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Hepatitis B Vaccination in HIV-Infected Youth: A Randomized Trial of Three Regimens

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Abstract

Background—HIV-infected youth are at risk of hepatitis B (HBV) infection and should be vaccinated. Previous reports suggest reduced response to standard HBV vaccine regimens.

Methods—HIV-infected youth, age 12 to <25 years, were randomly assigned to one of three treatment arms: Arm 1: Engerix B[®], 20 mcg HBsAg; Arm 2: Engerix B[®], 40 mcg; and Arm 3: Twinrix[®], 20mcg HBsAg combined with 720 ELU hepatitis A antigen. Vaccines were administered at weeks 0, 4 and 24.

Results—Characteristics of evaluable patients (n=336) at entry were similar in the study arms. At enrollment, median CD4+ T-cell count was 460 cells/mm³ (IQR: 305 to 668); 13% were < 200 cells/mm³. Among Engerix B[®], 20 mcg recipients, 60.4% responded to vaccine (HBsAb ≥ 10 IU/mL at week 28). Improved vaccine response was seen in recipients of Engerix B[®], 40 mcg, (73.2%, vs. Arm 1, p=0.04) and Twinrix[®] (75.4%, vs. Arm 1, p=0.02). In multivariate analysis, only baseline CD4+ T-cell count and study arm were independent predictors of vaccine response.

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Conclusions—In HIV-infected youth, a three dose vaccination regimen with Engerix B[®], 40 mcg, or Twinrix[®] and higher baseline CD4+ T-cell counts were independently associated with improved vaccine response.

Keywords

HIV; Hepatitis B Vaccination; Adolescents; Engerix B; Twinrix

INTRODUCTION

Suboptimal response to hepatitis B virus (HBV) vaccination in HIV-infected adults and children has been well documented. In children with perinatally acquired infection, response rates range from 20 – 78%.^{1–6} Correlation of response with CD4+ T-cell (CD4) counts or percentages, HIV-related symptoms, and younger age are reported but with inconsistent findings. Among HIV-infected adults, response rates for HBV vaccination vary between 17 – 71%.^{7–24} Factors thought to be associated with improved vaccine response include higher CD4 count, undetectable HIV-1 viral load, younger age, and increased dose and number of vaccines. While studies are difficult to compare because of varied study design and heterogeneous populations, disease and treatment status of subjects, higher CD4 count and undetectable HIV-1 viral load at the time of vaccination are considered important predictors of improved vaccine response among adults.

To date, there is no randomized trial of HBV vaccination in HIV-infected youth. A retrospective study from REACH, a cohort of youth infected with HIV via high risk behaviors and uninfected but at-risk youth, demonstrated only 41% of HBV previously immunized HIV-infected youth exhibited protective levels of antibody.²⁵ The temporal relationship of HBV vaccination to the HIV infection in this population could not be determined; however, reduced response rates were also seen among those HIV-infected subjects who were vaccinated during the study period (37%).

Excellent response rates to both hepatitis A virus (HAV) and HBV vaccination in healthy youth populations have been demonstrated with Twinrix[®].^{26–29} Ambrosch demonstrated higher titers of antibody in youth who received the combined vaccine compared to those receiving monovalent vaccines.²⁷ Likewise, Knoll demonstrated a trend toward higher antibody titers with the Twinrix[®] in healthy young adults.²⁹

We undertook a randomized trial of increased dose HBV antigen using Engerix B[®], 40 mcg HBsAg, compared to the recommended dose of Engerix B[®], 20 mcg, in HIV-infected youth. A third arm combined HBV and HAV vaccine using Twinrix[®]. Here, we report the immunogenicity, vaccine response predictors and safety of these vaccination regimens in HIV-infected youth.

METHODS

Study population

HIV-infected youth, regardless of route of infection, age 12 to < 25 years, with no history of previous HBV vaccine or only one previous HBV vaccine received ≥ 4 weeks prior to screening, and who had no serologic evidence of HBV surface antibody (HBsAb), surface antigen (HBsAg), or core antibody (HBcAb) were recruited from Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) Units, and International Maternal, Pediatric, and Adolescent AIDS Clinical Trials (IMPAACT) Units in the United States and South Africa, and NICHD sponsored international clinical trial sites in Brazil and Bahamas.

Prior HBV vaccination was ascertained via review of all available medical records, immunization cards, and subject and, when applicable, parent recall.

Females of childbearing potential were required to have a negative pregnancy test at screening and agree to avoid pregnancy through the completion of the vaccine phase of the study. Subjects were excluded for previous allergic reaction to any HBV or HAV vaccines or their constituents, any serious clinical or laboratory toxicity at time of screening, high dose or long-term steroid use (more than 10 mg/day of prednisone or equivalent for ≥ 2 consecutive weeks) within the prior 3 months, other diseases of the immune system, or receipt of immune globulin or plasma product within the prior 6 months, blood product or transfusion within the prior 4 weeks, or any vaccine within the prior 4 weeks. Prior infection with HAV or vaccination with HAV vaccine was not an exclusion criterion.

The study was approved by the Institutional Review Board or Ethics Committee at each site. An independent Data and Safety Monitoring Board monitored the trial for safety every 6 months during the course of the study.

Study procedures

Prior to entry subjects were assessed by history and physical examination. Medical records were reviewed to determine nadir CD4 count, highest HIV-1 viral load, presumed route of HIV infection, and antiretroviral therapy (ARV) history.

Subjects were randomized into one of three arms using blocks of size six, and stratified by absolute CD4 count (<500 and ≥ 500 cells/mL) and previous HBV vaccination (0 and 1). The randomization was restricted so that the percentage of subjects with CD4 count ≤ 200 cells/mL would not exceed 15% of subjects on any arm. The study was not blinded.

The three treatment arms were: Arm 1 - Engerix B[®], 20 mcg; Arm 2 - Engerix B[®], 40 mcg; and Arm 3 - Twinrix[®], 20 mcg HBV surface antigen and 720 ELU HAV antigen. Vaccinations were administered in the deltoid muscle at entry, week 4 and week 24. Engerix B[®], 40 mcg, was delivered as two injections of 20 mcg. A negative pregnancy test was required from all female subjects within seven days prior to each vaccination. Vaccination was delayed in subjects with acute febrile illness. Delayed administration of vaccine was allowed.

All subjects were observed for 20 minutes following vaccination and were contacted by telephone at days three and seven (± 24 hours) after vaccination to assess safety. Additionally, subjects were advised to contact study staff if concerned about any signs or symptoms, or if any symptom appeared severe.

Toxicity was assessed using the Division of AIDS Table for Grading the Severity of Adverse Events (<http://rcc.tech-res.com/safetyandpharmacyvigilance>). If neurological symptoms at any severity grade or non-neurological symptoms $\geq$ Grade 3 were reported, subjects were asked to return to the clinic within 48 hours for evaluation.

Subjects were evaluated at week 28 for vaccine response (primary endpoint) and interval medical history. A vaccine response was defined as an HBsAb measurement of ≥ 10 IU/mL. Subjects with a HBsAb response of < 10 IU/mL (non-responders) at week 28 received a fourth dose of vaccine, Engerix B[®] 40 mcg. Non-responders had repeat quantitative HBsAb assessed at least four weeks after the fourth dose, after which no further follow-up was performed. Vaccine responders had repeat assessment of HBV antibodies at weeks 48 and 72 to assess duration of vaccine response.

Subjects did not receive additional vaccines if they became pregnant; developed a confirmed Grade 3 vaccine-related toxicity that persisted for more than 14 days, did not resolve, or recurred; or if they developed a Grade 4 toxicity and relationship to the study vaccine could not be ruled out.

Laboratory assessments

Qualitative HBV and HAV serology, CD4 counts, HIV-1 viral load, and pregnancy tests were performed in local laboratories. Only subjects assigned to the Twinrix[®] arm had HAV serology performed. Quantitative HBsAb assays were performed at a central testing laboratory (Abbot EIA or Ortho Vitros ECI performed by Quest Diagnostics, Baltimore, MD). The serologic assay changed during the study; however, sufficient samples were available to provide pre and post immunization test results with the Ortho Vitros ECI test for all but 4 (1.2%) of the subjects. In those cases, results from the Abbot EIA were used. To assure that HBV seroconversion represented response to vaccine rather than new HBV infection, all subjects with a vaccine response had HBcAb testing performed.

Statistical considerations and analysis

This study was designed to compare vaccine response at 28 weeks in two experimental regimens (Arms 2 and 3) to the standard regimen (Arm 1). From previous studies, the expected response to Arm 1 was 42%, while a response of 60% for either Arm 2 or 3 would constitute a clinically significant improvement. For $\alpha = 0.05$ and power of 80%, 111 subjects per arm were needed. Anticipating 5% attrition, we targeted 123 subjects for each arm using the method of Lachin.³⁰

All subjects who received vaccine were evaluated for safety. The primary planned efficacy analysis included all subjects with week 28 serology results regardless of study vaccine receipt (modified intent to treat analysis, as specified in the study protocol); a per-protocol analysis was also done that included only subjects who met all eligibility and study requirements. We also planned and performed sensitivity analyses to determine the effect of missing endpoint data. Chi square tests were used to assess categorical variables and Student's T-test for continuous variables. Variables of interest included CD4 parameters (baseline count and percentage and historical nadir), baseline HIV-1 viral load, route of transmission, international location, ARV treatment, gender, ethnicity, body mass index (BMI), and cigarette smoking. Logistic regression analysis was used to evaluate the factors as predictors of initial vaccine response. Stepwise and best subsets methods were used to develop multivariate models for predicting vaccine response. Kaplan-Meier curves and proportional hazards modeling was used to evaluate predictors of duration of vaccine response. For responders at 28 weeks, duration was defined as the time to the first negative serology result, using a response cutoff of 10 IU/mL; subjects with missing data were censored at the last available time point. Sensitivity analyses were performed to determine the effect of missing endpoint data. All analyses were conducted using SAS, version 9.2 (SAS Corp., Cary, NC).

RESULTS

Three-hundred-seventy-one subjects were enrolled and randomized and 336 (90.6%) had HBV serology performed at week 28 and were considered evaluable (Figure 1). The evaluable group differed from the randomized group as shown in Table 1. Demographic, historical, and HIV disease and treatment characteristics for the latter group are shown in Table 1. Subjects in the three arms were similar with the exception of more subjects who never smoked cigarettes in Arm 3.

At week 28, the experimental arms demonstrated greater vaccine response than the control arm (Engerix B[®], 20 mcg). The increased dose arm (Engerix B[®], 40 mcg) had a response rate of 73.2% (95% CI, 65% to 81.4%) compared to 60% (95% CI, 50.8% to 69.2%) in the standard dose (Engerix B[®], 20 mcg) arm ($p=0.04$). Similarly, the Twinrix[®] arm showed improved response rate of 75.4%, (95% CI, 67.7% to 83.2%) compared to the standard dose ($p=0.02$). Other predictors of vaccine response in univariate analyses included female gender, higher nadir CD4, higher baseline CD4 and percentage, lower baseline viral load, and enrollment at a US site (Table 2). Ethnicity, BMI, smoking, and use or type of ARV were not related to response. Route of infection was also not related to response ($p=0.12$).

In addition, when perinatally infected subjects were compared to all others, no differences in response were observed ($p=0.07$). However, when perinatally infected subjects were compared to those infected by high risk behaviors (excluding missing, unknown, and transfusion categories), those infected perinatally had poorer response to vaccination (60.0% vs. 73.3%, $p=0.047$).

Vaccination with Twinrix[®] resulted in higher mean levels of HBsAb (97.7 IU/mL) compared to the Engerix B[®], 20 mcg arm (52.5 IU/mL, $p=0.03$). The difference between the two Engerix B[®] arms was not statistically significant (52.5 vs. 77.6 IU/mL, $p=0.17$).

In a multivariate analysis, treatment arm and baseline CD4 count remained statistically significant (Table 2), along with an interaction term that reflects how subjects in the increased dose Engerix B[®] arm responded differently depending on their CD4 count. This model indicates that the odds of responding to study vaccine are 1.99 times higher for subjects in the Twinrix[®] arm compared to the Engerix B[®], 20 mcg arm, regardless of CD4 count. Subjects receiving the Engerix B[®], 40 mcg vaccine with CD4 counts at the lowest quartile (305) had odds of 1.34 for vaccine response when compared with the Engerix B[®], 20 mcg arm; this OR increases to 2.91 for the median CD4 count (460) and to 8.23 at the third quartile (668). Further analysis indicated that male gender, international location, and perinatal infection all had significant associations with low CD4 counts (data not shown), thus further justifying CD4 count as the strongest predictor of vaccine response.

Results were similar when sensitivity analyses for missing data and per protocol analyses were conducted. Analyses were performed using two scenarios: all missing data indicating response and all missing data indicating lack of response. Specifically, the logistic regression analysis was repeated assuming that missing response data at week 28 indicated non-response; results for the adjusted analysis were similar to results shown in Table 2.

Among the 118 subjects in the Twinrix[®] arm, 53% had positive HAV qualitative serology at baseline and 98% at week 28. HBV response following Twinrix[®] administration was independent of baseline HAV antibody status ($p=0.2$).

Two-hundred-twenty vaccine responders were analyzed for duration of HBV response using both the nominal study visit week and actual time lapse since completion of vaccination series. After 72 weeks, 41.4% (SD 4.9%), 52.4% (SD 4.7%) and 50.4% (SD 4.8%) of the subjects arms 1, 2 and 3, respectively, had HBsAb levels ≥ 10 IU/mL (Figure 2); the differences between the standard of care (Arm 1) and the experimental arms (2 and 3) were not statistically significant. Similarly, the overall differences between Kaplan-Meier curves for response duration in Figure 2 were not statistically significant ($p = 0.10$). Thus, the difference in duration of response based on treatment arm was not statistically significant. Using proportional hazard modeling, only age and baseline CD4 count were associated with duration of vaccine response (data not shown).

No vaccine responder had evidence of new onset HBV infection. A fourth vaccine dose of Engerix B[®], 40 mcg, was administered to 82 subjects who were vaccine non-responders. Only 23% demonstrated antibody level of ≥ 10 IU/mL following this fourth vaccination.

All vaccine regimens were well tolerated and safe. No severe adverse events were observed. Vaccine associated events included headache (6), asthenia (1), arthralgia (2), somnolence (1), syncope (1), injection site pain (3), and myalgia (3) and most were mild in severity (grade 1 or 2). Only one grade 3 adverse event, arthralgia, was possibly related to study vaccine. There were no differences in events between vaccine arms.

DISCUSSION

In this study of HIV-infected youth, 70% of HBV vaccine recipients demonstrated vaccine response 28 days after completing the series, a substantial improvement over rates in prior reports. Only one study of patients in Thailand, aged 21 to 45 years and receiving HAART with undetectable HIV-1 viral loads, demonstrated a similar response rate of 71% following vaccination with Engerix B[®], 20 mcg.²¹ The improved response among our subjects may be due to younger age (mean = 20 years) or to higher CD4 counts. In adult trials, younger age has been associated with improved vaccine response,²²⁻³¹ while the median CD4 count of 460 cells/mL in our population (only 13% of our subjects had CD4 < 200 cells/mL) is greater than that in many of the adult studies of HBV vaccination.¹²⁻¹⁴⁻¹⁶⁻¹⁸⁻²⁰⁻²¹⁻²²⁻²⁴

A key finding of this study is that vaccination with increased dose of HBV antigen is an independent predictor of short term vaccine response, modified by CD4 count. This result supports previous studies in adults. Fonseca evaluated 210 HIV-infected adults randomized to receive Engerix B[®], either 20 mcg or 40 mcg per dose, in a three-dose series.¹⁸ Overall, they report a 34% response rate with the 20 mcg dose compared to a 47% response rate with the 40 mcg dose ($p=0.07$), but they found a statistically significant difference between doses when the analysis was limited to subjects with CD4 ≥ 350 cells/mL or to subjects with HIV-1 viral loads <10,000 copies/mL. Our study also found better response for the 40 mcg arm at higher CD4 counts. Similarly, Cornejo-Juarez demonstrated improved response to higher dose vaccines but only in patients with CD4 ≥ 200 cell/mL.³⁻²⁴ Our results support these findings by establishing the interaction between vaccine response and CD4 level, with the odds ratio for vaccine response rising from 1.34 for CD4 of 305 (first quartile for our participants) to 8.23 for CD4 of 668 (third quartile).

We also demonstrated improved vaccine response and higher levels of HBsAb to 20 mcg of HBV antigen when it was combined with HAV antigen in Twinrix[®]. Knoll et al and Ambrosch et al both demonstrated a trend toward higher levels of HBsAb when the combination vaccine was used compared to monovalent HBV vaccine in HIV-uninfected youth.²⁷⁻²⁹ We believe this is the first study to compare Twinrix[®] with monovalent HBV vaccine in an HIV-infected population. In a study of 97 HIV-infected adults reported by Kim, one third of the subjects received Twinrix[®]. However, no analysis of response in these subjects compared to monovalent HBV vaccine was performed.²² Twinrix[®] could potentially be used routinely in a clinic setting because it can be safely administered to HAV seropositive individuals. Therefore, it would not be necessary to assess HAV immune status prior to vaccination. Also of interest, while improved response was seen with combination vaccination, pre-existing antibody to HAV did not predict HBV response in subjects receiving Twinrix[®].

Factors previously reported to affect immunogenicity of HBV vaccine were explored, but only treatment arm and higher baseline CD4 count were independent predictors of response. BMI and smoking status did not influence immunogenicity. These factors are important

predictors among immunocompetent patients, but have not emerged as important factors in HIV-infected individuals,^{32,33} probably because immune status, evidenced by CD4 counts, HIV-1 viral loads, and HAART are stronger predictors of vaccine response in HIV-infected populations.

Route of infection was explored as a factor related to immune response. We observed no differences in response rates among perinatally infected youth compared to non-perinatally infected youth ($p=0.07$). However, we did observe marginally statistically significant response rates when perinatally infected youth were compared to those infected via high risk behaviors ($p=0.046$). We suggest that the status of the immune system as manifested by the CD4 count rather than the mode of infection underlies these findings.

Management of patients lacking immune response following vaccination remains controversial. Booster vaccines, using both standard and increased amounts of antigen, have been evaluated with highly variable success (5–78%).^{4,10,12,14,19,31,34,35} Our poor rate of seroconversion, 23%, following an additional dose of HBV vaccine was similar to Tayal¹⁴ and Bloom³⁴ where 1–3 additional doses of vaccine in non-responders following standard dose regimens resulted in seroconversion of 25% and 29%, respectively. Boosters with 1–3 double dose of vaccine has also been reported to be effective following initial failure of standard dose of antigen but again with highly variable results.^{4,19,31,35} In adult studies, 1–3 additional boosters resulted in 51 and 73% seroconversion.^{19,31} In perinatally infected children, 1–2 doses resulted in 14 and 73% seroconversion.^{4,35} Unfortunately the findings of this study do not further inform this controversy.

We observed high levels of vaccine response after completion of the vaccinations series, along with statistically significant differences between standard of care (Arm 1) and the experimental Arms (2 and 3). However, the differences between arms were not statistically significant at week 72, and antibody levels waned over this period. At week 72, approximately half of the subjects had HBsAb levels thought to be protective. This result is similar to the REACH cohort where approximately 40% of HIV-infected youth who had ever received HBV vaccination had protective antibody levels. Declining antibody levels may increase risk for HBV infections in this population.³⁶

Despite a history of prior HAV vaccination in only 5% of the evaluable subjects receiving Twinrix[®], 53% were seropositive at baseline. Response to HAV immunization was excellent with 98% seropositive at week 28. This finding is consistent with prior studies that reported seroresponse rates of 84.5% in HIV-infected children and adolescents following 2 doses of vaccine and 88.4% in HIV-infected adults following a 3-dose series.^{37,38} Higher CD4% and lower viral loads have been correlated with HAV response in HIV-infected children and adolescents.^{37,39} In HIV-infected adults, CD4 > 350 cells/mL was associated with improved response, though not statistically significant.³⁸

In summary, vaccination with Engerix B[®], 40 mcg, or Twinrix[®] resulted in greater HBV vaccine response compared to standard dose Engerix B[®], 20 mcg, at week 28. Since vaccination with both HBV and HAV is recommended in HIV-infected patients, protection for both infections may be achieved using one vaccine series with Twinrix[®], potentially improving patient acceptance and reducing cost. In addition, because higher CD4 count was an independent predictor of vaccine response, consideration may be given to stabilizing patients on HAART and increasing CD4 counts prior to initiating HBV vaccination, though the risk and benefit of delaying vaccination must be considered and the patient educated about transmission routes for HBV and avoidance of infection risk.

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Figure 1.
Patient flow based on intent-to-treat analysis.

Figure 2.
Proportion of subjects with HBsAb of ≥ 10 IU/mL by treatment arm at Weeks 28, 48, and 72.

Table 1

Baseline Characteristics of Study Population who were Randomized and had Week 28 Serology Result Available (Evaluable Population).

	Total Evaluable N=336	Arm 1 Engerix-B® 20mcg N = 106	Arm 2 Engerix-B® 40mcg N = 112	Arm 3 Twinrix® N = 118
Mean Age (range)	20.44 ^a	20.49	20.82	20.04
Gender				
Male	132 (39%)	41 (49%)	46 (41%)	45 (38%)
Female	204 (61%)	65 (61%)	66 (59%)	73 (62%)
Race				
Black	158 (47%)	52 (49%)	48 (42%)	58 (49%)
White	84 (25%)	23 (22%)	29 (26%)	32 (27%)
Other ^b	94 (28%)	31 (29%)	35 (31%)	28 (24%)
Hispanic Ethnicity	204 (61%) ^a	62 (61%)	72 (74%)	70 (77%)
Route of Infection				
Heterosexual Contact	187 (56%)	59 (56%)	61 (54%)	67 (57%)
MSM	62 (18%)	21 (20%)	23 (21%)	18 (15%)
Perinatal	65 (19%)	19 (18%)	22 (20%)	24 (20%)
Other ^c	22 (7%)	7 (6%)	6 (5%)	9 (8%)
One prior HBV Vaccination	47 (14%) ^a	13 (12%)	16 (14%)	18 (15%)
CD4+ T-Cell Count				
Median (IQR)	460 (305, 668)	452 (280, 668)	491 (296, 645)	451 (330, 668)
<200	44 (13%)	17 (16%)	16 (14%)	11 (9%)
200–350	69 (21%)	24 (23%)	19 (17%)	26 (22%)
351–500	77 (23%)	22 (21%)	24 (22%)	31 (26%)
>500	146 (43%)	43 (40%)	53 (47%)	50 (43%)
Nadir CD4+ T-Cell Count				
Median (IQR)	339 (207, 531)	322 (217,497)	386 (227, 598)	325 (184,527)
<200	65 (19%)	19 (18%)	20 (18%)	26 (22%)
200–350	74 (22%)	26 (24%)	24 (21%)	24 (20%)
351–500	50 (15%)	18 (17%)	14 (13%)	18 (15%)
>500	81 (24%)	20 (19%)	35 (31%)	26 (22%)
Missing	66 (20%)	23(22%)	19 (17%)	24 (20%)
HIV-1 Viral Load (log ₁₀)				
Median (IQR)	4.02 (3.35, 4.69)	4.19 (3.62, 4.73)	4.03 (3.22, 4.70)	3.83 (3.43, 4.46)
< 400	24 (7%)	9 (8%)	9 (8%)	6 (5%)
400 to 10,000	99 (29%)	22 (21%)	32 (29%)	45 (38%)
10,001 to 100,000	95 (28%)	40 (38%)	33 29%)	22(19%)
>100,001	36 (11%)	11 (10%)	12 (11%)	13 (11%)
Missing	82 (24%)	24 (23%)	26 (23%)	32 (27%)
Current ART Regimen				

	Total Evaluable N=336	Arm 1 Engerix-B® 20mcg N = 106	Arm 2 Engerix-B® 40mcg N = 112	Arm 3 Twinrix® N = 118
PI-based HAART	78 (23%)	24 (23%)	28 (25%)	26 (22%)
NNRTI-based HAART	49 (15%)	13 (12%)	12 (10%)	24 (20%)
NRTI-based HAART	5 (1.5%)	1 (1%)	3 (3%)	1 (1%)
Other	15 (4.5%)	6 (6%)	2 (2%)	7 (6%)
None	189 (56%)	62 (58%)	67 (60%)	60 (51%)
Current Smoking	102 (30%)	38 (36%)	33 (29.5%)	31 (26%)
Never Smoked	197 (59%)	52 (49%)	66 (59%)	79 (67%)
Site Location				
International	135 (40%)	44 (42%)	46 (41%)	45 (38%)
Domestic	201 (60%)	62 (58%)	66 (59%)	73 (62%)

^a Evaluable population differed from randomized population by age (20.4 vs. 21.8 yrs, $p=0.004$), Hispanic ethnicity (60.7% vs. 42.9%, $p=0.04$) and having received a prior HBV vaccine (14% vs. 31.4%)

^b Other includes mixed race, Native American, Alaskan Native, or Unknown

^c Other includes infection drug use, transfusion, combination of risk factors, and unknown routes

Table 2
Logistic Regression Analysis of Week 28 Vaccine Response Showing Results of Unadjusted and Adjusted Odds Ratios

	Unadjusted Model			Adjusted Model		
	OR	95% CI	P - Value	OR	95% CI	P - Value
Study Arm						
Engerix B®, 20 mcg, Arm	Ref.	--	--	Ref.	--	--
Engerix B®, 40 mcg, Arm	1.79	1.01 to 3.18	0.045	0.29 ¹	0.07 to 1.19	0.0853
Twinrix Arm®	2.01	1.14 to 3.57	0.016	1.99	1.09 to 3.63	0.0244
Gender						
Male	Ref.	--	--	-	-	-
Female	1.63	1.02 to 2.61	0.0434	-	-	-
Location						
Domestic	Ref.	--	--	-	-	-
International	0.58	0.36 to 0.93	0.0229	-	-	-
Baseline CD4+ Count (per 100 cells/mm ³)	1.48	1.31 to 1.68	<0.0001	1.32 ²	1.16 to 1.51	<0.0001
Baseline CD4+ Percentage	1.10	1.07 to 1.13	<0.0001	-	-	-
Nadir CD4+ Count (per 100 cells/mm ³)	1.28	1.13 to 1.45	0.0001	-	-	-
Baseline HIV-1 Viral Load (log 10)	0.700	0.52 to 0.94	0.0159	-	-	-
Interaction term (containing CD4+ count and Engerix B®, 40 mcg Arm)	-	-	-	1.65 ³	-	0.0048

Note: Variable with "--" did not occur in the model indicated by the column heading.

¹ Odds ratio depends on CD4 count due to interaction. For example, OR=0.29 for CD4 count = 0; OR=2.91 for CD4 count = 460 (median CD4 count for the evaluable study population).

² Odds ratio depends on Treatment due to interaction. OR=1.003 for Engerix 20 group; OR=1.008 for Engerix 40 group.

³ Odds ratio for interaction is the antilog of the corresponding logistic regression coefficient.