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Hepatitis B Vaccination and Risk of Hepatitis B Infection in HIV-Infected Individuals

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Abstract

Objective—To assess the association of HBV vaccination with risk of HBV infection among HIV-infected patients and HBV infection risk factors among vaccinees.

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Design—Observational cohort study

Methods—Participants enrolled from 1986 through 2004, unvaccinated and serologically negative for HBV infection at the time of HIV diagnosis, were followed longitudinally through 2007 for the occurrence of HBV infection. Risk factors for HBV infection were evaluated using time to event methods, including Kaplan-Meier survival curves and Cox proportional hazards models.

Results—During 11,632 person-years of follow-up, the rate of HBV infection was 2.01 (95% CI 1.75–2.27)/100 person-years. Receipt of at least one dose of vaccine was not associated with reduced risk of HBV (unadjusted HR 0.86, 95% CI 0.7–1.1; adjusted HR 1.08, 95% CI 0.8–1.4). Receipt of three or more doses of vaccine was also not associated with reduced risk (HR 0.96; 95% CI 0.56–1.64). Among 409 vaccinees with HBsAb <10 IU/L, 46 (11.2%) developed HBV infection compared to 11 of 217 (5.1%) vaccinees with HBsAb ≥10 IU/L (HR 0.51; 95% CI 0.3–1.0). In participants with initial HBsAb <10 IU/L, 16/46 (35%) infections were chronic, compared to 0/11 in those with initial HBsAb ≥10 IU/L ($p=0.02$).

Conclusion—Overall, HBV vaccination was not associated with reduced risk of HBV infection in our cohort of HIV-infected individuals. However, the small subset of vaccinees with a positive vaccine response may have had reduced HBV infection risk, including chronic disease. Improvements in vaccine delivery and immunogenicity are needed to increase HBV vaccine effectiveness in HIV-infected patients.

Keywords

Hepatitis B virus; hepatitis B vaccine; human immunodeficiency virus; vaccination; immunization

INTRODUCTION

The burden of hepatitis B virus (HBV) infection in human immunodeficiency virus (HIV)-infected individuals is substantial with as many as 10% of unvaccinated patients chronically co-infected with HBV.[1–4] Compared to patients who are HBV-positive but HIV-negative, co-infected individuals generally have increased rates of cirrhosis and liver-related mortality.[5,6] Therefore, prevention of HBV infection in those with HIV is extremely important, and one of the potential means of accomplishing this is vaccination, as recommended by guidelines.[7–10]

Previous investigations of HBV vaccine in HIV-infected patients have primarily investigated factors associated with vaccine response finding low rates of seroconversion following vaccination.[11–16] Risk factors for lack of a vaccine response include higher HIV RNA at the time of vaccination,[17,18] anti-hepatitis C virus (HCV) positivity,[19,20] and lower nadir CD4 cell count prior to vaccination,[21,22] while CD4 cell count at the time of vaccination has not been consistently predictive.[11,13,15–18,20,23,24] Several studies have also documented reduced durability of serologic responses to HBV vaccine in those infected with HIV compared to HIV-negative individuals[12,23,25,26] leading some to recommend booster doses for HIV-infected patients when antibody to HBV surface antigen (HBsAb) levels fall below 10 IU/L,[2] although data supporting this practice are very limited.

In HIV-uninfected individuals, the protective efficacy of HBV vaccination has been shown to correlate with the concentration of HBsAb following vaccination,[27,28] but similar data in HIV-infected patients also remain limited.[29] Hadler, et al. described 340 individuals with HBV infection following vaccination from a multicenter study of plasma-derived HBV vaccine in men who have sex with men.[30] In that study 64 participants were infected with HIV prior to HBV infection, and among those participants, receiving an incomplete vaccination series or serologic non-response to vaccine appeared to be associated with development of chronic

HBV. However, this post-hoc analysis included few HIV-infected patients, and both HIV status at the time of vaccination and the total number of HIV-infected patients included in the original trial were unknown, precluding any assessment of efficacy in those with HIV. In a more recent study history of receiving one or more doses of HBV vaccine was associated with reduced risk of developing acute HBV.[1] However, data regarding vaccine response and chronicity of HBV following vaccination were not reported and length of follow-up was limited to three years.

The long-term protection of HBV vaccine in HIV-infected individuals remains unknown, as well as correlates for protection in this patient population. Therefore, we assessed risk factors for HBV infection, including HBV vaccination, in our prospectively followed multicenter cohort, and evaluated risk factors for HBV infection among vaccine recipients, including vaccine response.

METHODS

Study Cohort

The U.S. Military HIV Natural History Study (NHS) is an ongoing, continuous enrollment observational cohort of HIV-infected Department of Defense (DoD) beneficiaries followed at seven participating military medical centers in the United States and has been previously described.[31] Enrolling since 1986, the NHS has over 4500 participants with signed written consent. All adult DoD beneficiaries with a diagnosis of HIV infection followed at a participating site and ability to provide consent are eligible for participation. Approval for this research was obtained from the institutional review board at each participating site.

Following enrollment patients are seen every six months. Data collected at each visit includes demographic information, past and interim medical histories and illnesses, medications, vaccinations, and standard clinical laboratory studies. Additionally, blood samples are obtained and stored in a repository. At enrollment, participants self-reported race/ethnicity as Caucasian, African American, Hispanic or Puerto Rican or Mexican, Asian or Pacific Islander, Native American or Alaskan native, or other. HIV exposure category is not routinely captured, however rates of HIV risk behaviors have been previously reported and intravenous drug use is rare (<3%).[32]

Participant Selection and Definitions

All NHS participants with a documented date of HIV seropositivity, and without HBV infection at the time of HIV seropositivity (defined as negative initial tests after HIV seropositivity for both hepatitis B surface antigen (HBsAg) and total antibody to hepatitis B core antigen (HBcAb)) were eligible for inclusion. Vaccination was defined as receipt of at least one dose of HBV vaccine after HIV seropositivity. Patients with a date of HBV vaccine administration prior to HIV seropositivity were excluded. Neither the amount of the administered dose nor vaccine preparation was captured in the database. HBV infection was defined as positive results for two of the following three tests on one occasion: HBsAg, HBcAb, and HBsAb; or the presence of HBcAb or HBsAg on at least two separate occasions. For those meeting the criteria for HBV infection, chronic HBV infection was defined as the presence of HBsAg on two or more separate occasions at least six months apart.

Highly active antiretroviral therapy (HAART) was defined as a combination of at least three antiretroviral agents, similar to previous investigations.[31] The presence of an AIDS-defining illness was defined using 1993 CDC criteria,[33] with the exception of isolated CD4 count <200 cells/ μ L. Infection with syphilis, *N. gonorrhea*, *C. trachomatis*, or genital herpes simplex virus was considered to be a sexually transmitted infection (STI).

Vaccine response (HBsAb) after the last recorded dose was captured at two time points: initial response (three to nine months after the last recorded dose of vaccine) and follow-up response (6 to 24 months after the initial response). For study participants without a determination of HBsAb following vaccination at these time points, available repository specimens were tested for HBsAb (ETI-AB-AUK PLUS, DiaSorin Inc., Stillwater, MN) according to the package insert.[34] Non-response to vaccine was defined as HBsAb <10 IU/L and positive response was defined as HBsAb ≥10 IU/L. Persistent response was defined as HBsAb ≥10 IU/L at both time points, and a waning response was defined as an initial HBsAb ≥10 IU/L followed by HBsAb <10 IU/L.

Design and Statistical Methods

Analyses were defined *a priori*. Eligible participants were classified into three nonexclusive groups: the overall group, the vaccinated group, and the vaccine response group (Figure 1). The association of factors, including HBV vaccination status, and risk of HBV infection was assessed with the overall group, for which baseline was the documented date of HIV infection. Sub-analyses with the vaccinated group (with the date of the first HBV vaccine dose defined as baseline) and the vaccine response group (with the date of initial HBsAb measurement defined as baseline) were performed to assess risk factors for HBV infection following vaccination. For all analyses, the censoring date for those with no HBV infection was the latest of the last recorded NHS visit or the date of the most recent HBV screening panel.

The analysis groups were summarized with descriptive statistics. The number of events, person-years at risk, and rates of HBV infection (per 100 person-years of follow-up) were calculated overall and for baseline subgroups. Differences in proportions were compared with Chi-square and Fisher's exact tests. For each group, Cox proportional hazard models, both unadjusted and stratified by era of HIV diagnosis (prior to 1996 or 1996 to 2004) were used to evaluate the association of covariates with subsequent HBV infection. Covariates which could change during follow-up (HIV RNA, CD4 cell count, history of a STI or AIDS event, antiretroviral therapy (ART) use, and HBV vaccination status) were considered as time-updated covariates, for which all available measurements through the event or censoring date were utilized. The multivariate models for the vaccinated groups were also adjusted for year of vaccination. The assumption of proportional hazards was tested for models including vaccination status and vaccine response. All results reported are from stratified models unless noted otherwise.

HBV vaccination within the NHS was by participant and provider choice. To consider the impact of potential selection bias, propensity score methods[35,36] were used as sensitivity analyses to evaluate the effect of vaccination on HBV infection for the overall group. Each person was assigned a propensity score estimated with a logistic regression model assessing the probability of initiating HBV vaccination given baseline characteristics. Five equal-sized propensity score subclasses were formed based on rank order of the propensity scores. The percentage of vaccinated participants in the five subclasses ranged from 25% to 75%. Cox proportional hazards models were then stratified by those propensity score subclasses. Additional analyses were performed using Kaplan-Meier survival methods. Medians are noted with inter-quartile ranges (IQR). All hazard ratios (HR) are stated with 95% confidence intervals (CI). Significance *a priori* was defined as $p < 0.05$. All p -values are two-sided. All analyses were conducted using SAS (version 8.2, Cary, NC).

RESULTS

Overall Risk of Hepatitis B Infection

Of 4586 participants in the NHS, 4308 have been screened for HBV infection at least once after HIV infection with a median of five screens per subject (IQR, 2.0–9.0), and a median interval between HBV screens of 6.7 months (IQR, 5.7–11.1). For the current analysis, a total of 1853 participants met inclusion criteria. (Figure 1) Participants were enrolled from inception of the NHS through May 2004, and the latest censoring date for this study was April 2007. For participants included in the current investigation who did not experience HBV infection, the median interval from the last HBV screen to censoring for the study was 6.7 months (IQR, 0.0–29.4). The overall group was followed for a total of 11,632 person years (median 5.4 years; IQR 2.8–8.7). The median year of HIV diagnosis was 1991 (IQR 1988–1996). The median age at HIV diagnosis was 27 years (IQR 23–32); 87.3% were male; and self-reported ethnicity was Caucasian, African American, and other for 44.8%, 42.8%, and 12.3%, respectively. Baseline CD4 cell count was available for 1570 (84.7%) participants, with a median of 521 cells/ μ L (IQR 361–682). Baseline HIV RNA was available for 645 (34.8%) participants with a median of 4.4 log₁₀ copies/mL (IQR 3.7 – 4.9). Overall, 234 (12.6%) participants developed HBV infection resulting in a rate of 2.01 (95% CI 1.75–2.27) per 100 person-years. (Table 1, Panel A)

In the overall group, 881 persons were never vaccinated and 972 received at least one dose of vaccine. Of vaccinated participants, 542 (55.7%) received three or more doses of vaccine. Characteristics at the time of HIV diagnosis were no different between participants never vaccinated and those which ultimately received vaccination, except for median year of HIV diagnosis, 1989 compared to 1993, respectively ($p < 0.001$). One hundred forty-four (16.3%) unvaccinated participants developed HBV infection compared to 90 (9.3%) vaccinated participants (unadjusted HR 0.86; 95% CI 0.7–1.1). After stratifying by era of HIV diagnosis to adjust for unmeasured differences between the pre-HAART and HAART eras, results were similar (HR 1.08; 95% CI 0.8–1.4). (Table 2, Panel A) Results were also comparable utilizing propensity score methods for initiating HBV vaccination to adjust for selection bias (HR 1.10; 95% CI 0.8–1.5). Vaccination with three or more vaccine doses was also not associated with reduced risk compared to no vaccination (HR 0.96, 95% CI 0.6–1.6). In multivariate analyses stratified by HIV diagnosis era, male gender (HR 5.38; 95% CI 2.5–11.4) and occurrence of an STI (HR 1.52; 95% CI 1.1–2.2) were significantly associated with increased risk of HBV infection, while use of HAART (HR 0.49; 95% CI 0.3–0.8) was associated with reduced risk (Table 3, Panel A). HIV RNA was not included in the final multivariate model because 27.6% of participants had no HIV RNA measurement during follow-up, as this test was not widely used prior to 1996.

Risk of HBV Infection After Vaccination

The distribution of baseline characteristics for the 972 participants in the vaccinated group is shown in Table 1, Panel B. Followed for a total of 5,445 years from the date of first vaccination (median, 4.7 years; IQR 2.4–8.1), there were 90 cases of HBV in this group resulting in an event rate of 1.65 (95% CI 1.31–1.99) per 100 person-years. In multivariate analyses male gender (HR 4.88; 95% CI 1.5–15.5) was associated with an increased risk of HBV infection, while HAART use (HR 0.46; 95% CI 0.2–0.9), but not mono/dual ART was associated with reduced risk. (Table 3, Panel B) Increasing age remained significantly associated with reduced risk of HBV among vaccine recipients (HR 0.63 per 10 year increase; 95% CI 0.4–0.9). HIV RNA was again not included in the final multivariate model, because it was unknown for a large portion of the group.

To determine the association of vaccine seroresponse and risk of HBV infection, subset analyses were performed with the 626 vaccine recipients with known vaccine response or non-response (vaccine response group; Table 1, Panel C). There were no baseline differences between those with and without an HBsAb determination following the last dose of vaccine. During 2,333 years of follow-up (median 3.0 years; IQR 1.2–5.4) there were 57 cases of HBV in this group, all of which occurred in men, resulting in a rate of 2.44 per 100 person-years (95% CI 1.81–3.08). A positive vaccine response was seen in 217 (34.7%). After adjusting for age, ethnicity, and ART use, those with a positive response had an approximately 50% reduced risk of HBV infection compared to those with non-response (HR 0.51; 0.3–1.0) (Table 3, panel C). Of participants with positive response, 11 (5.1%) developed HBV infection compared to 46 (11.2%) with non-response ($p=0.013$ by log rank, Figure 2). Proportions (95% CI) of those without HBV infection at three, five, and seven years follow-up for those with a positive response were 96.6% (94.0–99.0), 95.2% (91.7–98.8), and 95.2% (91.7–98.8), respectively; for those with non-response proportions at the same time points were 87.6% (83.4–91.8), 85.5% (80.8–90.2), and 84.3% (79.2–89.5). Of participants with an initial positive response, risk of HBV infection was no different between those with waning or persistent vaccine responses ($p=0.26$ by log rank).

Chronic HBV Infection

Overall, chronic HBV occurred in 55 (23.5%) of the 234 HBV-infected participants. Chronic infection occurred in 24% (35/144) of unvaccinated participants with HBV compared to 22% (20/90) of vaccinated participants ($p=0.75$). For participants with initial non-response, 16 of 46 HBV infections (35%) resulted in chronic infection ($p=0.18$ compared to unvaccinated participants). However, among those with a vaccine response, no chronic HBV infections were seen ($p=0.07$ compared to unvaccinated participants; $p=0.02$ compared to vaccinated, non-responders). Among participants with HBV infection in the vaccine response group, there were no significant differences between those who did and did not develop chronic HBV regarding age, ethnicity, gender, HIV RNA, CD4 cell count, or use of ART at the time of HBV infection.

DISCUSSION

We found receipt of HBV vaccine after diagnosis of HIV was associated with no reduction in risk of HBV infection overall. In a previous study by Kellerman et al., history of ever receiving one or more doses of HBV vaccine was associated with a 40% reduced risk of acute HBV infection.[1] The reasons for the different findings are likely related to several factors including different patient populations and study endpoints, as we captured serologic and chronic infections and not only acute HBV infections. In addition, we excluded participants with known receipt of HBV vaccine prior to HIV diagnosis, whereas Kellerman, et al. did not. Whether vaccination prior to HIV infection is associated with a reduced risk of HBV following HIV diagnosis is unknown. Other factors found to be associated with risk of HBV infection in our study were similar to previous investigations, including increased risk in those with a previous sexually transmitted infection, and reduced risk in those taking HAART.[1,37,38]

From our data we are unable to determine why vaccination was not associated with reduced risk of HBV infection. One possible contributing factor to the overall lack of protection may be the high rate of exposure to HBV in this HIV-positive population. This is supported by the overall rate of HBV infection we observed (2 per 100 person-years follow-up), approximately 100-fold higher than the rate of HBV in the U.S. military and 500-fold higher than the rate of acute HBV in the general U.S. population.[37,39] In addition, poor initial immunogenicity of the vaccine in patients with HIV may be a second contributing factor. A vaccine response, defined as HBsAb ≥ 10 IU/L, was found in 35% of vaccinees, consistent with other smaller investigations where response rates have varied from 20%–50%.[11–18] In non-HIV-infected

individuals where response rates following three doses of vaccine are generally >90%.[10] CD4 T cell function is essential for development of a response.[40,41] Therefore, weakly protective vaccine responses reflected by low seroresponse rates in HIV-infected individuals may not be sufficient to protect against the high rate of HBV exposure, and possible repeated exposures seen in this population. Strategies to improve immunogenicity, such as use of adjuvants,[42] are urgently needed.

Low vaccination coverage and low completion of the initial three dose series may also have reduced vaccine effectiveness. Of the overall group during the last two decades, 52% received at least one dose of vaccine, and of those 56% received at least three doses. The lack of coverage is partially explained by the fact that some participants in our cohort were enrolled prior to the release of universal recommendations for HBV vaccination. While lack of vaccine coverage and completion may appear to undermine the conclusions from our study, our experience is consistent with other clinics and likely reflects clinical practice more than the idealized setting of a clinical trial. In a recent investigation from nine U.S. metropolitan HIV clinics only 32% of those eligible for HBV vaccine received at least one dose, and of those 52% received at least three doses.[22] In this way, our study may give a more accurate depiction of the effectiveness of HBV vaccine in HIV-infected patients. The unexpectedly low rates of HBV vaccine delivery and completion only highlight some of the challenges of using of HBV vaccine in HIV-infected individuals, especially considering our participants are relatively healthy with high CD4 counts, have very low rates of illicit drug use, and are seen in an optimal setting for delivery of vaccines, the open access to care military health system. Poor vaccine immunogenicity only compounds these challenges. Extrapolating the observed vaccine response rate to all vaccinated participants, only 18% of all individuals obtained a response reflecting the combination of low coverage and limited immunogenicity. Multiplying the proportion of participants which developed a response, 18%, by the 49% reduction in HBV infection in those with a response, the expected vaccine effectiveness was approximately 9%, and well within the confidence limits we determined for overall effectiveness in any model.

Given that vaccine effectiveness may be low overall, public health officials and clinicians may speculate whether or not HBV vaccination should be routinely offered to patients with HIV. While not definitive, our results suggest that those developing an initial response to the vaccine derived benefit from vaccination through at least seven years of follow-up. Alternatively, development of a vaccine response may have indicated an improved ability of an individual's immune system to recognize HBV antigens associated with a reduced susceptibility to infection.[43] However, our finding that HBsAb ≥ 10 IU/L was associated with a reduced risk of infection, including chronic disease, is consistent with results from prospective trials of non-HIV-infected individuals.[27,28,44] Therefore, until more definitive data are known regarding vaccine effectiveness, HBV vaccination of HIV-infected patients should be continued as a portion of patients may obtain protection from receipt of vaccine. In addition, clinicians should consider checking HBsAb levels following vaccination and reimmunizing non-responders with additional doses of vaccine,[45] as well as informing such patients of their HBV risk.

While a high proportion of those with incident HBV infection developed chronic disease overall, the likelihood of developing chronic HBV infection was associated with vaccine response among vaccinated participants. In HIV-uninfected individuals spontaneous recovery from HBV infection involves a strong, polyclonal CD4 and CD8 response, whereas those developing chronic HBV display weak, mono- or oligoclonal responses.[46–49] Similar responses in HIV-infected patients were recently reported.[50,51] Therefore, lack of functional HBsAg-specific CD4 T cells necessary for vaccine response would predict a weaker and more homogeneous response to natural HBV infection, and an increased likelihood of chronicity. An alternative hypothesis for the observed association would be that antigenic stimulation by vaccination in the setting of immune activation would result in apoptosis[52] of HBsAg-

specific CD4 T cells with subsequent impairment of the immune response to HBV once infected. Arguing against this however, is the observation that vaccination was not associated with an increased risk of HBV infection overall.

There are limitations to our study. First, our cohort is unique compared to other large HIV cohorts in some respects, including enrollment early after infection due to routine military HIV screening, open access to care in the military health system, and virtually no intravenous drug use.[32] However, these characteristics should only improve vaccine delivery and effectiveness. Second, HBV serologies in HIV-infected individuals may fluctuate[53] making diagnosis and classification for investigation difficult, but participants in our study received periodic testing of HBV serological markers, and our criteria for inclusion and definitions for infection required results for multiple serologies. Third, there may have been an indication bias for vaccination. However, the only notable difference between unvaccinated and vaccinated participants was the year of HIV diagnosis, and results were essentially identical from unadjusted and stratified models, and after utilizing propensity scoring methods to account for potential selection bias regarding vaccination. The vaccine dose was also unknown, although providing higher doses of vaccine to patients with HIV is not clearly beneficial.[18,54] Lastly, HIV RNA levels, known to predict vaccine responses, were unknown for many participants, analyses of vaccine recipients were limited by the number of events, and analyses regarding vaccine response were further limited by HBsAb result ascertainment.

Though recommended by guidelines,[7,10] the effectiveness of HBV vaccine in HIV-infected individuals had not been thoroughly investigated.[29] While vaccination was not associated with reduced risk of HBV infection overall, it may be beneficial for some individuals, specifically those developing an initial vaccine response of HBsAb ≥ 10 IU/L. However, our data suggest overall vaccine effectiveness in this population currently appears very limited, as vaccine non-responders typically account for one-half to two-thirds of vaccine recipients, and the risk of exposure to HBV remains high in this patient population. Continued improvements in vaccination delivery in combination with further knowledge of methods to increase initial vaccine immunogenicity would substantially improve vaccine efficacy.

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Figure 1.
Eligibility of participants.

Cumulative Incidence of Hepatitis B

Figure 2.

Cumulative incidence of hepatitis B infection in HIV-infected patients from time of vaccine response, by vaccine response in patients with known HBsAb three to nine months after last vaccine dose. The estimated proportions (95% CI) of those with no events at three, five, and seven years follow-up for those with HBsAb ≥ 10 IU/L were 96.6% (94.0–99.0), 95.2% (91.7–98.8), and 95.2% (91.7–98.8), respectively; for those with HBsAb < 10 IU/L proportions at the same time points were 87.6% (83.4–91.8), 85.5% (80.8–90.2), and 84.3% (79.2–89.5).

Table 1
Rates (per 100 person years of follow-up) of hepatitis B for baseline characteristics for three nonexclusive groups.

Baseline date Median, (interquartile range)	Panel A: Overall Group			Panel B: Vaccinated Group			Panel C: Vaccine Response Group		
	No. people	No. cases	Rate	No. people	No. cases	Rate	No. people	No. cases	Rate
Documented HIV positive date 1991 (1988, 1996)									
Overall	1853	234	2.01	972	90	1.65	626	57	2.44
Age, years									
≤ 25	691	94	2.34	254	31	2.56	96	12	3.50
26 – 35	854	112	1.93	478	48	1.65	310	33	2.83
36 – 45	239	25	1.70	200	10	0.91	183	10	1.43
> 45	69	3	0.87	40	1	0.43	37	2	1.63
Self-identified ethnicity									
Caucasian	831	102	1.89	436	35	1.40	286	21	2.12
African American	794	116	2.40	408	49	2.20	258	33	3.22
Other ¹	228	16	1.14	128	6	0.85	82	3	0.95
Gender									
Male	1617	227	2.26	852	87	1.84	556	57	2.83
Female	236	7	0.44	120	3	0.42	70	0	0.00
HIV RNA, copies/mL (log₁₀)									
≤ 4	216	21	2.20	255	13	1.14	303	12	1.18
4–5	323	22	1.54	153	7	1.10	85	6	2.44
> 5	106	8	1.80	39	4	2.19	15	1	2.23
Not available	1208	183	2.08	525	66	1.89	223	38	3.71
CD4 cell count, cells/ μL									
≥ 500	849	110	2.11	415	37	1.53	307	25	2.19
200 – 499	608	83	2.42	401	40	1.85	258	27	2.65
< 200	113	12	2.66	55	4	1.73	59	4	2.36
Not available	283	29	1.15	101	9	1.43	2	1	156.1
Previous sexually transmitted infection									

Baseline date Median, (interquartile range)	Panel A: Overall Group				Panel B: Vaccinated Group				Panel C: Vaccine Response Group			
	Documented HIV positive date 1991 (1988, 1996)				First hepatitis B vaccination date 1995 (1992, 1999)				HBsAb testing date 1998 (1994, 2002)			
Baseline Characteristic	No. people	No. cases	Rate	No. people	No. cases	Rate	No. people	No. cases	Rate	No. people	No. cases	Rate
Yes	738	127	2.50	264	27	1.79	192	17	2.22			
No	1115	107	1.63	708	63	1.60	434	40	2.55			
History of AIDS-defining illness												
Yes	56	2	1.44	25	0	0.00	28	2	2.23			
No	1797	232	2.02	947	90	1.69	598	55	2.45			
Antiretroviral therapy use												
None	1390	187	2.02	602	64	1.85	207	23	2.72			
Mono/dual therapy	237	40	2.84	207	20	1.52	144	24	3.92			
HAART	226	7	0.72	163	6	0.88	275	10	1.14			
HBsAb status												
< 10 IU/L							409	46	3.02			
≥ 10 IU/L							217	11	1.36			

/ Hispanic/Puerto Rican/Mexican, Asian/Pacific Islander, Native American/Alaskan Native, Other

Table 2
Risk of Hepatitis B Infection (Univariate models stratified by HIV diagnosis era)

Univariate Predictors	Panel A: Overall Group ¹			Panel B: Vaccinated Group ²			Panel C: Vaccine Response Group ³		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Age, per 10 years	0.83	0.7–1.0	0.08	0.59	0.4–0.8	<0.01	0.65	0.4–1.0	0.04
Self-identified ethnicity									
Caucasian	Referent			Referent			Referent		
African American	1.27	1.0–1.7	0.08	1.51	1.0–2.3	0.06	1.60	0.9–2.8	0.09
Other	0.64	0.6–1.1	0.09	0.60	0.3–1.4	0.25	0.47	0.1–1.6	0.22
Male gender	5.19	2.5–11.0	<0.01	4.40	1.4–13.9	0.01			
HIV RNA ^{4,5} , per log ₁₀ increase	1.42	1.2–1.8	<0.01	1.55	1.2–2.0	<0.01	1.69	1.2–2.4	<0.01
CD4 cell count ⁴ , per 100 cells/ μ L	0.98	0.9–1.0	0.41	0.95	0.9–1.0	0.26	0.94	0.8–1.1	0.34
CD4 cell count ⁴ , cells/ μ L									
≥ 500	Referent			Referent			Referent		
200 – 499	1.12	0.9–1.5	0.42	1.11	0.7–1.8	0.67	1.60	0.8–3.4	0.22
< 200	1.25	0.8–1.9	0.28	1.65	0.9–3.1	0.12	1.61	0.6–4.3	0.34
Previous sexually transmitted infection ⁴	1.57	1.1–2.2	0.01	1.29	0.7–2.3	0.38	2.18	0.8–5.7	0.12
History of AIDS-defining illness ⁴	0.96	0.6–1.7	0.87	1.15	0.5–2.9	0.77	1.19	0.3–5.1	0.82
Recent ART use ⁴									
None	Referent			Referent			Referent		
Mono/dual therapy	1.00	0.74–1.36	0.97	0.88	0.5–1.4	0.59	0.87	0.5–1.6	0.65
HAART	0.46	0.3–0.8	<0.01	0.44	0.2–0.8	0.01	0.41	0.2–0.9	0.02
Hepatitis B vaccination status ⁴									
None	Referent								
At least one dose	1.08	0.8–1.4	0.61						
HBsAb following Vaccination									
< 10 IU/L							Referent		
≥ 10 IU/L							0.51	0.3–1.0	0.05

- ¹Time zero = documented HIV positive date; N = 1853.
- ²Time zero = first Hepatitis B vaccination date; N = 972.
- ³Time zero = date of first HBsAb testing following last Hepatitis B vaccination date; N = 626.
- ⁴Time-updated covariate, for which all available measurements through censoring were used.
- ⁵No HIV RNA measurement was available during follow-up for 28% of all participants; 15% of vaccinated participants with known HBsAb status following vaccination.

Table 3
Risk of Hepatitis B Infection (Multivariate models stratified by HIV diagnosis era)

Multivariate Predictors	Panel A: Overall Group ¹				Panel B: Vaccinated Group ²				Panel C: Vaccine Response Group ³			
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	HR	95% CI	P-value	P-value
Age, per 10 years	0.87	0.7–1.1	0.18	0.63	0.4–0.9	0.01	0.73	0.5–1.1				0.16
Self-identified ethnicity												
Caucasian	Referent			Referent			Referent		Referent			
African American	1.30	1.0–1.7	0.06	1.56	1.0–2.4	0.05	1.48	0.9–2.6				0.17
Other	0.66	0.4–1.1	0.12	0.57	0.2–1.4	0.21	0.44	0.1–1.5				0.19
Male gender	5.38	2.5–11.4	<0.001	4.88	1.5–15.5	0.007						
Previous sexually transmitted infection ⁴	1.52	1.1–2.2	0.02									
Recent ART use ⁴												
None	Referent			Referent			Referent					
Mono/dual therapy	1.06	0.8–1.4	0.69	0.90	0.6–1.5	0.66	0.85	0.5–1.6				0.61
HAART	0.49	0.3–0.8	0.008	0.46	0.2–0.9	0.02	0.49	0.2–1.1				0.07
HBsAb following vaccination												
< 10 IU/L							Referent					
≥ 10 IU/L							0.51	0.3–1.0				0.05

¹Time zero = documented HIV positive date; N = 1853.

²Time zero = first Hepatitis B vaccination date; N = 972.

³Time zero = date of first HBsAb testing following last Hepatitis B vaccination date; N = 626.

⁴Time-updated covariate, for which all available measurements through censoring were used.