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HIV outcomes in Hepatitis B virus coinfecting individuals on HAART

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Abstract

Background—Understanding the impact of hepatitis B virus (HBV) coinfection on HIV outcomes in the HAART era continues to be a critical priority given the high prevalence of coinfection and the potential for impaired immunologic, virologic and clinical recovery.

Methods—Participants from the U.S. Military HIV Natural History Study with an HIV diagnosis, on HAART and serologically confirmed HBV infection status at HAART initiation (HI) were classified into four HBV infection (HB) groups. HIV virologic, immunologic, and clinical outcomes were evaluated by HB status.

Results—Of 2536 HIV positive HAART recipients, with HBV testing results available to determine HB status in the HI window, HB status at HI was classified as HB negative (n=1505; 66%), resolved HB (n=518; 23%); isolated HBcAb (n=139; 6%) or; chronic HB (n=131; 6%). HIV virologic suppression and failure at 6 months or 1 year were not significantly different by HB

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status. A significantly faster rate of increase in CD4 cell count during the period between 4 and 12 years was observed for chronic HB relative to HB negative.

Chronic and resolved HB were associated with an increased risk of AIDS/death compared to HB negative individuals (chronic HB; HR=1.68; 95% CI 1.05–2.68, resolved HB; HR=1.61; 95% CI 1.15–2.25).

Conclusions—HB status did not have a significant impact on HIV virologic outcomes, however, CD4 cell count reconstitution post HI and the risk of an AIDS event or death post HI may be associated with HB status.

Keywords

Hepatitis B virus; chronic hepatitis B; human immunodeficiency virus; highly active antiretroviral therapy

INTRODUCTION

Hepatitis B virus (HBV) is more common in HIV-infected individuals than in the general population due to similar routes of transmission for viral acquisition [1–3]. Current evidence suggests that HIV infection has an adverse impact on HBV-related liver disease progression, with an increase in HBV replication, reduction in the rate of clearance of serum hepatitis B e antigen, and increased risk of cirrhosis, liver-related mortality and hepatocellular carcinoma at lower CD4+ T cell counts [1,4–6]. Coinfection rates are estimated between 5–10%, with up to 40% of immunocompromised patients developing chronic infection [6].

Clinical studies prior to the general availability of HAART evaluating the impact of HB on HIV progression have been mixed [7–9]. Some studies found no differences in HIV progression between those with and without chronic HB [1,8,10], while other studies have shown that chronic HB may negatively impact HIV progression with a significant increased risk of AIDS or death [11,12,13].

Studies evaluating the influence of HIV-HBV coinfection on HIV RNA suppression, immunologic CD4 cell count recovery and clinical outcomes in individuals on HAART have been limited and conflicting, with several studies finding no difference [14–18]. Several studies from HBV endemic countries have also found no difference on HIV outcomes [19–22]. Law et al showed a smaller early increase in CD4 response post HI, however this was not sustained [23]. Hawkins et al showed coinfecting compared to mono-infected individuals had significantly lower CD4+ counts throughout the period of recovery [24]. Other studies have shown coinfecting individuals are less likely to achieve virologic suppression (VS) as compared to HIV mono-infected individuals [25–26]. Recent studies have for the most part failed to show a substantial impact of HBV coinfection on immunologic or HIV virologic responses to ART [21,24,27]. Idoko et al, however, found a lower proportion of HBeAg positive individuals achieving HIV virologic suppression at 24 weeks as compared to HBeAg negative or HIV mono-infected individuals, but the findings were not seen at 48 weeks [22]. One recent study evaluating HIV outcomes during the first three years of ART found impaired CD4 cell recovery in HBsAg-positive and anti-HBc patients as compared to

HBV-uninfected patients [28]. Heterogeneity of available data warrant further evaluation of this key question.

Limitations and heterogeneity of results from other studies may be attributed to the small number of individuals analyzed, defining patients with chronic HB sometimes with only one positive test for HBsAg, or limited follow up post HI. We sought to evaluate the impact of HBV infection in HIV coinfecting HAART recipients in a large cohort with known and limited duration of HIV infection, free access to health care, racial diversity, minimal injection drug use (IDU), and long term follow-up.

METHODS

Study Participants and Definitions

The U.S. Military HIV Natural History Study (NHS) is a prospective multicenter continuous enrollment observational cohort of HIV-infected active duty military personnel and other beneficiaries (spouses, adult dependents, and retired military personnel), with over 5400 HIV-infected participants from the Army, Navy/Marines and Air Force enrolled since 1986. Participants are followed at five military medical centers in the United States.

Demographics, medical and medication histories, and standard laboratory studies are collected biannually as previously described [13]. In the NHS, dates of death are collected through the review of death certificates and medical records by study staff as well as by searching the Social Security Death Index and National Death Index databases annually. Although not captured in the NHS database, IDU has been reported to be very rare in this cohort [29]. All NHS participants provided informed consent, and approval for this research was obtained from the institutional review board at each participating site.

NHS participants with a documented HIV diagnosis who ever received HAART and had a categorizable HB status were considered for these analyses. HAART was defined according to guidelines from the DHHS/Kaiser Panel and was defined as: (a) two or more NRTIs in combination with at least one PI or one NNRTI (88% of observations classified as HAART); (b) one NRTI in combination with at least one PI and at least one NNRTI (5%); (c) a regimen containing ritonavir and saquinavir in combination with one NRTI and no NNRTIs (1%); and (d) an abacavir or tenofovir containing regimen of three or more NRTIs in the absence of both PIs and NNRTIs (6%), except for the three-NRTI regimens consisting of: abacavir + tenofovir + lamivudine or didanosine + tenofovir + lamivudine [30]. HBV-active HAART was defined as HAART containing lamivudine, emtricitabine or tenofovir disoproxil fumarate.

Screening for HB was performed in accordance with clinical standards of care and practice guidelines at the time, and included hepatitis B surface antigen (HBsAg), total antibody to hepatitis B core antigen (HBcAb), and hepatitis B surface antibody (HBsAb). Those whose HB status could not be categorized were excluded from these analyses. The remaining participants were classified into one of four mutually exclusive groups determined by HB status in the HAART initiation window (HIW, -396 to +90 days from HAART initiation), defined as follows: 1) Chronic HB: HBsAg reactivity on two or more separate occasions at least 6 months apart with at least one positive HBsAg within the HIW or one positive

HBsAg before HI and one after HI; 2) Isolated HBcAb: HBcAb reactivity on two or more occasions without any other reactive HBV marker; 3) Resolved HB: a panel with markers reactive for HBcAb and HBsAb concurrently closest to HI, or before and after the HIW and HBsAg negative; or 4) HB negative: both HBsAg and HBcAb negative in the HIW or after the HIW with no prior positive panels.

Hepatitis C virus (HCV) infection was defined as having at least one positive HCV antibody test prior to or in the HIW without any negative HCV antibody thereafter. For those not classified as positive for HCV infection, a negative HCV antibody anytime after HI was used to classify individuals as HCV antibody negative at HI. An HIV seroconverter was defined as having a documented negative and positive HIV date.

HIV virologic suppression (VS) after HI was defined as having at least one VL assay <400 copies/ mL within 6 months or 1 year after HI. Among subjects having ever suppressed VL, virologic failure (VF) was defined as having two consecutive VL assays $\geq$ 400 copies/mL.

AIDS-defining illnesses were defined using the 1993 CDC classification excluding an isolated CD4 count < 200 cells/ μ L [31]. Individuals whose visit occurred after HI were included in this model.

Participants were followed from the time of HI for the composite endpoint of an AIDS-defining illness or death from any cause through 18 months after the last study visit. For those without an event, data were censored 18 months after the last study visit.

Statistical analysis

The four groups, defined by baseline HB status, were summarized with descriptive statistics. All continuous covariates were tested for normality using Shapiro-Wilks; covariates with a P value < 0.05 were considered not normally distributed. All covariates were non-normal, so medians were compared using Kruskal-Wallis test for continuous data. Categorical data were evaluated with either Fisher's exact test when the cell contained small counts, or the Chi-squared test.

Logistic regression was used to estimate the adjusted odds ratios for ever achieving VS within six months and one year of HI. Subjects were excluded from analyses if no VL assays within either 6 months or 1 year of HI or any model covariates were missing. Sensitivity analyses were performed on all models to assess the effect of missing data on outcomes utilizing multiple imputation (MI) with predictive mean matching for missing data [32]. Backwards selection methods, based on significance levels in the full model ($P < 0.1$) and other clinically relevant covariates, were later added. The final adjusted models (within 6 and 12 months of HI) were adjusted for age at HI, gender, race, era of HI, HCV status, VL and CD4 cell count at HI, ART use prior to HI and number of VL assays during 6 or 12 months of HI. Odds ratios (OR) are given with 95% confidence intervals (CI). A Cox proportional hazard model was used to estimate the adjusted hazard rate of VF. Only those who ever achieved virologic suppression were included. Time to VF was defined as the number of years from the first suppressed VL after HI to the first VF after HI. Backward step-wise selection was used to choose statistically significant covariates then other

clinically relevant covariates were added to the model. Multiple imputations were used as a sensitivity analysis to assess the effect of missing data on parameter estimation. The final adjusted model was adjusted for age at HI, race, gender, HCV status at HI, year of HI, HIV VL at HI, CD4 count at HI, ART prior to HI, AIDS prior to HI, years from HI to VS. Hazard ratios are given with 95% confidence intervals.

To quantify the effect of covariates at HI on the rate of increase in CD4 cell count, analysis of immunologic outcomes was evaluated using linear spline mixed models to account for within-subject repeated CD4 measures and to assess the effect of HB status and other factors on CD4 trajectories. Knots for the linear spline model were selected by inspection of LOWESS curves. Backwards selection methods were used to select covariates. Mean rates of increase in CD4 were allowed to differ by CD4 at HI, HB status at HI and the era of HI. P values <0.05 were considered statistically significant. Given the Q-Q-plot comparing the standardized residuals to theoretical normal quantiles showed a lack of fit in the tails, a regression technique using the multivariate t distribution and bootstrapping was used as a sensitivity analysis with respect to normality and outlier to improve model fit and compare parameters with the standard mixed model approach. R programming 2.13.2 was used for all other analyses [33].

The number of events, person-years (PY) at risk, and unadjusted rates per 100 PY were calculated for the four baseline groups; proportional hazard ratios were estimated using Cox regression models.

RESULTS

Of 5403 HIV-positive participants enrolled in the NHS with a documented HIV positive date, 2797 were ever on HAART (after 1996), 2536 (81%) had HBV testing results available to determine HB status in the HIW and were included in these analyses. Individuals whose HB status were not classified differed from those who were in that they were older at HAART start, had a greater percentage of HCV seropositivity, had a longer duration of HIV prior to HAART initiation, were more often diagnosed in the pre HAART era and had lower CD4 nadirs (data not shown). HB status at HI was classified as HB negative (n=1505; 66%), resolved HB (n=518; 23%); isolated HBcAb (n=139; 6%) or chronic HB (n=131; 6%). Characteristics at time of HI by HB status are shown in Table 1. Age at HIV diagnosis and HI (overall median 29 years; IQR 24–35 and 33 years; IQR 28–39, respectively) were significantly different among the four HB groups, with HB negative individuals diagnosed with HIV in the later calendar years, initiating HAART at the youngest age, having the lowest number of individuals with prior AIDS, having the least number with prior ART use, and having the highest median CD4 count at HI. Isolated core subjects had the highest proportion of HCV (15%). The chronic HB group had the lowest median CD4 at HI (median 278; IQR 146–410), and highest alanine aminotransferase (ALT) values (median 59 IU/L; IQR 33–102). HIV RNA levels at the time of HI were available for 2005 (87%) participants, and were similar among the groups (median 4.5 log₁₀ copies/ml; IQR 3.8–5). Median follow-up was 9.2 years; IQR 4.4 – 16. Of all subjects, 93% received HBV-active HAART regimens at HI. Of individuals initiating HAART between 1996 and

1999, the majority were on unboosted PIs (78%); however, from 2000 to 2012, 68% were on an NNRTI regimen (data not shown).

HIV Virologic Suppression

In unadjusted analyses by HB status, HB status was associated with HIV VS in the first 6 months and 1 year (data not shown). Within 6 months, VS rates for 1015 subjects was 53% overall, with HB negative, chronic HB, isolate core and resolved HB achieving rates of 58%, 35%, 44% and 45%, respectively, $P<0.001$. Within 1 year, VS rates for 1250 subjects was 59% overall, with HB negative, chronic HB, isolate core and resolved HB achieving rates of 65%, 40%, 53% and 47%, respectively, $P<0.001$. Table 2 presents the adjusted odds ratios for achieving HIV VS within 6 months and one year of HI for the four HB groups. The number of subjects included in model 1 (6 months) and 2 (12 months) were 1922 and 2130 subjects, respectively. The adjusted odds ratio for achieving VS was not significantly different by HB status; while age, year of HI, VL at HI, prior ART and HIV VL assay count were significantly associated with the odds ratios for achieving VS within 6 months and 12 months of HI, and African-American race was significantly associated with achieving VS within 12 months of HI. HB status at HI, gender, HCV status at HI, CD4 count at HI, AIDS prior to HI were not predictive of VS.

In an unadjusted model, over 5533 years of follow-up, there were 863 events of virologic failure. The rate of VF was 15.6 events/100 person-years; 95% CI 14.6–16.7 overall. VF by HBV status was higher in the chronic HB status group (23.5 events/ 100 person-years; 95% CI 17.9–30.3) over the years of follow up as compared to the isolated, resolved and HB negative status groups (18.8 events per 100 person-years; 95% CI 14.4–24, 18.5 events per 100 person-years; 95% CI 16.3–21, and 13.7 events per 100 person-years; 95% CI 12.6–15, respectively) (data not shown). Predictors of VF in adjusted analyses however, did not show a significant difference by HB status, suggesting the association was confounded by other factors (see Table 3, Supplemental Digital Content 1, which demonstrates predictors of VF). Younger age, African-American race, HI in the period 1996–1999, and prior ART were significantly associated with an increased risk of VF. Higher VL at HI showed a trend towards increased risk of VF (HR=1.09; 95% CI 1.00–1.18).

CD4 Recovery

Unadjusted trends in CD4 reconstitution by HBV status are shown in Figure 1. CD4 slope did not significantly differ by HB status during the first six months after HI (chronic: $P=0.838$; isolated core: $P=0.270$; resolved HB: $P=0.239$) (Table 4). The rate increase in CD4 cell count in chronic HB compared to HB negatives during the period between six months and 4 years after HI was also not significantly different (chronic: $P=0.069$; isolated core: $P=0.289$; resolved HB: $P=0.099$). A significantly greater rate increase in CD4 cell count in chronic HB compared to HB negative, however, was seen during the period from 4 years to 12 years after HI (chronic: $P<0.001$; isolated core: $P=0.841$; resolved HB: $P=0.071$), after adjustment for age at HI, gender, race, HCV status at HI, AIDS prior to HI, CD4 cell count at HI, HIV VL at HI, ART prior to HI and year of HI.

Deaths and AIDS Defining Illnesses

During 14,458 person years of follow-up (range Jan 1996– Feb 2010), 269 participants experienced an AIDS event or death after HI. AIDS events occurred at a rate of 1.86 per 100 person-years; 95% CI 1.64–2.10. In multivariate analysis, chronic HB status and resolved HB status were significantly associated with an increased risk of AIDS or death (chronic HB; HR=1.68; 95% CI 1.05–2.68, isolated HB; HR=1.51; 95% CI 0.93–2.44, resolved HB; HR=1.61; 95% CI 1.15–2.25). The HR comparing individuals with isolated HBcAb to those who were HB negative was not significant (data not shown). Other covariates that were associated with a significantly increased risk of an AIDS or death included subjects with a positive HCV status (HR=1.99; 95% CI 1.26–3.16), CD4 cell count at HI <200 (HR 3.70; 95% CI 2.49 – 5.50) and 200–350 (HR=1.35; 95% CI 0.85–2.05), as compared with a CD4 cell count ≥ 350, and prior ART (HR=2.06; 95% CI 1.39 – 3.07). All models were stratified by AIDS prior to HI. The interaction between HBV and HCV was not significant.

DISCUSSION

We evaluated HIV outcomes in HBV coinfecting HAART recipients and found that in agreement with other studies, HB status did not have a significant impact on HIV virologic outcomes. To adjust for the disparity in ART between HBV infected and HBV negative groups, we used era of HAART initiation in all models as well as ran sensitivity analyses (data not shown) to adjust for regimen potency (unboosted PI vs boosted PI, 3 NRTI, and NNRTI-based regimens, excluding PI+NNRTI+NRTI). Expectedly, regimen potency was significant, while P values and odd ratios for HBV status did not greatly change, indicating that while disparity in ART regimen between HBV groups affect virologic and immunologic outcomes, it is accurately adjusted for in our analysis. Older age, HI in the era 2000–2010, lower HIV RNA, and absence of ART use prior to HI were associated with improved odds of achieving VS in our study in agreement with findings observed from other studies [14,18]. Of interest, our cohort demonstrated 53% of subjects achieving HIV VS at 6 months and 59% at 12 months, which is lower than a recent study evaluating patients in the Swiss HIV Cohort Study (SHCS) (85.3–90.1% at 12 months), as well as previously published results from NHS participants starting HAART after 2000 (81% VS at 12 months) [28,34]. This likely reflects differences in ARV potency as well as treatment practices and prior mono- and dual-NRTI exposure. While HB status was not significantly associated with VS, VL at HI was significantly associated with the odds of achieving VS within 6 months and 12 months of HI. We also found no difference in time to VF by HB status at HI.

Prior studies evaluating T cell recovery in HBV infection have been mixed, with several showing no difference or early lower median CD4 cell count gains in HIV-HBV coinfection with no differences by 48 weeks [14,16,23,24]. The SHCS, however, which evaluated CD4 count recovery over a 36 month period, showed impaired CD4 recovery in patients with both HBsAg and anti-HBc alone suggesting direct impairment of immunologic recovery in HBV-coinfecting patients [28]. Results from our study show that HB status may be associated with CD4 cell count reconstitution post HI, as seen with a trend for slower CD4 cell count trajectories in individuals with chronic HB and resolved HB between 6 months and 4 years after HI. However, any trend in impaired immunologic recovery was not

sustained as we observed a significantly greater rate increase in CD4 cell count in chronic HB compared to HB negative patients during the period from 4 years to 12 years after HI ($P<0.001$). Our study, with long median times of patient observation, is the first to demonstrate significantly greater long term CD4 cell count gains in chronic HB individuals. The explanation for this difference is not clear, but one possibility is a positive impact on CD4 regenerative capacity in individuals with chronic HB when placed on HAART as compared with ART regimens that were not as robust as HAART. We also reviewed ART regimen changes over follow-up. Initially, only 11% (Table 1) of the CHB group was on dual HBV-active therapy; however, we found that 47% of the CHB initially on non-dual HBV-active ART, were switched to dual HBV-active ART at a median of 7.2 years after HAART initiation (data not shown). This may account for the significant CD4 cell count increase in the CHB group to similar levels as the other groups. Despite individuals with CHB having lower CD4 cell counts and older age at HI, which would negatively impact CD4 cell count rise, long term increases were observed. Similar to other studies, we show that individuals initiating HAART in the later years have greater CD4 slope changes in CD4 cell count as compared with individuals who started HAART in the early years of HAART availability, with VL not affecting CD4 trajectory [35]. Factors associated with poorer immunologic outcomes in our study, such as AIDS prior to HI, prior ART, lower CD4 count at HI are well-established determinants of HIV disease progression and risk of death [36].

Similar to other studies, we found an increase in AIDS events or death in patients with chronic HB, but also found an increased risk in resolved HB compared to HB negative individuals, which has not been previously described. These findings in individuals with resolved HB were not expected, given there were no significant differences in virologic and immunologic responses to ART over time between individuals with resolved HB as compared to individuals who were HB negative.

Study limitations include the relatively small number of individuals with chronic HB and isolated HB in this cohort in comparison to individuals with resolved and HB negative status. The population whose HB status was not classified differed from those who were classified in that they were more often diagnosed in the pre HAART era, had lower CD4 nadirs, were older at HAART start, had a greater percentage of HCV seropositivity, and had a longer duration of HIV diagnosis prior to HAART initiation. This difference would likely contribute to worse outcomes in individuals not HB classified, therefore HB unclassified individuals were excluded from analyses. Whether the CD4 cell count recovery findings observed in our study reflect survivor bias in individuals with chronic HB is possible, however, our cohort had significantly longer follow up for the chronic HB compared to other groups. The interpretation of data regarding HCV status is limited as confirmatory HCV RNA results were unavailable for the majority of those who were anti-HCV positive. The quantification of the contribution of liver-related causes to death is not possible in our cohort. Findings from this study may be relevant to groups similar to our cohort, and may not be applicable to groups with high rates of IDU, women or those with limited access to care.

The NHS cohort provides a unique opportunity to understand the impact of HBV coinfection on HIV outcomes in HAART recipients. The low use of injection drugs in this cohort, as

well as open access to medical care, vaccinations and medications in the military health system also help reduce potential confounding. Additionally, the long median ART duration and person years of observation in our cohort allow for the observation of potential associations otherwise not seen in other studies. However, some of the cohort's features may limit external generalizability. In addition, given the limited number of women in our cohort, study findings may not be generalizable to women. Therefore, in our cohort, and likely for other HIV-infected persons with similar characteristics, HB status does not appear to be associated with worse immunologic or virologic HIV outcomes.

In conclusion, our study adds further insight into the understanding of the complex interactions between HBV- and HIV-infection, and demonstrates the possible association between HB status at the time of HI and subsequent HIV immunologic and clinical outcomes. Further evaluation of the impact of HBV on cellular immunity and clinical outcomes should be prioritized. Findings from this study add further support to the recommendations to expand HBV screening to potentially minimize the morbidity and mortality associated with HIV/HBV coinfection.

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Number of Subjects per Year							
Negative	1391	1046	771	603	482	369	300
Chronic	114	94	77	68	59	55	53
Isolated Core	129	112	91	73	61	49	41
Resolved	488	409	342	283	258	217	176

Figure 1.

CD4 Count Reconstitution by HBV Status at HI

CD4 trends determined using LOWESS (locally weighted scatter plot smoothing).

Abbreviations: Negative, negative HBV infection; Chronic, chronic HBV infection; Isolated Core, isolated core HBV infection; Resolved, resolved HBV infection; HI, HAART initiation.

Table 1

Baseline Characteristics

	Total	Negative	Chronic	Isolated Core	Resolved	P value
Subjects	2293	1505	131	139	518	
Age at HIV Dx,						<0.001
years	29 (24,35)	28 (24,34)	29 (25,33)	29 (25,37)	31 (26,37)	
Age at HI,						<0.001
years	33 (28,39)	31 (26,37)	37 (33,42)	38 (32,43)	37 (32,41)	
Gender						<0.001
Male	2118 (92%)	1345 (89%)	127 (97%)	134 (96%)	512 (99%)	
Female	175 (8%)	160 (11%)	4 (3%)	5 (4%)	6 (1%)	
Race						<0.001
Caucasian	978 (43%)	645 (43%)	48 (37%)	46 (33%)	239 (46%)	
African-American	983 (43%)	618 (41%)	69 (53%)	77 (55%)	219 (42%)	
Hispanic/Other	332 (14%)	242 (16%)	14 (11%)	16 (12%)	60 (12%)	
HCV at HI						<0.001
Negative	2187 (96%)	1458 (97%)	119 (91%)	118 (85%)	492 (95%)	
Positive	97 (4%)	39 (3%)	12 (9%)	21 (15%)	25 (5%)	
Year of HIV Dx,						<0.001
year	1997 (1991,2003)	1999 (1994,2005)	1989 (1986,1992)	1992 (1988,1997)	1992 (1988,1998)	
HIV Dx to HI,						<0.001
months	27 (3,4,79)	14 (2,5,51)	100 (52,123)	79 (29,116)	58 (9,7,109)	
Year of HI						<0.001
1996 – 1999	1259 (55%)	691 (46%)	107 (82%)	93 (67%)	368 (71%)	
2000 – 2012	1034 (45%)	814 (54%)	24 (18%)	46 (33%)	150 (29%)	
Seroconverter						<0.001
No	450 (20%)	210 (14%)	54 (41%)	47 (34%)	139 (27%)	
Yes	1843 (80%)	1295 (86%)	77 (59%)	92 (66%)	379 (73%)	

	Total	Negative	Chronic	Isolated Core	Resolved	P value
HBV Vaccine before HI						
No	348 (15%)	289 (19%)	6 (5%)	17 (12%)	36 (7%)	<0.001
Yes	1945 (85%)	1216 (81%)	125 (95%)	122 (88%)	482 (93%)	
AIDS before HI						
No	2111 (92%)	1414 (94%)	108 (82%)	118 (85%)	471 (91%)	<0.001
Yes	182 (8%)	91 (6%)	23 (18%)	21 (15%)	47 (9%)	
HIV VL at HI Available						
No	288 (13%)	179 (12%)	22 (17%)	17 (12%)	70 (14%)	0.363
Yes	2005 (87%)	1326 (88%)	109 (83%)	122 (88%)	448 (86%)	
HIV VL at HI						
log10(copies/mL)	4.5 (3.8,5)	4.5 (3.9,5)	4.5 (3.6,4.9)	4.4 (3.5,5)	4.5 (3.8,4.9)	0.619
CD4 at HI Available						
No	278 (12%)	184 (12%)	21 (16%)	14 (10%)	59 (11%)	0.44
Yes	2015 (88%)	1321 (88%)	110 (84%)	125 (90%)	459 (89%)	
CD4 at HI						
Cells/mm3	338 (224,460)	350 (243,471)	278 (146,410)	280 (122,422)	332 (217,454)	<0.001
ART before HI						
No	1334 (58%)	1046 (70%)	26 (20%)	52 (37%)	210 (41%)	<0.001
Yes	959 (42%)	459 (30%)	105 (80%)	87 (63%)	308 (59%)	
ALT at HI						
U/L	33 (24,48)	31 (23,45)	59 (33,102)	32 (24,52)	33 (24,49)	<0.001
Initial Regimen						
3 NRTI	110 (5%)	84 (6%)	4 (3%)	3 (2%)	19 (4%)	<0.001
Boosted PI	234 (10%)	168 (11%)	10 (8%)	13 (9%)	43 (8%)	
NNRTI	826 (36%)	636 (42%)	24 (18%)	36 (26%)	130 (25%)	<0.001
PI+NNRTI+NRTI	69 (3%)	33 (2%)	10 (8%)	6 (4%)	20 (4%)	
Unboosted PI	1054 (46%)	584 (39%)	83 (63%)	81 (58%)	306 (59%)	<0.001
HBV-active Regimen						
No	170 (7%)	76 (5%)	12 (9%)	14 (10%)	68 (13%)	<0.001

	Total	Negative	Chronic	Isolated Core	Resolved	P value
Yes						
Dual HBV-active ART	627 (27%)	519 (34%)	15 (11%)	25 (18%)	68 (13%)	
Mono HBV-active ART	1496 (65%)	910 (60%)	104 (79%)	100 (72%)	382 (74%)	
HIV Dx to last Med History,						<0.001
years	9.2 (4.4,16)	7.4 (3.5,13)	16 (9.9,21)	13 (8.6,20)	13 (7.2,20)	
Regimen Change in Follow-up						
No	773 (35%)	583 (40%)	26 (20%)	42 (31%)	122 (24%)	<0.001
Yes	1460 (65%)	878 (60%)	102 (80%)	92 (69%)	388 (76%)	
HI to last Med Hx						
Years	5.5 (2,12)	4.5 (1.9,10)	8 (2,14)	7.4 (2.5,14)	8.5 (2.6,14)	<0.001

All data are No. (%) for categorical data and median (IQR) for continuous data.

Abbreviations: Negative, negative HBV infection; Chronic, chronic HBV infection; Isolated Core, isolated core HBV infection; Resolved, resolved HBV infection; Dx, diagnosis; HI, HAART initiation, HIV, human immunodeficiency virus; HCV, hepatitis C virus; VL, viral load; ART, antiretroviral therapy; ALT, alanine aminotransferase.

Table 2**Predictors of HIV Virologic Suppression (Logistic Regression)**

	Six Months		One Year	
	OR (95% CI)	P value	OR (95% CI)	P value
HBV Status at HI				
Negative	1	(ref)	1	(ref)
Chronic	1.06 (0.59,1.88)	0.848	0.89 (0.51,1.53)	0.682
Isolated Core	0.81 (0.46,1.4)	0.448	1.06 (0.63,1.79)	0.828
Resolved	1.02 (0.74,1.4)	0.911	0.77 (0.56,1.04)	0.089
Age at HI,				
per 10 years	1.39 (1.19,1.63)	<0.001	1.37 (1.17,1.6)	<0.001
Race				
Caucasian	1	(ref)	1	(ref)
African-American	0.9 (0.69,1.17)	0.43	0.74 (0.56,0.96)	0.023
Hispanic	1.28 (0.88,1.89)	0.2	1.28 (0.86,1.91)	0.217
Gender				
Male	1	(ref)	1	(ref)
Female	0.88 (0.54,1.44)	0.62	0.89 (0.56,1.42)	0.634
HCV Status at HI				
Negative	1	(ref)	1	(ref)
Positive	0.91 (0.49,1.67)	0.753	1.11 (0.61,2.01)	0.733
HAART Initiation				
1996 – 1999	1	(ref)	1	(ref)
2000 – 2012	13.25 (9.89,17.92)	<0.001	16.27 (12,22.28)	<0.001
VL at HI				
log10 (copies/mL)	0.69 (0.6,0.8)	<0.001	0.73 (0.63,0.84)	<0.001
CD4 Count at HI				
<200	1.27 (0.88,1.84)	0.196	1.19 (0.83,1.72)	0.337
200 – 350	1.14 (0.86,1.51)	0.349	1.27 (0.95,1.69)	0.102
>350	1	(ref)	1	(ref)
ART prior to HI				
No	1	(ref)	1	(ref)
Yes	0.61 (0.44,0.85)	0.003	0.52 (0.38,0.7)	<0.001
AIDS prior to HI				
No	1	(ref)	1	(ref)
Yes	0.78 (0.45,1.32)	0.355	0.87 (0.53,1.42)	0.582
HIV VL Assay Count				
log(n)	2.2 (1.77,2.74)	<0.001	2.24 (1.84,2.74)	<0.001

HIV virologic suppression defined as having at least one HIV VL assay <400 copies/mL within 6 months or 1 year after HI.

Abbreviations: Negative, negative HBV infection; Chronic, chronic HBV infection; Isolated Core, isolated core HBV infection; Resolved, resolved HBV infection; HI, HAART initiation; ART, antiretroviral therapy.

Table 3**Predictors of HIV Virologic Failure (Cox Regression)**

	HR (95% CI)	P value
HBV Status at HI		
Negative	1	(ref)
Chronic	1.1 (0.81,1.51)	0.53
Isolated Core	0.98 (0.73,1.31)	0.873
Resolved	1.1 (0.91,1.31)	0.32
Age at HI		
per 10 years	0.85 (0.77,0.94)	0.002
Race		
Caucasian	1	(ref)
African-American	1.24 (1.06,1.45)	0.008
Hispanic	0.89 (0.7,1.15)	0.386
Gender		
Male	1	(ref)
Female	1.04 (0.78,1.37)	0.803
HCV Status at HI		
Negative	1	(ref)
Positive	1.02 (0.73,1.44)	0.901
HAART Initiation		
1996 – 1999	1	(ref)
2000 – 2012	0.2 (0.16,0.25)	<0.001
VL at HI		
log10(copies/mL)	1.09 (1,1.18)	0.056
CD4 Count at HI		
<200	0.99 (0.8,1.23)	0.949
200 – 350	0.84 (0.71,1.01)	0.058
>350	1	(ref)
ART prior to HI		
No	1	(ref)
Yes	1.67 (1.39,2.01)	<0.001
AIDS prior to HI		
No	1	(ref)
Yes	1.04 (0.78,1.38)	0.809
Time to Suppression,		
years	0.86 (0.82,0.9)	<0.001

HIV virologic failure defined as two consecutive HIV VL assays > 400 copies/mL.

Abbreviations: Negative, negative HBV infection; Chronic, chronic HBV infection; Isolated Core, isolated core HBV infection; Resolved, resolved HBV infection; HI, HAART initiation; VL, viral load; ART, antiretroviral therapy; HR, hazard ratio; CI, confidence interval.

Table 4**CD4 Trajectory (Linear Spline Mixed Regression)**

HBV Status at HI	Difference in Cells/mm3 per year (95% CI)	P value
0 – 0.5 years after HI		
Negative	0	(ref)
Chronic	–12.28 (–130.14,105.59)	0.838
Isolated Core	–54.62 (–151.67,42.44)	0.27
Resolved	–33.77 (–89.98,22.45)	0.239
0.5 – 4 years after HI		
Negative	0	(ref)
Chronic	–7.92 (–16.46,0.61)	0.069
Isolated Core	4.02 (–3.4,11.43)	0.289
Resolved	–3.66 (–8.01,0.69)	0.099
4 – 12 years after HI		
Negative	0	(ref)
Chronic	9.76 (5.68,13.83)	<0.001
Isolated Core	0.39 (–3.39,4.17)	0.841
Resolved	2.16 (–0.18,4.49)	0.071
CD4 Count at HI		
0 – 0.5 years after HI		
<200	–102.38 (–164.89,–39.88)	0.001
200 – 350	–84.85 (–138.97,–30.72)	0.002
>350	0	(ref)
0.5 – 4 years after HI		
<200	13.17 (8.23,18.11)	<0.001
200 – 350	14.31 (9.89,18.73)	<0.001
>350	0	(ref)
4 – 12 years after HI		
<200	17.34 (14.77,19.92)	<0.001
200 – 350	6.27 (3.78,8.77)	<0.001
>350	0	(ref)
HAART initiation		
0 – 0.5 years after HI		
1993 – 1999	0	(ref)
2000 – 2010	112.82 (63.04,162.61)	<0.001
0.5 – 4 years after HI		
1993 – 1999	0	(ref)
2000 – 2010	2.31 (–2.05,6.67)	0.3
4 – 12 years after HI		

HBV Status at HI	Difference in Cells/mm ³ per year (95% CI)	<i>P</i> value
1993 – 1999	0	(ref)
2000 – 2010	8.28 (4.33,12.23)	<0.001

Adjusted for age at HI, gender, race, HCV status at HI, AIDS prior to HI, CD4 count at HI, HIV VL at HI, ART prior to HI and year of HI at baseline.

Abbreviations: Negative, negative HBV infection; Chronic, chronic HBV infection; Isolated core, isolated core HBV infection; Resolved, resolved HBV infection; HI, HAART initiation; VL, viral load.