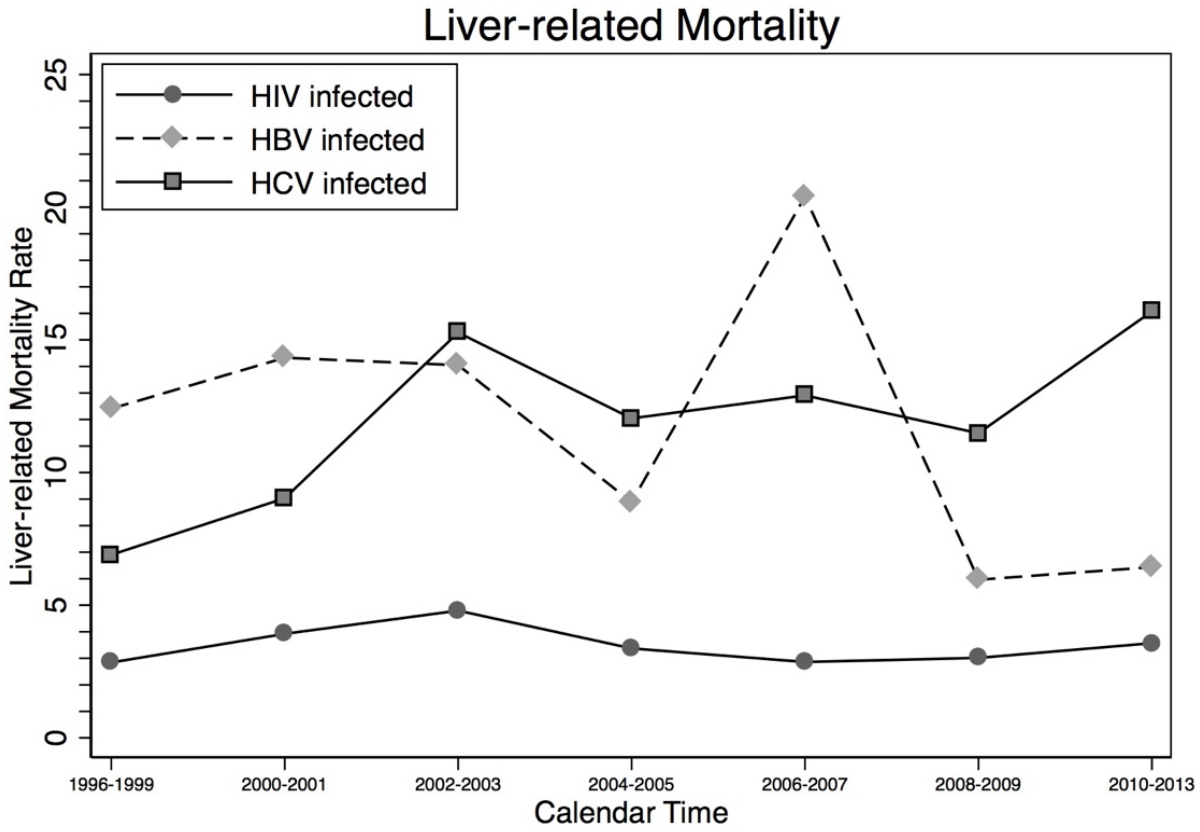

Figure 4. Liver-related Mortality Rates per 1000 PYs by Calendar Year and Infection Status

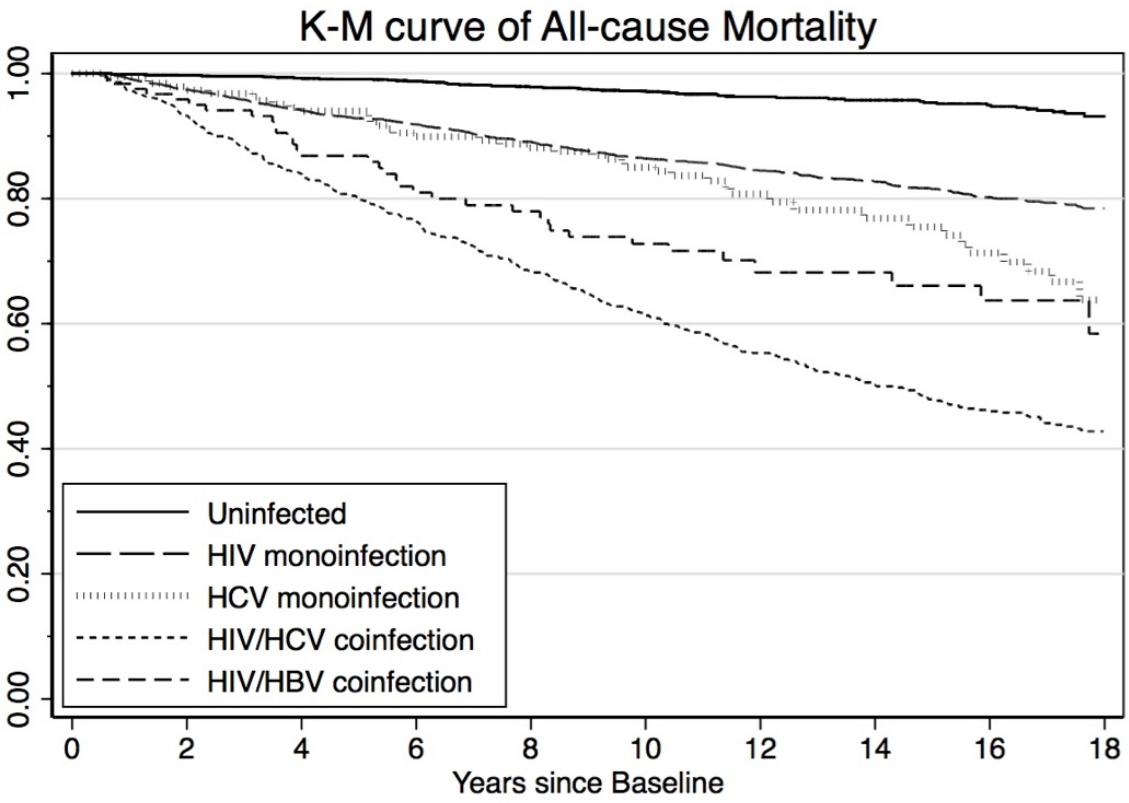

Figure 5. Kaplan-Meier Survival Probability of All-cause Mortality by HIV, HBV, HCV infection

Note: Mono-infection with HBV, co-infection with HBV and HCV, triple-infection with HIV, HBV, and HCV were excluded because of limited observations.

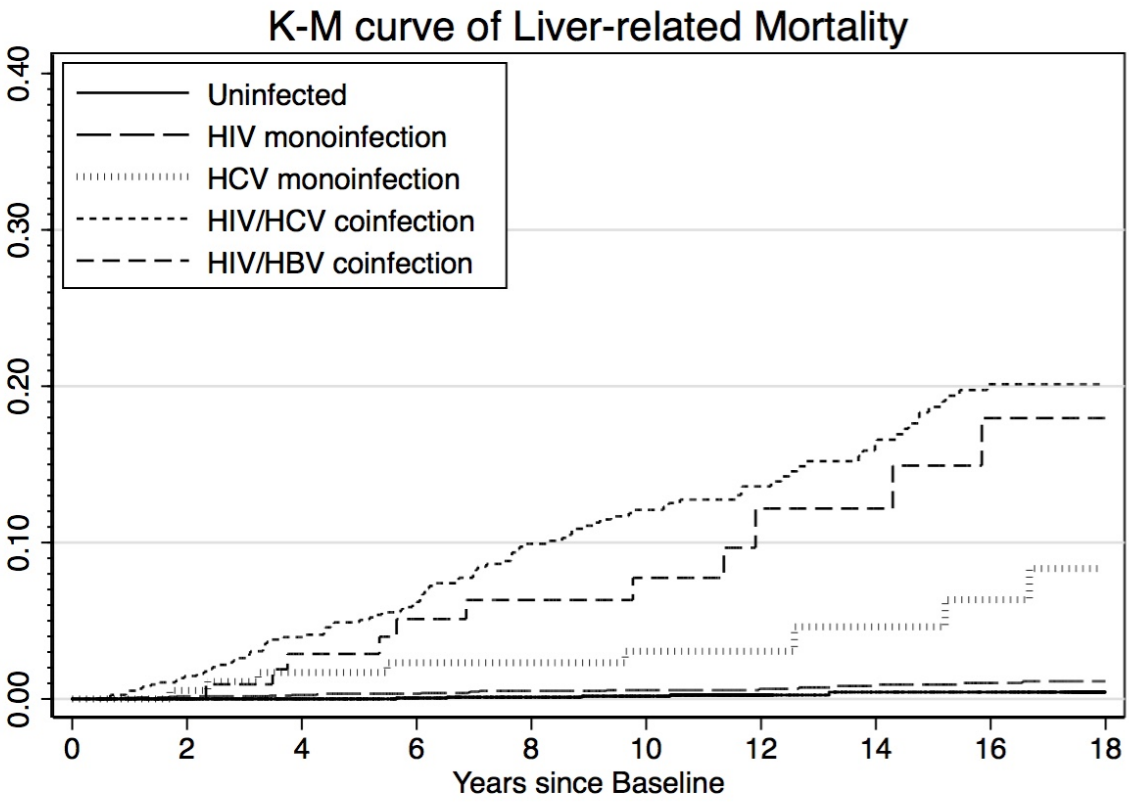

Figure 6. Kaplan-Meier Cumulative Incidence of Liver-related Mortality by HIV, HBV, HCV infection

Note: Mono-infection with HBV, co-infection with HBV and HCV, triple-infection with HIV, HBV, and HCV were excluded because of limited observations.

Table 3. Univariate and Multivariate Analysis for All-cause Mortality

	Univariate		Multivariate		
	HR	95% CI	HR	95% CI	p-value
Cohort					
MACS	1		1		
WIHS	2.44	2.12 – 2.80	1.16	0.95 – 1.43	0.145
Age category					
< 45 years	1		1		
45 – 54 years	1.35	1.17 – 1.56	1.18	1.00 – 1.39	0.049
55 – 64 years	1.46	1.21 – 1.76	1.77	1.41 – 2.21	0.000
>= 65 years	1.50	1.10 – 2.04	3.25	2.25 – 4.69	0.000
Race (white vs. others)	0.51	0.45 – 0.59	1.04	0.87 – 1.23	0.682
High school education or lower	2.13	1.88 – 2.43	1.15	0.98 – 1.35	0.090
Income < 10,000 per year*	3.24	2.84 – 3.70	1.67	1.42 – 1.95	0.000
Currently under employment	0.26	0.23 – 0.30			
History of smoking	2.38	1.98 – 2.86	1.57	1.29 – 1.92	0.000
More than one drink per day	1.02	0.80 – 1.31			
Drug use status					
Never	1				
Only non-injection drug use	1.20	0.94 – 1.52			
Injection drug use	4.09	3.23 – 5.17			
Have hypertension	1.54	1.35 – 1.74	1.56	1.35 – 1.80	0.000
Have diabetes	1.48	1.24 – 1.76			
Have depression	2.78	2.45 – 3.15	1.69	1.47 – 1.95	0.000
HIV infection	4.31	3.58 – 5.20	2.10	1.68 – 2.64	0.000
Diagnosed with AIDS	5.45	4.82 – 6.18	2.71	2.31 – 3.17	0.000
Any hepatitis infection	4.27	3.77 – 4.83			
Hepatitis B infection	2.22	1.68 – 2.93	2.38	1.76 – 3.22	0.000
Hepatitis C infection	4.25	3.75 – 4.81	2.04	1.75 – 2.37	0.000

* The cutoff point for low income is 10,000 USD per year for MACS, and 12,000 USD per year for WIHS

Table 4. Univariate and Multivariate Analysis for Liver-related Mortality

	Univariate		Multivariate					
			Model 1			Model 2		
	HR	95% CI	HR	95% CI	p-value	HR	95% CI	p-value
Cohort								
MACS	1		1			1		
WIHS	2.32	1.63 – 3.31	0.92	0.56 – 1.52	0.757	1.06	0.63 – 1.78	0.872
Age category								
< 45 years	1		1			1		
45 – 54 years	1.84	1.26 – 2.69	1.09	0.72 – 1.67	0.675	1.18	0.78 – 1.81	0.435
55 – 64 years	1.90	1.18 – 3.07	1.38	0.77 – 2.45	0.277	1.47	0.83 – 2.62	0.185
>= 65 years	0.75	0.23 – 2.43	1.63	0.47 – 5.63	0.438	1.64	0.47 – 5.67	0.437
Race (white vs. others)	0.76	0.55 – 1.06	2.42	1.63 – 3.59	0.000	2.39	1.60 – 3.55	0.000
High school education or lower	2.68	1.90 – 3.78	1.72	1.12 – 2.65	0.013	1.80	1.17 – 2.79	0.000
Income < 10,000 per year*	4.36	3.05 – 6.22	2.09	1.37 – 3.19	0.001	2.13	1.41 – 3.24	0.000
Currently under employment	0.26	0.18 – 0.37						
History of smoking	3.30	1.94 – 5.63						
More than one drink per day	1.01	0.53 – 1.93						
Drug use status								
Never used drugs	1							
Only non-injection drug use	1.36	0.57 – 3.26						
Injection drug use	12.04	5.28 – 27.42						
Have hypertension	2.22	1.57 – 3.12	2.17	1.50 – 3.15	0.000	2.20	1.51 – 3.20	0.000
Have diabetes	1.54	0.98 – 2.41						
Have depression	2.72	1.96 – 3.77						
HIV infection	5.45	3.20 – 9.29	1.96	1.06 – 3.62	0.032	1.84	0.99 – 3.42	0.053
Diagnosed with AIDS	5.54	4.01 – 7.67	2.21	1.50 – 3.27	0.000	2.30	1.56 – 3.41	0.000
Any hepatitis infection	24.26	15.79 – 37.26	17.53	10.66 – 28.82	0.000			
Hepatitis B infection	5.96	3.68 – 9.64				9.09	5.35 – 15.43	0.000
Hepatitis C infection	16.77	11.61 – 24.22				11.63	7.52 – 17.98	0.000

* The cutoff point for low income is 10,000 USD per year for MACS, and 12,000 USD per year for WIHS

Table 5. Univariate and Multivariate Analysis for Liver-related Mortality among HIV-positive individuals

	Univariate		Multivariate					
			Model3			Model 4		
	HR	95% CI	HR	95% CI	p-value	HR	95% CI	p-value
Cohort								
MACS	1		1			1		0.807
WIHS	1.80	1.23 – 2.65	0.96	0.56 – 1.66	0.886	.93	0.53 – 1.64	
Age category								
< 45 years	1		1			1		
45 – 54 years	1.88	1.27 – 2.79	1.14	0.74 – 1.77	0.553	1.14	0.74 – 1.78	0.549
55 – 64 years	2.58	1.54 – 4.32	1.62	0.88 – 2.97	0.118	1.62	0.88 – 2.97	0.120
>= 65 years	0.57	0.08 – 4.22	0.88	0.12 – 6.69	0.900	0.87	0.11 – 6.66	0.897
Race (white vs. others)	0.97	0.68 – 1.36	2.37	1.56 – 3.59	0.000	2.37	1.57 – 3.60	0.000
High school education or lower	2.20	1.53 – 3.16	1.83	1.16 – 2.89	0.010	1.83	1.16 – 2.90	0.010
Income < 10,000 per year*	3.51	2.40 – 5.11	1.92	1.24 – 2.98	0.003	1.92	1.31 – 2.85	0.003
Currently under employment	0.34	0.24 – 0.50						
History of smoking	3.56	2.01 – 6.31						
More than one drink per day	1.16	0.57 – 2.37						
Drug use status								
Never used drugs	1							
Only non-injection drug use	1.31	0.54 – 3.19						
Injection drug use	10.18	4.46 – 23.23						
Have hypertension	2.24	1.57 – 3.19	1.93	1.31 – 2.84	0.001	1.93	1.31 – 2.85	0.001
Have diabetes	1.38	0.85 – 2.24						
Have depression	2.36	1.67 – 3.34						
Diagnosed with AIDS	3.88	2.73 – 5.52	2.37	1.56 – 3.59	0.000	2.37	1.57 – 3.60	0.000
Hepatitis B infection	4.34	2.61 – 7.22	8.07	4.62 – 14.08	0.000	8.04	4.61 – 14.04	0.000
Hepatitis C infection	14.39	9.64 – 21.49	11.95	7.46 – 19.14	0.000	11.89	7.42 – 19.05	0.000
HAART	0.55	0.39 – 0.78	0.61	0.42 – 0.88	0.009			
HBV-active HAART						0.65	0.41 – 1.04	0.071
Not HBV-active HAART						0.58	0.37 – 0.90	0.016

* The cutoff point for low income is 10,000 USD per year for MACS, and 12,000 USD per year for WIHS

REFERENCES

1. Wada, N., et al., *Cause-specific life expectancies after 35 years of age for human immunodeficiency syndrome-infected and human immunodeficiency syndrome-negative individuals followed simultaneously in long-term cohort studies, 1984-2008.* Am J Epidemiol, 2013. **177**(2): p. 116-25.
2. Palella, F.J., Jr., et al., *Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study.* J Acquir Immune Defic Syndr, 2006. **43**(1): p. 27-34.
3. Bhaskaran, K., et al., *Changes in the risk of death after HIV seroconversion compared with mortality in the general population.* JAMA, 2008. **300**(1): p. 51-9.
4. Fischl, M.A., et al., *The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial.* N Engl J Med, 1987. **317**(4): p. 185-91.
5. Hammer, S.M., et al., *A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team.* N Engl J Med, 1997. **337**(11): p. 725-33.
6. Gulick, R.M., et al., *Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy.* N Engl J Med, 1997. **337**(11): p. 734-9.
7. Moore, R.D., J.C. Keruly, and J.G. Bartlett, *Improvement in the health of HIV-infected persons in care: reducing disparities.* Clin Infect Dis, 2012. **55**(9): p. 1242-51.
8. O'Malley, M., et al., *Maryland Vital Statistics Annual Report 2010*, Department of Health and Mental Hygiene. Retrieved from http://dhmh.maryland.gov/vsa/Documents/10annual.pdf
9. Engels, E.A., et al., *Cancer risk in people infected with human immunodeficiency virus in the United States.* Int J Cancer, 2008. **123**(1): p. 187-94.
10. Shahbaz, S., et al., *Cardiovascular disease in human immunodeficiency virus infected patients: A true or perceived risk?* World J Cardiol, 2015. **7**(10): p. 633-44.
11. Sarkar, M., et al., *Lower liver-related death in African-American women with human immunodeficiency virus/hepatitis C virus coinfection, compared to Caucasian and Hispanic women.* Hepatology, 2012. **56**(5): p. 1699-705.
12. Smit, C., et al., *Effective therapy has altered the spectrum of cause-specific mortality following HIV seroconversion.* AIDS, 2006. **20**(5): p. 741-9.
13. Weber, R., et al., *Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study.* Arch Intern Med, 2006. **166**(15): p. 1632-41.

14. Puoti, M., et al., *Hepatitis B virus co-infection in human immunodeficiency virus-infected subjects.* AIDS Rev, 2002. **4**(1): p. 27-35.
15. Kellerman, S.E., et al., *Prevalence of chronic hepatitis B and incidence of acute hepatitis B infection in human immunodeficiency virus-infected subjects.* J Infect Dis, 2003. **188**(4): p. 571-7.
16. Koziol, D.E., et al., *A comparison of risk factors for human immunodeficiency virus and hepatitis B virus infections in homosexual men.* Ann Epidemiol, 1993. **3**(4): p. 434-41.
17. Alter, M.J., *Epidemiology of viral hepatitis and HIV co-infection.* J Hepatol, 2006. **44**(1 Suppl): p. S6-9.
18. Operskalski, E.A., et al., *Factors associated with hepatitis C viremia in a large cohort of HIV-infected and -uninfected women.* J Clin Virol, 2008. **41**(4): p. 255-63.
19. Sherman, K.E., et al., *Hepatitis C Virus prevalence among patients infected with Human Immunodeficiency Virus: a cross-sectional analysis of the US adult AIDS Clinical Trials Group.* Clin Infect Dis, 2002. **34**(6): p. 831-7.
20. Kovacs, A., et al., *Activation of CD8 T cells predicts progression of HIV infection in women coinfected with hepatitis C virus.* J Infect Dis, 2010. **201**(6): p. 823-34.
21. Sulkowski, M.S., et al., *Hepatitis C and progression of HIV disease.* JAMA, 2002. **288**(2): p. 199-206.
22. Chun, H.M., et al., *Hepatitis B virus coinfection negatively impacts HIV outcomes in HIV seroconverters.* J Infect Dis, 2012. **205**(2): p. 185-93.
23. Nikolopoulos, G.K., et al., *Impact of hepatitis B virus infection on the progression of AIDS and mortality in HIV-infected individuals: a cohort study and meta-analysis.* Clin Infect Dis, 2009. **48**(12): p. 1763-71.
24. Di Martino, V., et al., *Influence of HIV infection on the response to interferon therapy and the long-term outcome of chronic hepatitis B.* Gastroenterology, 2002. **123**(6): p. 1812-22.
25. Colin, J.F., et al., *Influence of human immunodeficiency virus infection on chronic hepatitis B in homosexual men.* Hepatology, 1999. **29**(4): p. 1306-10.
26. Thio, C.L., et al., *HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS).* Lancet, 2002. **360**(9349): p. 1921-6.
27. Puoti, M., et al., *Natural history of chronic hepatitis B in co-infected patients.* J Hepatol, 2006. **44**(1 Suppl): p. S65-70.
28. Vento, S., et al., *Reactivation of hepatitis B in AIDS.* Lancet, 1989. **2**(8654): p. 108-9.
29. Kirk, G.D., et al., *HIV, age, and the severity of hepatitis C virus-related liver disease: a cohort study.* Ann Intern Med, 2013. **158**(9): p. 658-66.
30. Patel, P., et al., *Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003.* Ann Intern Med, 2008. **148**(10): p. 728-36.

31. Graham, C.S., 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): p. 562-9.
32. Thein, H.H., et al., *Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis.* AIDS, 2008. **22**(15): p. 1979-91.
33. Gunthard, H.F., et al., *Antiretroviral treatment of adult HIV infection: 2014 recommendations of the International Antiviral Society-USA Panel.* JAMA, 2014. **312**(4): p. 410-25.
34. Hoffmann, C.J., et al., *Hepatitis B virus infection and response to antiretroviral therapy (ART) in a South African ART program.* Clin Infect Dis, 2008. **47**(11): p. 1479-85.
35. Cornberg, M., et al., *[New direct-acting antiviral agents for the treatment of chronic hepatitis C in 2014].* Internist (Berl), 2014. **55**(4): p. 390-400.
36. Ng, V. and S. Saab, *Effects of a sustained virologic response on outcomes of patients with chronic hepatitis C.* Clin Gastroenterol Hepatol, 2011. **9**(11): p. 923-30.
37. Singal, A.G., et al., *Long-term benefit of hepatitis C therapy in a safety net hospital system: a cross-sectional study with median 5-year follow-up.* BMJ Open, 2013. **3**(9): p. e003231.
38. Health, H.C.N.D.R.A.L., *Approved Treatments for Hepatitis C*. 2016.
39. Limketkai, B.N., et al., *Relationship of liver disease stage and antiviral therapy with liver-related events and death in adults coinfected with HIV/HCV.* JAMA, 2012. **308**(4): p. 370-8.
40. Greub, G., 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): p. 1800-5.
41. Anderson, J.P., et al., *Antiretroviral therapy reduces the rate of hepatic decompensation among HIV- and hepatitis C virus-coinfected veterans.* Clin Infect Dis, 2014. **58**(5): p. 719-27.
42. Shafran, S.D., *Early initiation of antiretroviral therapy: the current best way to reduce liver-related deaths in HIV/hepatitis C virus-coinfected patients.* J Acquir Immune Defic Syndr, 2007. **44**(5): p. 551-6.
43. Bonacini, M., et al., *Survival in patients with HIV infection and viral hepatitis B or C: a cohort study.* AIDS, 2004. **18**(15): p. 2039-45.
44. Soriano, V., et al., *Treatment of chronic hepatitis B or C in HIV-infected patients with dual viral hepatitis.* J Infect Dis, 2007. **195**(8): p. 1181-3.
45. Kaslow, R.A., et al., *The Multicenter AIDS Cohort Study: rationale, organization, and selected characteristics of the participants.* Am J Epidemiol, 1987. **126**(2): p. 310-8.

46. Barkan, S.E., et al., *The Women's Interagency HIV Study. WIHS Collaborative Study Group.* Epidemiology, 1998. **9**(2): p. 117-25.
47. The Center for the Analysis of MACS Data (CAMACS), (Dec. 2013), *Dossier Multicent AIDS Cohort Study.* Retrieved from https://www.statepi.jhsph.edu/macs/dossier/MACSdossier.pdf.
48. WIHS Data Management and Analysis Center (WDMAC), (Oct. 2015), *WIHS Dossier.* Retrieved from https://statepiaps.jhsph.edu/wihs/invest-info/dossier.pdf
49. Falade-Nwulia, O., et al., *Comparative risk of liver-related mortality from chronic hepatitis B versus chronic hepatitis C virus infection.* Clin Infect Dis, 2012. **55**(4): p. 507-13.
50. Fine, J.P. and R.J. Gray, *A proportional hazards model for the subdistribution of a competing risk.* Journal of the American Statistical Association, 1999. **94**(446): p. 496-509.
51. Konopnicki, D., et al., *Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort.* AIDS, 2005. **19**(6): p. 593-601.
52. Sarkar, M., et al., *Association of IFNL3 and IFNL4 polymorphisms with liver-related mortality in a multiracial cohort of HIV/HCV-coinfected women.* J Viral Hepat, 2015.

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RESEARCH EXPERIENCE

Researcher — 11/2015 - present
Department of Epidemiology
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- Conducted original research for thesis project
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- Conducted survival analysis, longitudinal data analysis using STATA
- Prepared manuscript and poster for thesis

Student Trainee 10/2015 -
Generation Tomorrow Program present
Center for AIDS Research (CFAR), Johns Hopkins University, Baltimore, MD

- Performed HCV testing and counseling in Baltimore community
- Directing and connecting patients to health care in Hepatitis C Clinic
- Designed and distributed flyers and business cards, assisting in Cure Clubs and outreach events to increase awareness of HCV

Research Assistant 04/2015 -
Jhpiego, an affiliate of Johns Hopkins University, Baltimore, MD; Centers for Disease Control and Prevention (CDC), Atlanta, GA present

- Conducting systematic review to evaluate the effect of Voluntary Medical Male Circumcision (VMMC) on their female partners
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Research Assistant 08/2015 -
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Johns Hopkins Institute for Clinical and Translational Research (ICTR), Baltimore, MD

- Recruited and interviewed patients from Johns Hopkins Outpatient Center, Bayview Medical Center, Health Care & Surgery Center - Green Spring Station
- Assisted in data management using REDCap

Research Assistant 07/2011 -
Centers for Disease Control and Prevention (CDC), Wuhan, China 10/2013

- Amplified Hepatitis C virus (HCV) RNA using RT-PCR and constructed phylogenetic trees for HCV using MEGA software to investigate HCV genotype distribution among injection drug users under Methadone Maintenance Treatment (MMT) Program
- Wrote a manuscript and presented at 75th the College on Problems of Drug Dependence (CPDD) Annual Scientific Meeting and the 2013 National Institute on Drug Abuse (NIDA) International Forum, San Diego, USA
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Research Assistant 03/2010-
Department of Histology & Embryology 12/2010
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- Fed laboratory animals for Huntington Disease (HD) model
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Research Assistant 07/2009-
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- Reviewed the literatures on Human Papilloma Virus (HPV) genotype distribution
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- Directly interacted with patients, wrote medical records
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ARTICLES (Published and Under Review)

S. Zhou, E. Cella, et al. Population dynamics of HCV subtypes in injecting drug-users on methadone maintenance treatment in China associated with economic and health reform (Submitted to Scientific Reports) 12/2015

W. Zhou, X. Wang, **S. Zhou**, et al., Hepatitis C seroconversion in methadone maintenance treatment programs in Wuhan, China. Addiction, 2015. **110**(5): p. 796-802. 01/2015

W. Zhou, M. Zhao, X. Wang, R. Schilling, **S. Zhou**, et al., Treatment adherence and health outcomes in MSM with HIV/AIDS: patients enrolled in "one-stop" and standard care clinics in Wuhan China. PLoS One, 2014. **9**(12): p. e113736. 10/2014

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M. Zhao, J. Cai, **S. Zhou**, et al. An epidemiological analysis on genital warts and subtyping of Human Papillomavirus. Chinese Journal of AIDS & STD, vol16 no.3, p. 281-283.

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