Hepatitis B vaccine: a seven-year study of adherence to the immunization guidelines and efficacy in HIV-1-positive adults

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Introduction

Since the adoption of universal vaccination of newborns and adolescents in 1991, overall new hepatitis B infection rates have dropped dramatically. New infections currently are seen primarily in high-risk adults. In the Centers for Disease
Control and Prevention (CDC) 2006 report, they estimate 51,000 new infections and an estimated 1.2 million people in the USA with chronic hepatitis B infection. Of these, 4000–5000 people will die each year from hepatitis B virus (HBV)-related liver disease.\(^1\),\(^2\)

Both the United States Public Health Service (USPHS)/Infectious Diseases Society of America (IDSA) and the Advisory Committee on Immunization Practices (ACIP) currently recommend screening for HBV and vaccination for all adults at increased risk for infection due to occupational, behavioral, social, or medical reasons. These risk groups include persons infected with HIV, healthcare workers, men who have sex with men (MSM), injection drug users, heterosexuals with sexually transmitted diseases, household and sexual contacts of HBV carriers, morticians, and incarcerated persons.\(^2\),\(^3\) In 2005, 79% of new HBV infections were associated with either high-risk sexual behaviors and/or intravenous drug use (IVDU).\(^2\)

For persons at risk for suboptimal response to the HBV vaccine, such as those with HIV infection, hepatitis B surface antibody (HBsAb) levels should be checked within 6 months of completion of the vaccination series. Currently, it is not recommended to vaccinate persons with isolated hepatitis B core antibody (HBcAb) positivity.\(^2\)–\(^4\)

Adherence to these guidelines for HIV-infected patients has not been well studied. One recent review of screening and vaccination practices for hepatitis A and hepatitis B virus in an HIV outpatient population, found low screening and vaccination rates even among providers experienced in treating HIV.\(^5\) Studies done to evaluate the immunogenicity of the hepatitis B vaccine in persons infected with HIV have had varying results.\(^5\)–\(^8\)

This study reviews the screening and adherence to HBV vaccination guidelines and immunologic outcomes in a large inner city adult HIV primary care clinic. We evaluated a number of variables to determine their significance for immunologic response to the HBV vaccine.

**Methods**

We performed a seven-year (September 1997–September 2004) retrospective, cross-sectional cohort study of all HIV-positive adults seen in an urban, inner city, primary HIV care clinic. Institutional review board approval was obtained prior to review of charts. Demographic data were collected, including age, sex, weight, income level, and race. Other data collected included CD4 count and HIV viral load at time of first vaccine dose, use of highly active antiretroviral therapy (HAART), smoking history, HBsAb and hepatitis B surface antigen (HBsAg), isolated hepatitis B core antibody (HBcAb), hepatitis B e antigen (HBeAg) and antibody (HBeAb), hepatitis C co-infection, number of vaccine doses received, time from seronegative study eligibility determination to the time the first dose of vaccine was given, and reason for not completing the vaccine series, if available. All persons were screened prior to administration of HBV vaccine. HAART was defined as three or more antiretroviral drugs, including at least one protease inhibitor or non-nucleoside reverse transcriptase inhibitor plus two other agents.

Exclusion criteria for vaccine eligibility included persons who tested positive for HBsAb, HBsAg, and/or HBeAb. Persons seropositive for isolated HBcAb were also considered ineligible, as the current guidelines do not support vaccination (Figure 1). No patient had a hepatitis B viral load performed.

Each patient was followed for a minimum of one year after their initial clinic visit for screening and initiation of the HBV vaccination series. Patients were given the standard dose of recombinant hepatitis B vaccine, either Engerix-B (GlaxoSmithKline) or Recombivax-HB (Merck). Patients were considered vaccine responders if their HBsAb levels were tested and were greater than 10 mIU/ml.

SAS software packages (SAS Institute, version 9.1) were used for statistical analysis. The Pearson’s Chi-square test, the two-sided Fisher’s exact test, and the Wilcoxon rank sum test were used to compare the categorical and continuous variables, respectively, between the two subject groups. \(p\)-Values less than 0.05 were considered significant. In the multivariate stepwise regression analysis, variables were analyzed to determine independent risk factors for vaccine failure. The variables tested included age, sex, race, weight, use of HAART, hepatitis C co-infection, CD4 count, and HIV viral load.

**Results**

A total of 1601 charts were reviewed, of which 25 were excluded due to missing data or being out of the time range of the study period. The remaining 1576 charts were included in the study. Demographically, 69% of the patients were male, 68% were African-American, 54.7% were diagnosed with HIV, not AIDS, and 58% lived below the level of poverty (Table 1). Risk factors for HIV and HBV infection included homosexual activity (23%), IVDU (10%), heterosexual activity (39%), and healthcare-associated (2%).

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**Figure 1** Results of screening and HBV vaccination.
Fifty-three patients were not screened for hepatitis B during the study period and were therefore excluded. Eight hundred and six patients were not eligible for vaccination for the following reasons: prior HBV infection was identified in 510 (63.3%), 93 (11.5%) had active or chronic HBV disease, 89 (11%) had the presence of HBcAb only, and 114 (14.1%) had already received hepatitis B vaccination (Figure 1). No adverse events related to the vaccine or its administration were documented.

Of the 717 patients eligible to receive the hepatitis B vaccine, 503 (70.2%) received at least one dose and 356 of the 717 (49.7%) completed the three-dose series. Of those who had completed the HBV vaccination series, 125 patients had HBsAb titers tested. Fifty-nine (47.2%) patients had detectable HBsAb (Figure 1). For this group of seroconverters, the median CD4 count was 502 cells/mm$^3$ (range 60–1225) and the median HIV viral load was <400 copies/ml (range <50–140). Fifteen patients were hepatitis C co-infected.

Sixty-six (52.8%) patients were HBsAb non-converters. The median CD4 count of this group was 346 cells/mm$^3$ (range 9–1230), median HIV viral load was 5356 copies/ml (range <50–750 000), and thirteen were hepatitis C co-infected. Three were not tested. Of these 66 patients who did not respond to the initial series, 29 received a second vaccination series (Figure 1). Nine of these patients had detectable HBsAb after the second series, nine had no detectable HBsAb, and 11 were not tested.

Response to HBV vaccination was significantly associated with CD4 count greater than 350 cells/mm$^3$ ($p = 0.006$) and undetectable HIV viral load ($p = 0.001$). A CD4 count of <200 cells/mm$^3$ versus CD4 >350 cells/mm$^3$ had an odds ratio of four times greater of non-response (point esti-
mate = 4.3, confidence limits 1.3–14.5). However, response was seen even at CD4 counts <50 cells/mm³. Lack of response to vaccine was most significantly associated with high HIV viral load (Figure 2). No association was detected with age, race, weight, tobacco use, use of HAART, or hepatitis C co-infection.

During the course of the study, in the group of 214 patients who were eligible but not offered vaccination, sixteen patients had documented exposure to HBV and seroconverted (HBsAb-positive and HbcAb-positive). Four patients developed active hepatitis B. No patient that received full vaccine series seroconverted or developed active HBV disease.

The documented reasons for not administering vaccination or completing the vaccination series were failure of the provider to offer vaccination (85%), loss to follow-up (10%), patient refusal (1.7%), and the remainder were unknown. The average time from serologic screening to administration of the first vaccine dose was 21.1 months (range 0–155 months). Reasoning for delaying vaccination was not well documented. If cited, the providers most commonly expressed concern for poor immunogenicity of the vaccine at low CD4 counts. As a result, vaccination was either delayed or not given at all during the study period, despite increased CD4 count on follow-up visits.

Discussion

Because HIV and HBV share common routes of transmission, it is recommended that all HIV-positive adults be screened for HBV. Any person who is HBsAb, HBsAg, and HbcAb-negative should receive the three-dose HBV vaccination series, regardless of CD4 count or HIV viral load. 2,9,10 Within 6 months after completion of the vaccination, the HBsAb should be checked to verify adequate response. Those who have HBsAb levels <10 mIU/ml should be given a second vaccine series. 11

Kellerman et al. looked at adults and adolescents infected with HIV from 1998 to 2001. 12 The highest rates of HBV disease were seen in black subjects, alcohol users, intravenous drug users, and subjects with AIDS, with a prevalence of 7.6%. An earlier study by Goldstein et al. showed similar risk factors. 13 Our cohort showed similar risk factors and a similar prevalence of 6.1% of subjects with active or chronic HBV disease at enrollment.

Larger studies in immunocompetent adults have shown response rates to hepatitis B vaccination of 85–100%. Decreased vaccine response has been seen due to obesity, smoking, site or dose of vaccine, and gender. 14 Prior studies of the immunogenicity of HBV vaccine in HIV-infected adults have had small numbers and reported response rates varying from 0% to 87%. 5–8,15–19 The association of seroconversion and CD4 count is not well defined. Some studies have shown higher response rates associated with higher CD4 counts, but others have not (Table 2). 5–8,16–18 Improved response rates have been shown with suppressed HIV viral load in some studies. 5,16

The response rate to initial vaccination in our cohort was 47% of those vaccinated persons who had antibodies checked. No vaccine recipient, regardless of antibody response, acquired HBV during the study period. Higher CD4 counts (p = 0.006) and undetectable HIV viral loads (p = 0.001) at the time of first vaccine dose were significantly associated with seroconversion to HBsAb-positive.

Vaccination against HBV in an HIV-positive population has the goal of preventing the morbidity and mortality associated with clinical disease. HIV/HBV co-infection, especially in persons with low CD4 counts, is associated with an increased

![Figure 2](image_url)  
**Figure 2** Logistic regression model demonstrating HIV viral load as a predictor of non-response to the hepatitis B vaccine. (Note: The multivariate analysis included CD4 count, age, weight, use of HAART, sex, race, and presence of hepatitis C co-infection. Only the HIV viral load was found to be an independent predictor of vaccine response.).
risk for liver-related mortality, such as cirrhosis and hepatocellular carcinoma. Chronic or active HBV infection also appears to increase the hepatotoxicity of HAART.20 Many eligible HIV-positive adults do not receive HBV vaccination. At screening 7.5% of our patients had evidence or documentation of prior HBV immunization. In a prior study of 342 homosexual males, only 9% had received HBV vaccination.21 There may be a number of reasons for missed vaccination including: (1) patient vaccination refusal, (2) loss to follow-up, resulting in fewer than all three doses being administered, (3) provider failure to screen or order the administration of the full vaccination series, (4) patient and/or provider failure to perceive the risk, (5) failure to offer vaccination, due to the assumption it will have decreased efficacy in patients with low CD4 counts, and (6) financial barrier to vaccination, the vaccine may not be reimbursed by the patient’s insurance company.

Our study was conducted in a clinic specializing in the care of HIV-positive adults. All providers were trained in HIV care or board-certified in infectious diseases. Despite 96.6% of patients having HBV serologic screening at their initial visit, 49% of those patients eligible for vaccination completed the three-dose series. Thirty percent of the vaccine eligible patients did not receive a single vaccine dose. Other studies have reported completion rates ranging from 29% to 50%.12,21—23 The reason for missed vaccination opportunity in our study was most often provider failure to offer vaccination or missed completion of all three doses. Similar to other studies, the most commonly cited reason for delaying vaccination was concern for decreased immunogenicity in patients with lower CD4 counts. In our study no correlation was identified between missed vaccination and the number of clinic visits or patient demographics. Because vaccinations were provided without charge to the patient, cost was not considered a barrier in our cohort.

Current guidelines do not recommend HBV vaccination for persons with isolated HBcAb positivity.3 The significance of HBcAb is unclear. Although it is seen in nearly all persons exposed to hepatitis B, it does not appear protective against infection. Furthermore, the presence of isolated HBcAb does not distinguish between early acute infection, a chronic carrier state with very low levels of HBsAg, remote HBV infections with loss of HBsAb, or cross-reacting antibody (false-positive test). Due to shared routes of transmission, patients are often co-infected with HCV, and the presence of HCV may decrease hepatitis B viral load.24—26 Other studies have also shown only 0—10% of patients with isolated HBcAb have detectable HBV-DNA.24,27,28 HBV vaccination might benefit those patients who have either lost HBsAb, and thus are at risk for reactivation or re-infection, or those who have a false-positive HBcAb test. There currently is no means of identifying which persons are at increased reactivation or infection risk.

We were unable to assess the rate of false-positive HBcAb in our cohort because none of the patients with this finding

### Table 2 Immunogenicity of hepatitis B vaccine in HIV-positive adults

<table>
<thead>
<tr>
<th>Study</th>
<th>CD4+ T-cell count range</th>
<th>HIV viral load (responders)</th>
<th>Number tested (HBsAb-pos)</th>
<th>Response (%)</th>
<th>Control number tested (HIV-neg)</th>
<th>Control response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collier et al. (1988)18</td>
<td>CD4 &gt;500</td>
<td>ND</td>
<td>8</td>
<td>7 (87.5)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CD4 &lt;500</td>
<td>ND</td>
<td>12</td>
<td>4 (33.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hess et al. (1989)7</td>
<td>All stages</td>
<td>ND</td>
<td>13</td>
<td>0 (0)</td>
<td>7</td>
<td>5 (71%)</td>
</tr>
<tr>
<td>Rey et al. (2000)8</td>
<td>CD4 &gt;500</td>
<td>ND</td>
<td>8</td>
<td>7 (87.5)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CD4 200—500</td>
<td>ND</td>
<td>12</td>
<td>4 (33.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilson et al. (2001)6</td>
<td>All stages</td>
<td>&lt;10 000 (9)</td>
<td>35</td>
<td>13 (37.1)</td>
<td>28</td>
<td>17 (60.1)</td>
</tr>
<tr>
<td></td>
<td>CD4 &lt;400</td>
<td>&gt;10 000 (4)</td>
<td>20</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CD4 &gt;400</td>
<td></td>
<td>15</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tedaldi et al. (2004)5</td>
<td>All stages</td>
<td>Range 1—5900</td>
<td>51</td>
<td>19 (37.2)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Gandhi et al. (2005)17</td>
<td>All stages</td>
<td>ND</td>
<td>69</td>
<td>43 (62.3)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Overton et al. (2005)16</td>
<td>All stages</td>
<td>&lt;400 (23)</td>
<td>194</td>
<td>34 (17.5)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CD4 &gt;200</td>
<td>&gt;400 (11)</td>
<td>40</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CD4 200—500</td>
<td></td>
<td>84</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CD4 &gt;500</td>
<td></td>
<td>70</td>
<td>13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ND, not determined.

### Table 3 Significance of isolated hepatitis B core antibody

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of subjects</th>
<th>HBV-DNA VL-positive (%)</th>
<th>Hepatitis C-positive (%)</th>
<th>Response to vaccine dose 1 (%)</th>
<th>Response to 3 doses (%)</th>
<th>No response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lok et al. (1988)19</td>
<td>32</td>
<td>ND</td>
<td>ND</td>
<td>15 (16)</td>
<td>18 (56)</td>
<td>9 (28)</td>
</tr>
<tr>
<td>Ural et al. (2001)29</td>
<td>48</td>
<td>ND</td>
<td>ND</td>
<td>24 (50)</td>
<td>43 (89)</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Alhababi et al. (2003)27</td>
<td>155</td>
<td>6 (4)</td>
<td>14 (9)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Gandhi et al. (2005)17</td>
<td>29</td>
<td>ND</td>
<td>23 (79)</td>
<td>7 (24)</td>
<td>18 (63)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Neau et al. (2005)24</td>
<td>160</td>
<td>1 (&lt;1) (1/160)</td>
<td>82 (51)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND, not determined; VL, viral load.

a HBV-DNA <400 copies/ml.
b HBV viral DNA <200 copies ml.
had a hepatitis B viral load performed. Nearly half of these
patients (41/89) were co-infected with HCV. Past studies of
HBV vaccination of HIV-positive persons with isolated HBcAb
positivity and negative HBEAb have shown amnestic response
rates of 16–50% after the first vaccine dose with up to a 63%
seroconversion after the third dose (Table 3).17,24,27,29,30

Given the significant prevalence of hepatitis B infection in
HIV-infected populations, failure to implement the vaccina-
tion guidelines represents a missed opportunity to prevent the
morbidity and mortality associated with this disease. HBV
vaccination should be done in all HIV populations regardless
of CD4 count or viral load, although patients with a lower CD4
count or high HIV viremia may have a lower seroresponse rate.

Current recommendations do not include vaccination
of persons seropositive for isolated HBcAb. Given the high rates
of hepatitis C co-infection in many HIV-infected patients,
that HBcAb may be falsely positive in persons co-infected
with hepatitis C, and that HBcAb is not protective against HBV
infection, vaccination should be considered.17,29,31 Further
studies are warranted to investigate the cost-effectiveness of
HBV-DNA screening for occult hepatitis B infection versus
vaccination in these populations.

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