Published in final edited form as:

AIDS. 2009 September 10; 23(14): 1881–1889. doi:10.1097/QAD.0b013e32832e463a.

Hepatitis B and long-term HIV outcomes in co-infected HAART recipients

Christopher J Hoffmann¹, Eric C Seaberg², Stephen Young³, Mallory D Witt⁴, Kristin D'Acunto⁵, John Phair⁶, and Chloe L Thio¹

¹ Division of Infectious Diseases, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD

² Division of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

³ University of New Mexico School of Medicine, Albuquerque, NM

⁴ David Geffen School of Medicine at UCLA, Los Angeles Biomedical Research Institute at Harbor-UCLA, Torrance, CA

⁵ Department of Infectious Diseases and Microbiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA

⁶ Division of Infectious Diseases, Northwestern University Feinberg School of Medicine, Chicago, IL

Abstract

Chronic hepatitis B (CH-B) is common among HIV-infected individuals and increases liver-related mortality in the absence of highly active antiretroviral therapy (HAART). The impact of CH-B on long-term HAART outcomes has not been fully characterized.

Methods—To address this question, HAART initiators enrolled in the Multicenter AIDS Cohort Study (MACS) were retrospectively analyzed. Subjects were classified by hepatitis B category based on serology at the time of HAART initiation. The association of CH-B with mortality, AIDS defining illnesses, CD4 rise, and HIV suppression was assessed using regression analysis.

Corresponding Author: Christopher J Hoffmann, Johns Hopkins School of Medicine, 1830 E. Monument St. Rm 401, Baltimore, MD 21205, fax: 410-955-7889. choffmann@jhmi.edu.

Conflicts of Interest: No conflicts

The Multicenter AIDS Cohort Study (MACS) includes the following: Baltimore: The Johns Hopkins University Bloomberg School of Public Health: Joseph B. Margolick (Principal Investigator), Haroutune Armenian, Barbara Crain, Adrian Dobs, Homayoon Farzadegan, Joel Gallant, John Hylton, Lisette Johnson, Shenghan Lai, Ned Sacktor, Ola Selnes, James Shepard, Chloe Thio. Chicago: Howard Brown Health Center, Feinberg School of Medicine, Northwestern University, and Cook County Bureau of Health Services: John P. Phair (Principal Investigator), Joan S. Chmiel (Co-Principal Investigator), Sheila Badri, Bruce Cohen, Craig Conover, Maurice O'Gorman, David Ostrow, Frank Palella, Daina Variakojis, Steven M. Wolinsky. Los Angeles: University of California, UCLA Schools of Public Health and Medicine: Roger Detels (Principal Investigator), Barbara R. Visscher (Co-Principal Investigator), Aaron Aronow, Robert Bolan, Elizabeth Breen, Anthony Butch, Thomas Coates, Rita Effros, John Fahey, Beth Jamieson, Otoniel Martínez-Maza, Eric N. Miller, John Oishi, Paul Satz, Harry Vinters, Dorothy Wiley, Mallory Witt, Otto Yang, Stephen Young, Zuo Feng Zhang. Pittsburgh: University of Pittsburgh, Graduate School of Public Health: Charles R. Rinaldo (Principal Investigator), Lawrence Kingsley (Co-Principal Investigator), James T. Becker, Robert W. Evans, John Mellors, Sharon Riddler, Anthony Silvestre. Data Coordinating Center: The Johns Hopkins University Bloomberg School of Public Health: Lisa P. Jacobson (Principal Investigator), Alvaro Muñoz (Co-Principal Investigator), Stephen R. Cole, Christopher Cox, Gypsyamber D'Souza, Stephen J. Gange, Janet Schollenberger, Eric C. Seaberg, Sol Su. NIH: National Institute of Allergy and Infectious Diseases: Robin E. Huebner; National Cancer Institute: Geraldina Dominguez; National Heart, Lung and Blood Institute: Cheryl McDonald. UO1-AI-35042, 5-MO1-RR-00722 (GCRC), UO1-AI-35043, UO1-AI-37984, UO1-AI-35039, UO1-AI-35040, UO1-AI-37613, UO1-AI-35041. Website located at <http://www.statepi.jhsph.edu/mac/mac.html>.

Results—Of 816 men followed for a median of 7 years on HAART, 350 were never HBV infected, 357 had past infection, 45 had CH-B, and 64 were only core-antibody positive. Despite HAART, AIDS-related mortality was the most common cause of death (8.3/1000 person-years (PYs)). It was highest in those with CH-B (17/1000 PYs, 95% CI 7.3, 42) and lowest among never HBV infected (2.9/1000 PYs, 95% CI 1.4, 6.4). In a multivariable model, patients with CH-B had a 2.7-fold higher incidence of AIDS-related mortality compared to those never infected ($P=0.08$). Non-AIDS-related mortality was also highest among those with CH-B (22/1000 PYs), primarily due to liver disease (compared to never infected, adjusted HR 4.1, $p=0.04$). There was no significant difference in AIDS defining events, HIV RNA suppression, and CD4 increase.

Conclusion—In HIV-infected patients receiving long-term HAART, HBV status did not influence HIV suppression or CD4 increase. However, mortality was highest among those with CH-B and was mostly due to liver disease despite HBV-active HAART.

Keywords

hepatitis B; HIV; HAART; CD4; mortality; isolated core hepatitis B

Background

Highly active antiretroviral therapy (HAART) has increased the life expectancy of HIV-infected individuals who maintain long-term suppression of HIV replication and restore their CD4 counts [1–3]. Factors such as the initial HAART regimen, baseline HIV RNA, adherence, and side effects influence the success of achieving long-term HIV RNA suppression; however, it is unclear whether hepatitis B virus (HBV) co-infection affects long-term response to HAART. Chronic hepatitis B (CH-B) occurs in 5–10% of HIV-infected individuals and its long-term influences on HIV RNA suppression, CD4 recovery, and mortality while on HAART are not fully characterized. Several studies of HIV-HBV co-infected individuals have examined the short-term response to HAART and are inconsistent. An Italian study found no difference in CD4 response between HIV-HBV co-infected and HIV mono-infected individuals [4]. A Thai study found a smaller increase in CD4 cell count during the first 4 to 8 weeks of HAART among hepatitis B surface antigen (HBsAg) positive compared to HBsAg negative subjects [5]. In two Taiwanese studies, HIV-HBV co-infected subjects were less likely to achieve HIV RNA suppression than HIV mono-infected individuals receiving 24 months of HAART [6,7]. Two other studies have found similar rates of HIV suppression and CD4 rise when comparing subjects with and without HBsAg [8,9].

As HAART use expands in areas with high rates of CH-B, it is important to determine if past or current HBV infection influences the long-term HAART response. To address this question, we studied HIV-infected subjects enrolled in the prospective Multicenter AIDS Cohort Study (MACS), assessing the effect of HBV status on mortality and HIV outcomes for up to ten years following HAART initiation.

Methods

Study Population

The MACS prospectively follows men who report having had sex with men from four metropolitan areas in the USA (Baltimore, MD; Chicago, IL; Pittsburgh, PA; and Los Angeles, CA) and has had three recruitment periods: April 1984 to March 1985, 1987 to 1991, and 2001 to 2003 [10]. This current study included men who initiated HAART while enrolled in the MACS and who had sufficient HBV serologic data to be classified into a specific HBV infection category, as described below.

HAART was defined according to guidelines from the DHHS/Kaiser Panel [11]. The following regimens were considered to be HAART: (a) two or more nucleoside reverse transcriptase inhibitors (NRTIs) in combination with at least one protease inhibitor (PI) or one non-nucleoside reverse transcriptase inhibitor (NNRTI); (b) one NRTI in combination with at least one PI and at least one NNRTI; (c) ritonavir and saquinavir in combination with one NRTI and no NNRTIs; and (d) abacavir or tenofovir with three NRTIs in the absence of both PIs and NNRTIs.

The date of HAART initiation (HI) was estimated as the midpoint between the last visit at which the subject was not on HAART and the first visit at which a subject reported having started HAART. Only subjects whose HI date could be estimated within one year were included in this study.

Men were prospectively followed every six months from HI (earliest 1996) until death, date of last visit, or March 31, 2006. Alcohol consumption and injection drug use were assessed by self report at each follow-up visit and categorized as never, former, or current use. Causes of death were obtained from death certificates, autopsy report, or personal contacts.

HBV infection status

We classified each participant's HBV status using the HBsAg, hepatitis B surface antibody (anti-HBs), and hepatitis B core antibody (anti-HBc) results obtained before HI using the following categories: (1) 'never infected' defined as either negative for all HBV serology or only anti-HBs positive; (2) 'past infection' defined as anti-HBs and anti-HBc positive; (3) 'CH-B' defined as HBsAg positive on two occasions >6 months apart; and (4) 'isolated core' defined as positive for anti-HBc and negative for the other serologies. To select the specific results on which to base each participant's HBV status, we first looked for the latest serology results obtained prior to HI. If these results were not obtained within 18 months prior to HI, we then looked for serology results obtained at the first visit <6 months following HI. All participants whose serology results were available during this window ranging from 18 months before HI to 6 months after HI were classified according to the HBV algorithm defined above. For all other HIs, we looked for the latest results obtained prior to HI and the earliest results obtained following HI. If these two results yielded the same HBV classification as defined above, then HBV status was based on these results. All participants who only had serology results obtained >6 months following HI were reviewed, and those who were never infected with HBV (category 1 above) were also included. Finally, all persons classified as having CH-B were reviewed to confirm that they had a second HBsAg positive result obtained more than 6 months before or following the index result. The study was approved by the Institutional Review Boards at each MACS site, and all participants provided written informed consent.

Laboratory testing

HBV serologic testing was performed with EIA assays (Abbott Laboratories, Abbott Park, IL, USA). HBV DNA levels were determined on subjects with isolated core serology using the Artus HBV LC PCR kit (Qiagen, Valencia, CA, U.S.A.) with a detection limit of 40 IU/ml. HCV antibody status was assayed by approved third-generation EIA. HCV positive was defined as a single positive assay without HCV RNA testing. Hepatitis B resistance mutations were identified by sequencing a nested 1122 base-pair HBV Polymerase product (primers available upon request). Substitutions were identified by comparison to a reference sequence using SeqScapeR version 2.5 (Applied Biosystems). CD4 count was assayed by flow cytometry (Becton Dickinson, Mountain View, California). HIV RNA levels were determined using Roche Ultrasensitive RNA PCR assay (Hoffman-LaRoche, Nutley, NJ, U.S.A.) with a detection limit of 50 copies/ml.

Analysis

The primary outcome was death, which was divided into AIDS- and non-AIDS-related causes based on the CDC AIDS case definitions [12]. Secondary outcomes included the incidence of an AIDS-defining illness (ADI), HIV RNA suppression (< 400 copies/mL), and CD4 count rise.

Continuous data were compared using the Kruskal-Wallis test and proportions were compared using chi-square tests. We calculated incidence rate ratios (IRR) to assess the association of selected covariates with survival and ADI events using Poisson regression.

For the HIV RNA suppression analysis, we used logistic regression with robust variance estimates using generalized estimating equations (GEE) with unstructured correlation matrices to estimate the crude and adjusted odds ratios (OR). The GEE approach was used to account for the within subject correlation generated by the inclusion of all visits following HAART initiation for each subject.

The analysis of the CD4 count rise was divided into the initial three months of HAART and subsequent time on HAART because of the biphasic characteristic of CD4 rise [13]. We used the time period from baseline to the first on-HAART visit (assuming an average time of visit to be three months from HI) to model the first phase of CD4 rise and the second to the tenth on-HAART visits to model the second phase of CD4 rise during the subsequent five years. We also calculated overall CD4 rise for subjects with suppressed HIV RNA to compare with previous reports [14,15]. For these analyses we used linear regression with GEE methods to account for within subject repeated measures.

For all analyses, we assessed associations between the outcome of interest and year of HI (1996 versus 1997 to 2006), age at HI (continuous variable), baseline absolute CD4 count (continuous variable), baseline $\log_{10}$ HIV RNA (continuous variable), history of IDU, history of alcohol abuse, HCV status, proportion of HAART visits with HIV RNA suppression prior to and including each visit (time-dependent covariate), HIV RNA suppression at each visit, and HBV status. In building multivariate models, we initially included HBV status indicator variables and all other independent variables with a $P < 0.1$ in univariate analysis. We then obtained final models by using a modified backward stepwise algorithm based on significance levels in the full model ($P < 0.1$). We used a p -value < 0.05 to indicate statistical significance. STATA 10.0 (StataCorp, College Station, TX) was used for all analyses.

Results

Of 1371 HAART initiators in the MACS, 816 met our inclusion criteria. 443 men were excluded because of unknown HBV status at HI, 106 were excluded because the date of HI occurred during a window greater than 1 year, and 6 were excluded because HI was before 1996. The HBV status of the 816 men included 350 never infected, 357 with past infection, 45 with CH-B, and 64 with isolated core. Of the 64 isolated core, 62 had successful HBV DNA testing of which 11 (17%) had detectable HBV DNA with a median of 74 IU/mL (range 28–323). The subjects who were never infected initiated HAART at the youngest age, the latest calendar years, and had the highest median CD4 count at HI (Table 1). Isolated core subjects had the highest proportion of ever IDU and HCV. The CH-B group had the lowest median CD4 at HI and highest baseline alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels.

Median follow-up was 7 years [interquartile range (IQR): 3.5 to 9.0]. Of all subjects, 95% received an HBV active agent with either lamivudine, emtricitabine, tenofovir disoproxil fumarate (tenofovir DF) or both tenofovir DF and lamivudine or emtricitabine, as part of

HAART during the observation period. Ninety percent received lamivudine at any point during the observation period and 48% received tenofovir DF, with or without concomitant lamivudine or emtricitabine, during the observation period.

Deaths and AIDS Defining Illnesses

Overall, 87 subjects died after HI [rate: 17/1000 person-years (PYs), 95% CI 13, 21]. Despite HAART, AIDS-related mortality was the most common cause of death with 43 deaths due to AIDS (8.4 per 1000 PYs, 95% CI 6.2, 11.2). There were 30 non-AIDS-related deaths (5.9 per 1000 PYs, 95% CI 4.1, 8.5), and 14 subjects died from an unknown cause (2.8 per 1000 PYs, 95% CI 1.6, 4.7).

In univariate analysis, the AIDS-related mortality rate was highest among subjects with CH-B (17 per 1000 PYs, 95% CI 7.3, 42), followed by isolated core (14 per 1000 PYs, 95% CI 5.9, 34), past infection (11 per 1000 PYs, 95% CI 7.7, 16), and never infected (2.9 per 1000 PYs, 95% CI 1.4, 6.4). After adjustment for baseline CD4, proportion of visits with HIV RNA suppression, IDU, and HI after 1996, CH-B remained associated with a higher but not statistically-significant risk of AIDS-related death (IRR=2.7, $p=0.08$) compared to those who were never infected with HBV (Table 2).

The non-AIDS death rate was highest among those with CH-B (22 per 1000 PYs, 95% CI: 7.9, 47) compared to never infected (2.4 per 1000 PYs, 95% CI: 0.77, 5.5), past infection (5.8 per 1000 PYs, 95% CI: 3.2, 9.7), and isolated core (14 per 1000 PYs, 95% CI: 5.7, 34) (Figure 2). After adjustment for age and baseline CD4, both CH-B (HR 4.1, $p=0.04$) and isolated core (HR 3.6, $p=0.06$) remained associated with a higher risk of non-AIDS-related death compared to the HBV never infected group (Table 2).

Among subjects with CH-B, 4 of 6 non-AIDS-related deaths (66.7%) were liver-related (liver specific mortality rate 18 per 1000 PYs, 95% CI 5.8, 42), significantly higher than in the other groups ($p=0.05$) (Table 3). The time on HAART among the four individuals with liver-related death ranged from 2.3 to 7.3 years (median 5.0 years) and all received lamivudine. One of these four subjects received tenofovir DF starting approximately one year prior to death. Three of the 4 subjects with liver-related death had HBV DNA level assayed within one year of death. Of these three, one had a high HBV DNA (3.0×10^7 IU/ml), one had low but detectable HBV DNA (296 IU/ml), and one had HBV DNA <20 IU/ml. The two with detectable HBV DNA had documented lamivudine-resistant HBV; however, the subject with the HBV DNA of 296 IU/mL was receiving tenofovir DF.

Surprisingly, among the isolated core group, 4 of the 5 deaths (80%) were cardiovascular-related. Of the four who died, one of these men was HCV antibody positive and one (a different subject) reported IDU. Only one of the men whose death was cardiovascular-related had detectable HBV DNA (occult HBV).

ADI events occurred at a rate of 28 per 1000 person-years (95% CI: 24–33; 116 events). In a multivariate analysis, CH-B did not increase the risk of ADI events (Table 2).

HIV RNA Suppression

HIV RNA suppression was achieved among 60% of subjects by the second HAART visit and by 53% at >80% of HAART visits. In the univariate analysis, the isolated core subjects were least likely to achieve HIV RNA suppression (OR 0.54, 95% CI 0.32, 0.90, $p=0.02$) when compared with the never infected group. When adjusted for significant covariates – baseline HIV RNA, ever IDU, and HI after 1996 – isolated core status was no longer associated with decreased likelihood for HIV RNA suppression. The adjusted odds ratio for HIV RNA

suppression when compared to never infected was 0.68 (95% CI: 0.39, 1.2) for isolated core, 0.87 (95% CI 0.64, 1.2) for past infection, and 0.88 (95% CI 0.46, 1.6) for CH-B ($p=0.17$).

CD4 Recovery

HBV status was not associated with CD4 rise over the first 3 months of HAART ($p=0.58$) or in the second phase of HAART ($p=0.9$) (Figure 1). In both phases, the covariates associated with larger CD4 rise were lower baseline CD4 and proportion of visits with HIV RNA suppression ($p=0.01$ and <0.001 , respectively). There were no interactions between any of the covariates and HBV status (data not shown). In a multivariate model, HBV status remained unassociated with CD4 recovery in either phase of HAART ($p>0.05$).

Discussion

In this long-term, prospective analysis of 816 men with a median of 7 years of follow-up on HAART, past or present hepatitis B infection did not impact long-term response to HAART as measured by HIV RNA suppression, CD4 rise, or ADI incidence. However, even after receiving HAART that included drugs active against HBV, individuals with CH-B had an increased risk for non-AIDS defining illness mortality, primarily due to liver disease. There was also a trend for increased AIDS-related death among those with CH-B. Importantly, isolated core status did not impact the response to HAART or liver-related mortality. These findings are particularly timely as HAART is being made available in countries where hepatitis B is highly endemic.

Another study examined clinical outcomes among HBV-HIV co-infected individuals who were all receiving HAART for greater than 12 months, but, our study differs in important ways [8]. Omland et al. evaluated similar clinical end points of mortality and liver-related mortality; however, they classified the study subjects based on a single HBsAg test obtained either pre-HAART or on-HAART. This study design can result in misclassification since the serologies can shift over time especially with the initiation of HAART [7] which can affect the validity of the results. In our analysis, we classified hepatitis B status for each participant by requiring a minimum of two consistent serologic tests separated in time by at least six months. In all cases, at least one of these tests was obtained prior to HI. Second, our study separated subjects without CH-B into isolated core, past infection, and never infected, which other studies, including Omland et al. were not able to do [4–6,9]. Heterogeneity in groups can be problematic because even those with past HBV infection may have active HBV replication [16]. Our categorization allowed a clear demonstration that HBV infection, past or current, does not impact the immunologic or virologic response to HAART compared to those who were never infected with HBV.

Other studies have evaluated the impact of CH-B in subjects not on HAART [17] and with heterogeneous HAART experience [9]. The latter includes a study by Konopnicki et al. evaluating the impact of CH-B in the Euro-SIDA cohort for short-term HAART response (to 12 months). The longer term outcomes, such as overall and liver-related mortality, were examined among a mixed population of HAART-naïve and HAART initiator subjects.

Our study is also unique in that we separated CD4 recovery into first and second phases, which has not been previously done in assessing CH-B. Consistent with some reports [8,9] and in contrast to other previous reports of attenuated initial CD4 recovery, we found no difference in CD4 response between HBV groups [5] early during HAART or later during HAART [4]. Assessing the two phases of CD4 recovery separately enhances the potential of finding a difference in CD4 rise because the different mechanisms believed to lead to the early CD4 rise versus the second phase of rise.

Although HAART response, as measured by CD4 rise and HIV RNA suppression, was not compromised by CH-B in our study, it is notable that AIDS-related mortality rate was higher in this group compared to the HBV uninfected group. After adjustment for baseline CD4, proportion of visits with HIV RNA suppression, and time of HI, a trend remained for increased AIDS-related death, but it was no longer statistically significant. Thus, it is difficult to rule out an effect of CH-B also on AIDS-related death. Men with CH-B started HAART at lower CD4 cell counts which could partially explain an increase in AIDS-related mortality. However, if this explained the entire association, one would expect the association to disappear in the adjusted model.

Unfortunately, liver-related mortality remained significantly increased in patients co-infected with CH-B despite a suppressive HAART regimen that generally included an agent active against HBV, lamivudine or tenofovir DF. A study by Puoti et al. compared risk of liver-related death by ART agent among HIV-HBV co-infected individuals receiving <4 years of HAART [18]. That study reported a decreased risk of liver-related death with use of lamivudine (adjusted relative risk of 0.73 per year). In our study, the liver attributable mortality rate on HAART was similar to that previously reported from the MACS before and on-HAART (14 per 1000 PYs in an earlier study of the MACS [17] and 17 per 1000 PYs in this study). There are several possible explanations for this finding that are not inconsistent with the partially protective effect of lamivudine reported by Puoti et al. Firstly, liver-related death was a major cause of death in the Puoti et al. study, accounting for 26% of all deaths. Although there was a slightly decreased risk among patients receiving lamivudine, the incidence remained high. Second, men who died of liver-related disease in our study, and were taking lamivudine, may have developed more lamivudine-resistant hepatitis B due to a longer duration of follow-up than in the Puoti et al. study. Studies of HBV mono-infected people demonstrate that liver disease advances in the setting of lamivudine-resistant virus [19]. This is a plausible contributing factor since two of the four men with liver-related death in this study had known lamivudine-resistant CH-B. Only one of the men who died of liver disease received tenofovir DF, so it is plausible that with more effective anti-HBV HAART, liver mortality would decrease. In HBV monoinfection, potent anti-HBV therapy improves liver outcomes, but whether this occurs in HIV co-infection needs to be evaluated once sufficient data are available on patients with CH-B who are treated with tenofovir DF-containing HAART. While treatment of HIV-HBV co-infection with tenofovir DF is recommended in the United States, it is not the current practice in many of the regions, such as Africa, with high prevalence of CH-B. Among individuals co-infected with HIV-HBV living in low-income countries, consideration should also be given to including tenofovir DF in first-line regimens. A second plausible explanation for similar liver-related mortality during HAART compared to the pre-HAART era is that these men had more severe liver disease before initiation of HAART and that HAART was not able to reverse their disease; however, the long time on HAART before liver-related mortality, a median of five years, among the men who died of liver-related disease makes this less likely. A third plausible explanation is that immune reconstitution syndrome associated inflammation, which is increased among CH-B co-infected individuals and usually occurs soon after HAART initiation [20], led to an accelerated long-term progression to liver disease.

Interestingly, there was an increase in mortality among subjects in the isolated core group, which was not attributable to liver disease. We do not anticipate that this was a result of HBV reactivation because (a) reactivation occurs with waning immunity not with the increasing CD4 counts that we observed [21] and (b) liver disease was not a cause of death for any of the isolated core group. Surprisingly, most of the mortality in this group was from cardiovascular causes, leading to the possibility of differences in behavior rather than an intrinsic property of isolated core status. Differing patterns of drug use, including the possibility of more non-injection cocaine use, could potentially explain increased cardiovascular mortality [22]. Chronic hepatitis C has also been associated with increased cardiovascular mortality [23];

however, only one of the four subjects who died of cardiovascular causes had detectable HCV antibody. Significantly increased mortality among isolated core individuals was not reported in the previously described study from Taiwan supporting the possibility that a behavioral or environmental factor, may explain the difference.

In adjusted analysis, we did not observe an increased risk for mortality among the past infection versus the never infected groups. Crude mortality was higher among those with past infection, however, this is explained by the lower CD4 count and older age at HAART initiation amongst those with past infection compared to the never infected group. The absence of a difference in mortality is reassuring, given the high fraction of the population with past HBV infection.

Several limitations to this study are worth noting. An assessment of the potential impact of the HBV suppressive effect of lamivudine, tenofovir DF, or both on liver-related outcomes was not possible due to the small numbers of subjects and the later introduction of tenofovir DF. Second, we did not analyze hepatotoxicity risks because it is usually a transient event that may be missed with the infrequent (every six months) transaminase testing in this cohort. Third, underlying liver disease may have been under-reported on death certificates. This would have lead to an underestimate of the total burden of liver disease in this cohort. However, we do not believe that a systematic bias lead to differential under-reporting by HBV group.

In summary, this study demonstrates that HBV status at HAART initiation does not affect the long-term ability of HIV-infected patients to respond to HAART in terms of HIV RNA suppression and immunological recovery. Thus, CH-B should not diminish enthusiasm for prescribing HAART nor should long-term virologic or immunologic failure on HAART be attributed to CH-B. However, despite effective HAART that includes agents active against HBV, individuals with CH-B did not have an improvement in rate of liver-related mortality and thus remain at considerably higher risk for progressive liver disease, possibly because of incomplete HBV suppression with lamivudine as HBV suppression is an important component of slowing disease progression. Further work is needed to assess the impact of long-term suppressive HBV therapy with agents that are more durable than lamivudine (such as tenofovir DF), earlier HAART initiation in co-infected patients, and screening for liver disease during HAART to improve liver-related outcomes among the large population of individuals co-infected with HIV and CH-B.

Acknowledgments

Data in this manuscript were collected by the Multicenter AIDS Cohort Study (MACS) with centers (Principal Investigators) at The Johns Hopkins University Bloomberg School of Public Health (Joseph B. Margolick, Lisa Jacobson), Howard Brown Health Center and Northwestern University Medical School (John Phair), University of California, Los Angeles (Roger Detels), and University of Pittsburgh (Charles Rinaldo). The MACS is funded by the National Institute of Allergy and Infectious Diseases, with additional supplemental funding from the National Cancer Institute and the National Heart, Lung and Blood Institute. U01-AI-35042, 5-MO1-RR-00722 (GCRC), U01-AI-35043, U01-AI-37984, U01-AI-35039, U01-AI-35040, U01-AI-37613, U01-AI-35041. Website located at <http://www.statepi.jhsph.edu/mac/mac.html>. Additional support for the MACS at Harbor-UCLA comes from M01 RR00425 National Center for Research Resources grant awarded to the GCRC at the Los Angeles Biomedical Research Institute at Harbor-UCLA. CJH was supported by NIH DK074348.

References

1. Walensky RP, Paltiel AD, Losina E, Mercincavage LM, Schackman BR, Sax PE, et al. The survival benefits of AIDS treatment in the United States. *J Infect Dis* 2006;194:11–19. [PubMed: 16741877]
2. Lewden C, Chene G, Morlat P, Raf FF, Dupon M, Dellamonica P, et al. HIV-Infected Adults With a CD4 Cell Count Greater Than 500 Cells/mm³ on Long-Term Combination Antiretroviral Therapy Reach Same Mortality Rates as the General Population. *J Acquir Immune Defic Syndr*. 2007

3. Lohse N, Hansen AB, Pedersen G, Kronborg G, Gerstoft J, Sorensen HT, et al. Survival of persons with and without HIV infection in Denmark, 1995–2005. *Ann Intern Med* 2007;146:87–95. [PubMed: 17227932]
4. de Luca A, Bugarini R, Lepri AC, Puoti M, Girardi E, Antinori A, et al. Coinfection with hepatitis viruses and outcome of initial antiretroviral regimens in previously naive HIV-infected subjects. *Arch Intern Med* 2002;162:2125–2132. [PubMed: 12374521]
5. Law WP, Duncombe CJ, Mahanontharit A, Boyd MA, Ruxrungtham K, Lange JM, et al. Impact of viral hepatitis co-infection on response to antiretroviral therapy and HIV disease progression in the HIV-NAT cohort. *AIDS* 2004;18:1169–1177. [PubMed: 15166532]
6. Sheng WH, Chen MY, Hsieh SM, Hsiao CF, Wang JT, Hung CC, et al. Impact of chronic hepatitis B virus (HBV) infection on outcomes of patients infected with HIV in an area where HBV infection is hyperendemic. *Clin Infect Dis* 2004;38:1471–1477. [PubMed: 15156487]
7. Sheng WH, Kao JH, Chen PJ, Huang LM, Chang SY, Sun HY, et al. Evolution of hepatitis B serological markers in HIV-infected patients receiving highly active antiretroviral therapy. *Clin Infect Dis* 2007;45:1221–1229. [PubMed: 17918088]
8. Omland LH, Weis N, Skinhoj P, Laursen A, Christensen PB, Nielsen HI, et al. Impact of hepatitis B virus co-infection on response to highly active antiretroviral treatment and outcome in HIV-infected individuals: a nationwide cohort study. *HIV Med* 2008;9:300–306. [PubMed: 18400077]
9. Konopnicki D, Mocroft A, De WS, Antunes F, Ledergerber B, Katlama C, et al. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. *AIDS* 2005;19:593–601. [PubMed: 15802978]
10. Kaslow RA, Ostrow DG, Detels R, Phair JP, Polk BF, Rinaldo CR Jr. The Multicenter AIDS Cohort Study: rationale, organization, and selected characteristics of the participants. *Am J Epidemiol* 1987;126:310–318. [PubMed: 3300281]
11. DHHS. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health & Human Services; Jan 6. 2006
12. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep* 1992;41:1–19.
13. Goicoechea M, Smith DM, Liu L, May S, Tenorio AR, Ignacio CC, et al. Determinants of CD4+ T cell recovery during suppressive antiretroviral therapy: association of immune activation, T cell maturation markers, and cellular HIV-1 DNA. *J Infect Dis* 2006;194:29–37. [PubMed: 16741879]
14. Bosch RJ, Wang R, Vaida F, Lederman MM, Albrecht MA. Changes in the slope of the CD4 cell count increase after initiation of potent antiretroviral treatment. *J Acquir Immune Defic Syndr* 2006;43:433–435. [PubMed: 17183628]
15. Viard JP, Burgard M, Hubert JB, Aaron L, Rabian C, Pertuiset N, et al. Impact of 5 years of maximally successful highly active antiretroviral therapy on CD4 cell count and HIV-1 DNA level. *AIDS* 2004;18:45–49. [PubMed: 15090828]
16. Rehermann B, Ferrari C, Pasquinelli C, Chisari FV. The hepatitis B virus persists for decades after patients' recovery from acute viral hepatitis despite active maintenance of a cytotoxic T-lymphocyte response. *Nat Med* 1996;2:1104–1108. [PubMed: 8837608]
17. Thio CL, Seaberg EC, Skolasky RL, Phair J, Visscher B, Munoz A, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter AIDS Cohort Study (MACS). *Lancet* 2002;360:1921–1926. [PubMed: 12493258]
18. Puoti M, Cozzi-Lepri A, Paroninfo G, Arici C, Moller NF, Lundgren JD, et al. Impact of lamivudine on the risk of liver-related death in 2,041 HBsAg- and HIV-positive individuals: results from an inter-cohort analysis. *Antivir Ther* 2006;11:567–574. [PubMed: 16964824]
19. Nishida T, Kobashi H, Fujioka SI, Fujio K, Takaguchi K, Ikeda H, et al. A prospective and comparative cohort study on efficacy and drug resistance during long-term lamivudine treatment for various stages of chronic hepatitis B and cirrhosis. *J Gastroenterol Hepatol*. 2007
20. Hirsch HH, Kaufmann G, Sendi P, Battegay M. Immune reconstitution in HIV infected patients. *Clin Infect Dis* 2004;38:1159–1166. [PubMed: 15095223]
21. Cohen Stuart JW, Velema M, Schuurman R, Boucher CA, Hoepelman AI. Occult hepatitis B in persons infected with HIV is associated with low CD4 counts and resolves during antiretroviral therapy. *J Med Virol* 2009;81:441–445. [PubMed: 19152397]

22. Lange RA, Hillis LD. Cardiovascular complications of cocaine use. *N Engl J Med* 2001;345:351–358. [PubMed: 11484693]
23. Bedimo, R.; Westfall, A.; Mugavero, M.; Khanna, N.; Saag, M. HCV is an independent risk factor for acute myocardial infarction among HIV-infected veterans. 15th Conference on Retroviruses and Opportunistic Infections; Boston, February. 2008.

Figure 1. Median weekly CD4 change during phase 1 and phase 2 after HAART initiation for subjects with HIV RNA suppression, by HBV status

Medians with 95% confidence intervals (boxes) and upper and lower values (whiskers). CH-B, chronic hepatitis B. Mean weekly CD4 change during the first phase: never infected, 2.7 cells/mm³; past infection 1.4 cells/mm³; CH-B, 4.2 cells/mm³; isolated core, 3.5 cells/mm³. Mean weekly CD4 change during the second phase: never infected, 0.36 cells/mm³; past infection 0.39 cells/mm³; CH-B, 0.31 cells/mm³; isolated core, 0.52 cells/mm³.

Number at risk					
never infected	350	326	250	191	125
past infection	357	324	278	246	193
CHB	45	41	31	27	16
isolated core	64	53	35	31	23

Figure 2. Kaplan-Meier curve of non-AIDS mortality by HBV status as determined at time of HAART initiation

HBV, hepatitis B virus; CH-B, chronic hepatitis B

Table 1

Baseline population characteristics

	Never infected	Past infection	CH-B	Isolated core	* p
Subjects n (%)	350 (42.9)	357 (43.8)	45 (5.5)	64 (7.8)	
Age, HAART initiation median (IQR)	36 (31, 44)	44 (39, 48)	43 (40, 48)	42 (38, 46)	<0.001
HCV Antibody Positive, n (%)	38 (11)	36 (10)	7 (16)	14 (22)	0.04
Alcohol, Moderate, heavy or binge, n (%)	127 (37)	101 (28)	16 (36)	23 (37)	0.1
IDU Ever used, n (%)	26 (7)	53 (15)	4 (9)	13 (21)	0.003
Baseline CD4 median (IQR)	418 (268, 631)	350 (208, 515)	310 (168, 465)	332 (221, 463)	0.01
Baseline log ₁₀ HIV RNA, median (IQR)	4.8 (4.4, 5.4)	5.0 (4.5, 5.4)	4.7 (4.5, 5.1)	5.1 (4.5, 5.5)	0.005
Baseline ALT, IU/L, median (IQR)	22 (20, 37)	31 (21, 47)	86 (52, 113)	24 (20, 30)	<0.001
Baseline AST, IU/L, median (IQR)	26 (20, 33)	28 (22, 36)	70 (47, 88)	28 (24, 31)	<0.001
HAART initiation year					
1996	59 (17)	134 (38)	15 (33)	20 (31)	<0.001
1997–2006	291 (83)	223 (62)	30 (67)	44 (69)	
Follow-up time, years median (IQR)	6.6 (3.8, 8.7)	8.0 (3.9, 9.2)	6.6 (3.0, 9.2)	4.2 (2.1, 8.7)	0.002

* p for difference between HBV groups assessed by Kruskal-Wallis for medians and Chi-square for proportions; CH-B, chronic hepatitis B

Table 2

Events, rate, and adjusted analysis according to HBV group of non-AIDS related death, AIDS-related death, and ADI events

	Never infected	Past infection	CH-B	Isolated core
AIDS-related mortality				
Deaths (n)	6	27	5	5
Rate per 1000 person- years (95% CI)	2.9 (1.4, 6.4)	11 (7.7, 16)	17 (7.3, 42)	14 (5.9, 34)
Adjusted IRR (95% CI) **	1	1.6 (0.55, 4.5)	2.7 (0.90, 8.2)	1.6 (0.46, 5.3)
Non-ADI mortality				
Deaths (n)	5	14	6	5
Rate per 1000 person years (95% CI)	2.4 (0.77, 5.5)	5.8 (3.2, 9.7)	22 (9.7, 47)	14 (5.7, 34)
Adjusted IRR (95% CI) *	1	1.4 (0.46, 4.5)	4.1 (1.0, 16)	3.6 (0.93, 14)
ADI				
Events (n)	35	64	9	8
Rate/1000 PYs (95% CI)	16 (12, 22)	26 (21, 34)	32 (16, 61)	23 (12, 46)
Adjusted IRR (95% CI) ***	1	0.79 (0.49, 1.3)	1.1 (0.49, 2.5)	0.68 (0.31, 1.5)

ADI, AIDS defining illnesses; CH-B, chronic hepatitis B; CI, confidence interval; HR, hazard ratio; IRR, incidence rate ratio

* Adjusted for baseline CD4 and age

** Adjusted for baseline CD4, proportion of visits with HIV RNA suppression, HAART initiation after 1996, and IDU

*** Adjusted for baseline CD4, proportion of visits with HIV RNA suppression, and IDU.

Table 3

Cause of non-AIDS defining illness deaths

	Never infected	Past infection	CH-B	Isolated core
	n (%)	n (%)	n (%)	n (%)
Liver-related	1 (20)	2 (14)	4 (67)	0
Cardiovascular	1 (20)	3 (21)	0	4 (80)
Cancer	1 (20)	0	0	1 (20)
Infection	1 (20)	4 (28)	1 (17)	0
Trauma	0	1 (7)	0	0
Toxin/Medication	1 (20)	1 (7)	0	0
Renal/Metabolic	0	1 (7)	1 (17)	0
Pancreatitis/GI bleed	0	2 (14)	0	0
TOTAL	5	14	6	5

CH-B, chronic hepatitis B; GI, gastrointestinal