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Immunogenicity and Immunologic Memory after Hepatitis B Virus Booster Vaccination in HIV-Infected Children Receiving Highly Active Antiretroviral Therapy

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Abstract

Background—Hepatitis B virus (HBV) is an important cause of comorbidity in human immunodeficiency virus (HIV)–infected individuals. The immunogenicity of HBV vaccination in children receiving highly active antiretroviral therapy (HAART) was investigated.

Methods—HIV-infected children receiving HAART who had low to moderate HIV loads and who had previously received 3 doses of HBV vaccine were given an HBV vaccine booster. Concentrations of antibody to hepatitis B surface antigen (anti-HBs) were determined before vaccination and at weeks 8, 48, and 96. A subset of subjects was administered a subsequent dose, and anti-HBs was measured before and 1 and 4 weeks later.

Results—At entry, 24% of 204 subjects were seropositive. Vaccine response occurred in 46% on the basis of seropositivity 8 weeks after vaccination and in 37% on the basis of a 4-fold rise in antibody concentration. Of 69 subjects given another vaccination 4–5 years later, immunologic memory was exhibited by 45% on the basis of seropositivity 1 week after vaccination and by 29% on the basis of a 4-fold rise in antibody concentration at 1 week. Predictors of response and memory included higher nadir and current CD4 cell percentage, higher CD19 cell percentage, and undetectable HIV load.

Conclusions—HIV-infected children frequently lack protective levels of anti-HBs after previous HBV vaccination, and a significant proportion of them do not respond to booster vaccination or demonstrate memory despite receiving HAART, leaving this population insufficiently protected from infection with HBV.

Hepatitis B virus (HBV) is an important cause of comorbidity in individuals infected with human immunodeficiency virus (HIV). High rates of HBV infection among HIV-infected adolescents and young adults are documented [1]. Coinfection is associated with greater HBV replication and viremia, persistence of hepatitis B surface antigen, and higher rates of chronic carriage, superinfection, reactivation, transmission, and chronic active hepatitis, cirrhosis, and death [2–4]. Therefore, there is a need to protect HIV-infected populations against HBV. Many studies have indicated that seroconversion rates after HBV vaccination are low among children (12%–78%) and among adolescents and adults (18%–56%) infected

with HIV, compared with rates of >90% among HIV-uninfected populations [1–16]. Although some studies have suggested that seroconversion rates are improved among HIV-infected adults treated with highly active antiretroviral therapy (HAART), they remain in the range of 32%–59% [2–4,16]. The effect that HAART has on the response to HBV vaccine among children has not been sufficiently studied. P1024 is a multicenter study of the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) designed to evaluate immunogenicity and safety of vaccines in HIV-infected children receiving HAART, and P1061s is a substudy that evaluated immunologic memory after vaccination in P1024. The present report focuses on immunogenicity, safety, and memory responses associated with HBV vaccination.

Methods

Study population

HIV-infected children 2 to <19 years old at 39 sites were eligible if they fit into the immunologic strata defined in table 1. Inclusion criteria included perinatal infection (strata 2–4 only), treatment with the same HAART regimen (3 antiretrovirals from 2 classes) for 6 months (3 months for stratum 1), and plasma HIV RNA level (Amplicor; Roche) <30,000 copies/mL (<60,000 copies/mL for stratum 1) [17,18]. Subjects who completed P1024 between June 2001 and March 2002 were eligible for P1061s, which enrolled subjects between February 2006 and August 2006.

Study protocol

Written informed consent was obtained, and the human experimentation guidelines of the US Department of Health and Human Services and participating institutions were followed. Subjects who had completed an approved primary HBV vaccine series and had no history of HBV infection per medical-record review were eligible for the HBV vaccine portion of P1024 [19]. HBV vaccine (Recombivax HB recombinant hepatitis B vaccine, pediatric/adolescent formulation [5 µg of hepatitis B surface antigen]; Merck & Co; 0.5-mL dose administered intramuscularly) and pneumococcal conjugate vaccine were administered at entry, and additional vaccines were given at other visits [17,18]. Antibody to hepatitis B surface antigen (anti-HBs), plasma HIV RNA, and quantitative lymphocyte subsets were measured at entry and at weeks 8, 48, and 96.

Subjects who received HBV vaccine in P1024 without experiencing a grade 3 or higher adverse event and who had neither received HBV vaccine nor had been infected with HBV per medical-record review since the conclusion of P1024 were eligible to have immunologic memory to HBV vaccine evaluated in P1061s. These subjects were administered HBV, pneumococcal, and measles-mumps-rubella vaccines at entry. Anti-HBs was measured at entry and on days 7 and 28, and plasma HIV RNA and lymphocyte subsets were measured at entry.

Laboratory assays and immunologic definitions

Anti-HBs concentrations were determined with the ETI-AB-AUK PLUS immunoassay (DiaSorin). World Health Organization IgG anti-HBs standards (ABAU-STD-SET assay; DiaSorin) were included, and a linear standard curve ranging from 0 to 160 mIU/mL was generated with each run. The lower limit of quantitation was 5 mIU/mL. Subject specimens were diluted 1:2, and those yielding a result >160 mIU/mL were further diluted and retested to yield readings between 5 and 160 mIU/mL. A concentration >10 mIU/mL was considered to be seropositive and protective. Concentrations <5 mIU/mL were set at 2.5 mIU/mL for quantitative analyses.

Vaccine response in P1024 was defined and analyzed on the basis of (1) week 8 seropositivity or (2) week 8 seropositivity with an antibody concentration at least 4-fold greater than that at baseline. Immunologic memory in P1061s was analyzed on the basis of (1) seropositivity at P1061s entry or day 7 or (2) 4-fold rise in antibody concentration between P1061s entry and day 7. Evidence of a memory or primary response in P1061s was defined as (1) seropositivity on day 28 or (2) 4-fold rise in antibody concentration between P1061s entry and day 28.

Statistical analysis

HBV vaccine recipients for whom results were available at entry and at week 8 (± 4 weeks) were included in the P1024 analyses. P1061s HBV vaccine recipients for whom results were available at entry, on day 7 (± 2 days), and on day 28 (± 8 days) were included in the P1061s analyses. Univariate logistic regression analyses were performed to identify potential predictors ($P < .1$) of a protective anti-HBs concentration at P1024 entry and of a vaccine response after the P1024 booster to be included in multivariate logistic regression analyses. They were also used to identify predictors of memory in P1061s.

Results

P1024 study population

Of 263 children enrolled, 221 qualified for the HBV vaccine portion of P1024 on the basis of previous HBV vaccination and a negative history of HBV infection. Of these, 204 had entry and week 8 anti-HBs results and constituted the P1024 analysis group. Baseline characteristics are displayed in table 1.

P1024 antibody concentrations—immunologic strata combined

At entry, 24% of subjects had anti-HBs concentrations ≥ 10 mIU/mL. The proportion with concentrations ≥ 10 mIU/mL increased by week 8 to 46%, then fell slightly, with 38% being seropositive at week 96 (table 2 and figure 1). A response to booster vaccination based on an anti-HBs concentration ≥ 10 mIU/mL at week 8 and a 4-fold rise in antibody concentration occurred in 37% (95% confidence interval, 31%–44%). Median antibody concentrations among the entire population were low at entry and showed only a modest gain at week 8. The median concentration among the subgroup with anti-HBs concentrations ≥ 10 mIU/mL at week 8 reached 190.0 mIU/mL at week 8 and decreased thereafter (decrements of 72%, 23%, and 78% between weeks 8 and 48, 48 and 96, and 8 and 96, respectively).

P1024 antibody concentrations according to immunologic strata

At entry, a minority in all strata had anti-HBs concentrations ≥ 10 mIU/mL. The percentages with protective levels increased significantly between baseline and week 8 in strata 2–4, although it reached $>50\%$ only in stratum 4 (table 2 and figure 1). These percentages remained relatively stable beyond week 8 for stratum 4, whereas the percentage dropped in the other strata between weeks 8 and 48. The proportion with anti-HBs concentrations ≥ 10 mIU/mL remained significantly higher at week 96 versus baseline for strata 2 and 4. At weeks 8, 48, and 96, the percentage of subjects who were seropositive generally increased with higher immune stratum; pairwise analysis found significant differences at each time point between stratum 4 and each of the other strata, but not among strata 1–3. Similarly, response rates based on a 4-fold rise in antibody concentration at week 8 were greater with higher immune stratum ($P = .001$, Fisher exact test); pairwise analysis demonstrated differences between the stratum 4 response rate of 56% and that of each of the other strata ($P = .01$), but no significant differences in response rates among strata 1–3 were observed (10%, 30%, and 30%, respectively).

Antibody concentrations in strata 1–3 were low and rose minimally or not at all between baseline and week 8, with no differences between week 96 and entry median concentrations. The increase in antibody concentration was larger for stratum 4, and its median concentration remained higher at week 96 than at entry (table 2). Within each of immunologic strata 2–4, median levels among the subgroup with anti-HBs concentrations ≥ 10 mIU/mL at week 8 increased from entry to week 8, with similar decrements within each stratum thereafter (65%–89% between weeks 8 and 96). Antibody concentrations among this subgroup remained significantly higher at week 96 than at baseline for strata 2 and 4. Among subjects with anti-HBs concentrations ≥ 10 mIU/mL at week 8, antibody levels among strata 2–4 did not differ significantly at baseline, whereas at subsequent time points concentrations for stratum 4 exceeded those for strata 2 and 3.

P1024 antibody concentrations and HIV RNA level

There was a significant inverse relationship between the proportion with anti-HBs concentrations ≥ 10 mIU/mL and ascending HIV load group at each time point after vaccination, with significant differences between subjects with HIV loads ≤ 400 versus >5000 copies/mL (figure 2). Additionally, the proportion with a vaccine response defined as a week 8 anti-HBs concentration ≥ 10 mIU/mL and ≥ 4 -fold rise in antibody concentration was inversely related to ascending HIV load group (46%, 26%, and 21%, respectively; $P = .005$, Fisher exact test), with pairwise analyses showing significant differences between subjects with an HIV load ≤ 400 versus 401–5000 ($P = .04$) or >5000 ($P = .006$) copies/mL.

Predictors of P1024 entry seropositivity

Univariate analyses identified associations between baseline seropositivity and immune stratum, age, and time since the last previous HBV vaccination. In a multivariate model, seropositivity remained associated with immune stratum (odds ratio [OR] for group 4 versus groups 1–3 combined, 2.01; $P = .04$) and previous HBV vaccine within 4 years of entry (OR, 4.57; $P < .001$); age did not add significantly to the model. In a separate multivariate analysis examining the components of immune stratification, a higher nadir CD4 cell percentage before HAART was predictive of entry seropositivity (OR, 1.27; $P = .004$), whereas the CD4 cell percentage at study screening did not add predictive power.

Predictors of P1024 vaccine response

Univariate analyses identified strong associations between response and baseline seropositivity and immune stratum (figure 3), plus associations with age, entry HIV load, and entry CD19 cell percentage. The best-fitting multivariate model found that response defined as a ≥ 4 -fold rise in antibody concentration was associated with a baseline antibody level ≥ 10 mIU/mL (OR, 5.54; $P < .001$), immune stratum 4 (OR, 2.69; $P = .005$), entry HIV load ≤ 400 copies/mL (OR, 2.03; $P = .05$), and CD19 cell percentage (OR for every 5% increase in CD19 cell percentage, 1.23; $P = .10$). Age, associated with immune stratum, was not included in the final model. A separate multivariate analysis examining the components of immune stratification found that screening CD4 cell percentage was predictive of a response (OR for every 5% increase in CD4 cell percentage, 1.31; $P = .002$), whereas nadir CD4 cell percentage before HAART did not add predictive power.

The main predictor of vaccine response using the alternative definition—week 8 anti-HBs concentration ≥ 10 mIU/mL—was a protective antibody level at entry: 49 (98%) of 50 subjects who were seropositive at entry maintained protective levels at week 8. In contrast, only 44 (29%) of 154 subjects with anti-HBs concentrations <10 mIU/mL at entry achieved protective levels. Among these 154 subjects, predictors of week 8 seropositivity in univariate models were similar to predictors of a ≥ 4 -fold rise in antibody concentration: immune stratum 4 (OR, 2.77; $P = .01$), entry HIV load ≤ 400 copies/mL (OR, 4.03; $P = .$

001), and CD19 cell percentage (OR, 1.32; $P = .03$). Because of the high correlation among these variables, they could not be entered in a multivariate model.

P1061s study population

Of 224 eligible P1024 subjects, 101 were enrolled into P1061s; 85 received HBV vaccine in both P1024 and P1061s, and 69 had sufficient data for inclusion in P1061s analyses. Their P1024 baseline characteristics and P1024 serologic results were similar to those of the entire P1024 HBV analysis group. The median time from P1024 HBV vaccination to P1061s entry was 4.6 years (range, 4.0–5.1 years). The median CD4 cell percentage at P1061s entry was 34%; 86% had a CD4 cell percentage $\geq 25\%$, 7% had one 15% to $<25\%$, and 7% had one $<15\%$. Only 4 of 69 had a CD4 cell percentage that would no longer have placed them in their original P1024 stratum. Eighty-six percent continued to receive HAART, 7% were receiving non-HAART antiretroviral therapy, and 7% were receiving no antiretroviral medications; 59% had an HIV load ≤ 400 copies/mL.

P1061s antibody concentrations

At P1061s entry, 17 (25%) of 69 subjects were seropositive, similar to the seropositivity rate at P1024 entry (24%) but less than that at week 96 (38%). Seropositivity at P1061s entry was more likely in subjects who manifested seropositivity at P1024 entry, seropositivity 8 weeks after the P1024 HBV vaccination, or a 4-fold rise in antibody concentration in P1024 than in those who had not (87% vs 8%, 46% vs 3%, and 41% vs 14%, respectively; $P = .02$). At week 1, 31 (45%) of 69 were seropositive and had immunologic memory defined as seropositivity at entry or 1 week, whereas 20 (29%) of 69 demonstrated memory defined as a 4-fold rise in antibody concentration between entry and week 1. At week 4, 45 (65%) of 69 were seropositive (31 memory and 14 primary responses), and 40 (58%) of 69 exhibited a 4-fold rise in antibody concentration from entry (20 memory and 20 primary responses). Median antibody concentrations among all subjects were 2.5 mIU/mL (interquartile range [IQR], 2.5–9.2 mIU/mL) at P1061s entry, 2.5 mIU/mL (IQR, 2.5–107.4 mIU/mL) at week 1, and 131.9 mIU/mL (IQR, 2.5–951.9 mIU/mL) at week 4. Median antibody concentrations among subjects who demonstrated memory on the basis of seropositivity at entry or week 1 were 27.6 mIU/mL (IQR, 2.5–170.4 mIU/mL) at entry, 113.2 mIU/mL (IQR, 72.9–1692.3 mIU/mL) at week 1, and 1005.8 mIU/mL (IQR, 290.2–7541.0 mIU/mL) at week 4.

There were no significant differences in the proportion of subjects who were seropositive at P1061s entry according to immune strata (26%, 28%, and 20% in immune strata 2–4, respectively). However, the proportion demonstrating memory increased with higher immune stratum (26%, 48%, and 65% [$P = .04$] for seropositivity at entry or week 1 and 9%, 32%, and 50% [$P = .01$] for a 4-fold rise in antibody concentration between entry and week 1; Fisher exact test). At week 4 (memory or primary response), there were no significant differences among strata 2–4 in the rates of seropositivity (61%, 68%, and 70%) or a 4-fold rise in antibody concentration (52%, 64%, and 60%).

The proportion of subjects who were seropositive at P1061s entry did not differ according to HIV load at P1024 or P1061s entry. In contrast, the proportion with memory defined either as seropositivity at P1061s entry or week 1 or as a 4-fold rise in antibody concentration between P1061s entry and week 1 was greater in subjects with an HIV load ≤ 400 at P1024 entry (58% vs 14% [$P = .001$] and 42% vs 0% [$P = .001$], respectively; Fisher exact test) or at P1061s entry (56% vs 25% [$P = .02$] and 39% vs 13% [$P = .03$], respectively). Rates of seropositivity by week 4 after the P1061s vaccination (memory or primary response) and of a 4-fold increase in antibody concentration by week 4 (memory or primary response) were also greater in subjects with an HIV load ≤ 400 copies/mL either at P1024 entry (75% vs

43% [$P = .01$] and 69% vs 33% [$P = .008$], respectively; Fisher exact test) or at P1061s entry (78% vs 42% [$P = .006$] and 76% vs 29% [$P = .001$], respectively).

Predictors of memory identified in P1061s

Predictors of memory defined as seropositivity at entry or 1 week after boosting in P1061s included P1024 entry seropositivity, week 8 seropositivity, and a 4-fold rise in antibody concentration; HIV load; and previous HBV vaccine within 4 years of P1024 entry (table 3). There was also evidence of an effect of immune stratum (with pairwise comparisons finding a difference only between immunologic strata 2 and 4) and CD19 cell percentage. Among CD4 cell percentage parameters, both higher nadir CD4 cell percentage before HAART and higher CD4 cell percentage at P1061s entry were associated with memory response. Analyses of predictors of memory defined as a 4-fold rise in antibody concentration between P1061s entry and week 1 yielded generally similar results (table 3).

HBV vaccine safety (P1024 and P1061s)

One subject (0.5%) developed grade 3 erythema and induration (≥ 25 mm but $<50\%$ of extremity) at the HBV vaccination site and generalized erythema after concurrent HBV and pneumococcal conjugate vaccination in P1024. No HBV vaccine-related grade 3 events occurred in P1061s. No grade 4 or life-threatening adverse events or deaths related to study vaccination occurred.

Discussion

Several factors contributed to the low rate of seropositivity (24%) at P1024 entry. Many subjects likely received primary HBV vaccination before starting HAART. Seroconversion rates and antibody titers after primary HBV vaccination in HIV-infected populations are lower than those in HIV-uninfected groups, even if given in the context of HAART [1–16]. The median interval from the last previous HBV vaccine to P1024 entry was almost 5 years. Rapid declines in anti-HBs concentrations, with a loss of protective levels in 15%–97% within 3–19 years after vaccination, have been described in HIV-uninfected populations [20–30]. Among HIV-infected patients, anti-HBs is less durable, with seroreversion being frequent within 1 year after vaccination [2,3,15,31]. The low rate of seropositivity at entry contrasts with one study that found that 91%–100% of children receiving HAART were seropositive several years after primary HBV vaccination but is consistent with another in which 1% of children >5 years old receiving HAART who were vaccinated during infancy were seropositive [2,32].

Booster vaccination in P1024 modestly increased the proportion with protective antibody concentrations to 46%, despite all subjects receiving sustained HAART, 84% having a CD4 cell percentage $\geq 25\%$, and 61% having an HIV load <400 copies/mL. Among responders, the median antibody concentration after boosting (190 mIU/mL) was low, compared with mean concentrations of 7096–15,623 mIU/mL among HIV-uninfected children 1 month after boosting 5 years after primary vaccination [23,29]. Even among subjects in stratum 4, who had never experienced low CD4 percentages, only 64% achieved protective antibody concentrations after boosting, and the median concentration among responders (303 mIU/mL) was low relative to that among HIV-uninfected children. The rate of decline in anti-HBs concentration among all responders was consistent with the 79%–96% fall in titers 1 year after boosting in HIV-uninfected children, but residual antibody concentrations were 10–100-fold lower than those in HIV-uninfected populations [23,29]. The low percentage with protective concentrations after the P1024 booster suggests that the majority lacked immunologic memory from primary vaccination and did not manifest a meaningful primary response to the subsequent single dose. That responses among children who have never had

a CD4 cell percentage <25% were inferior to those among HIV-uninfected populations provides evidence of immunologic dysfunction even with preserved CD4 cell percentages.

At P1061s entry, only 25% of subjects were seropositive, similar to the seropositivity rate at P1024 entry. Anamnestic responses after the P1061s booster were identified in a minority, with a relatively low median antibody concentration among responders. Among subjects who never had a low CD4 cell percentage (stratum 4), only 50%–65% had evidence of memory. These findings indicate a low frequency of memory induction after primary vaccination and the P1024 HBV vaccine booster, even with that booster having been administered during HAART. This contrasts with the experience in HIV-uninfected children and adults, of whom the majority achieve protective antibody levels after a booster remote from primary vaccination, including anamnestic responses in 73% to >95% of those who had lost detectable anti-HBs after primary vaccination, but is consistent with low rates of anamnestic responses to booster vaccination observed among HIV-infected subjects [23,26–31,33–37]. Our subjects did mount response rates of 58%–65% by 4 weeks after their P1061s booster (their fifth to seventh dose of vaccine), reflecting a combination of memory or primary responses. The results suggest that multiple vaccine doses in the context of HAART are safe and may improve response rates and provide support for a possible strategy of periodic checking of antibody titers and boosting when indicated [38]. However, this strategy would still leave a substantial proportion without protective antibody levels and, likely, long-lasting memory.

CD4 cell percentage, HIV load, and CD19 cell percentage were predictors of various measures of response to HBV vaccination, including HBV seropositivity at P1024 entry, response to the P1024 vaccine booster, and memory identified in P1061s. For entry seropositivity, the historical nadir CD4 cell percentage was a key determinant, whereas important parameters for response to P1024 booster vaccination were higher CD4 cell percentage and CD19 cell percentage and lower HIV load at P1024 entry, rather than historical values. Interestingly, for memory responses detected in P1061s there was evidence that historical data (nadir CD4 cell percentage) and more recent values (CD4 cell percentage, CD19 cell percentage, and HIV load at P1024 and/or P1061s entry) were predictive. Experience in other HIV-infected populations demonstrated that antibody response and persistence after primary HBV vaccination correlate with higher total and memory CD4 cell counts, lower HIV load, and levels of interleukins 4 and 10 [1,3–6,10,11,16,31,39]. Suppressed viral replication is associated with decreased proinflammatory cytokines and restoration of T cell responses, whereas ongoing viremia is associated with depletion of memory CD4 cells and activation of CD8 cells, which may account for poor response to HBV vaccine [5,9]. Studies of HIV-infected individuals also indicate that CD19 (B) cells, including memory B subsets, are associated with responsiveness to vaccines and memory [40]. Although not consistent across all studies, the literature and our findings collectively suggest that response to HBV vaccine is likely to be best in the context of stable HAART, higher CD4 cell counts, and controlled HIV replication [5,41]. This mirrors findings with pneumococcal conjugate, pneumococcal polysaccharide, and pertussis vaccination in P1024 and with varicella, measles, and hepatitis A vaccines [17,18,42–44]. The strong additional association between baseline antibody concentration in P1024 and both response to the P1024 HBV vaccine booster and memory detected in P1061s was similar to observations with pneumococcal and pertussis vaccines in our population and in a study of HBV vaccine in HIV-uninfected children and may reflect non-HIV-related determinants of HBV vaccine response, such as HLA alloantigens and polymorphisms in immunoregulatory cytokine genes [3,17,18,30,45].

Our study has several limitations. We were unaware of whether subjects were responders to their previous HBV vaccination or whether they were receiving HAART when they received

their primary series. Our study administered 2 standard pediatric vaccine doses; we did not evaluate a repeat 3-dose series during HAART or higher doses recommended in healthy and immunosuppressed adults [3,11,19,41]. Available data are conflicting as to whether higher doses improve immunogenicity in HIV-infected adults and children [3,6,8,16]. We did not assess adjuvants (eg, granulocyte-macrophage colony-stimulating factor), which increased HBV vaccine responses in HIV-infected adults [46]. In P1024, antibody measurements 8 weeks after the booster may have missed earlier peak responses, and in P1061s some responses between days 7 and 28 could have reflected memory responses and been miscategorized as primary responses, especially if memory responses manifested at a slower rate in HIV-infected children [30].

The data from P1024 and P1061s suggest that HIV-infected children frequently lack protective antibody levels after previous HBV vaccination. A significant proportion do not respond to booster vaccination despite effective HAART, nor do they demonstrate immunologic memory that may protect against future challenge; thus, many HIV-infected children are likely insufficiently protected from HBV infection. These data suggest that immune reconstitution with HAART may be incomplete. Further research into the reasons for this continued immunologic deficit is necessary. Although the response to HBV vaccine is likely improved if vaccine is given with higher CD4 and CD19 cell counts and a lower HIV load, novel strategies are required for more successful immunization of this population.

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References

1. Hoffman, ND.; Futterman, D.; Monte, D. Response to hepatitis B virus vaccination among a cohort of HIV+ youth [abstract Th B.4169]. Program and abstracts of the 11th International Conference on AIDS (Vancouver); International AIDS Society; 1996. p. 11
2. Siriakorn S, Puthanakit T, Sirisanthana T, Sirisanthana V. Prevalence of protective antibody against hepatitis B virus in HIV-infected children with immune recovery after highly active antiretroviral therapy. *Vaccine*. 2006; 24:3095–9. [PubMed: 16488516]
3. Laurence JC. Hepatitis A and B immunizations of individuals infected with human immunodeficiency virus. *Am J Med*. 2005; 118(Suppl 10A):75S–83S. [PubMed: 16271546]
4. Pasricha N, Datta U, Chawla Y, et al. Immune responses in patients with HIV infection after vaccination with recombinant hepatitis B vaccine. *BMC Infect Dis*. 2006; 6:65. [PubMed: 16571140]
5. Overton ET, Sungkanuparph S, Powderly WG, Seyfried W, Groger RK, Aberg JA. Undetectable plasma HIV RNA load predicts success after hepatitis B vaccination in HIV-infected persons. *Clin Infect Dis*. 2005; 41:1045–8. [PubMed: 16142673]
6. Fonseca MO, Pang LW, Cavaleiro NdP, Barone AA, Lopes MH. Randomized trial of recombinant hepatitis B vaccine in HIV-infected adult patients comparing a standard dose to a double dose. *Vaccine*. 2005; 23:2902–8. [PubMed: 15780739]
7. Thaithumyanon P, Punnahitananda S, Praisuwanna P, Thisyakorn U, Ruxrungtham K. Antibody response to hepatitis B immunization in infants born to HIV-infected mothers. *J Med Assoc Thai*. 2002; 85:277–82. [PubMed: 12117014]

8. Watanaveeradej V, Samakoses R, Kerdpanich A, et al. Antibody response to hepatitis B vaccine in infants of HIV-positive mothers. *Int J Infect Dis.* 2002; 6:240–1. [PubMed: 12718844]
9. Wilson CM, Ellenberg JH, Sawyer MK, et al. Serologic response to hepatitis B vaccine in HIV infected and high-risk HIV uninfected adolescents in the REACH cohort. *J Adolesc Health.* 2001; 29:123–9. [PubMed: 11530313]
10. da Mota Silveira Sasaki MG, Sobroza De Mello R, Focaccia Siciliano R, Wang L. Response of HIV/AIDS patients to hepatitis B recombinant vaccine. *Braz J Infect Dis.* 1998; 2:236–40. [PubMed: 11103014]
11. Rey D, Krantz V, Partisani M, et al. Increasing the number of hepatitis B vaccine injections augments anti-HBs response rate in HIV-infected patients: effects on HIV-1 viral load. *Vaccine.* 2000; 18:1161–5. [PubMed: 10649616]
12. Arrazola MP, de Juanes JR, Ramos JT, et al. Hepatitis B vaccination in infants of mothers infected with human immunodeficiency virus. *J Med Virol.* 1995; 45:339–41. [PubMed: 7775958]
13. Rutstein RM, Rudy B, Codispoti C, et al. Response to hepatitis B immunization by infants exposed to HIV. *AIDS.* 1994; 8:1281–4. [PubMed: 7802981]
14. Zuccotti GV, Riva E, Flumine P, et al. Hepatitis B vaccination in infants of mothers infected with human immunodeficiency virus. *J Pediatr.* 1994; 125:70–2. [PubMed: 8021789]
15. Zuin G, Principi N, Tornaghi R, et al. Impaired response to hepatitis B vaccine in HIV infected children. *Vaccine.* 1992; 10:857–60. [PubMed: 1455911]
16. Veiga AP, Casseb J, Duarte AJS. Humoral response to hepatitis B vaccination and its relationship with T CD45RA+ (naïve) and CD45RO+ (memory) subsets in HIV-1-infected subjects. *Vaccine.* 2006; 24:7124–8. [PubMed: 16884833]
17. Abzug MJ, Pelton SI, Song L, et al. Immunogenicity, safety, and predictors of response following a pneumococcal conjugate and pneumococcal polysaccharide vaccine series in human immunodeficiency virus-infected children receiving highly active antiretroviral therapy. *Pediatric AIDS Clinical Trials Group P1024. Pediatr Infect Dis J.* 2006; 25:920–9. [PubMed: 17006288]
18. Abzug MJ, Song L, Fenton T, et al. Pertussis booster vaccination in human immunodeficiency virus-infected children receiving highly active antiretroviral therapy. *Pediatrics.* 2007; 120:e1190–e1202. [PubMed: 17938165]
19. American Academy of Pediatrics. Hepatitis B. In: Pickering, LK.; Backer, CJ.; Long, SS.; McMillan, JA., editors. *Red book: 2006 report of the committee on infectious diseases.* 27th. Elk Grove Village, IL: American Academy of Pediatrics; 2006. p. 342–4.
20. Huang LM, Chiang BL, Lee CY, Lee PI, Chi WK, Chang MH. Long-term response to hepatitis B vaccination and response to booster in children born to mothers with hepatitis B surface antigen. *Hepatology.* 1999; 29:954–9. [PubMed: 10051503]
21. Liao SS, Li RC, Li H, et al. Long-term efficacy of plasma-derived hepatitis B vaccine: a 15-year follow-up study among Chinese children. *Vaccine.* 1999; 17:2661–6. [PubMed: 10418916]
22. Viviani S, Jack A, Hall AJ, et al. Hepatitis B vaccination in infancy in the Gambia: protection against carriage at 9 years of age. *Vaccine.* 1999; 17:2946–50. [PubMed: 10462228]
23. Williams IT, Goldstein ST, Tufa J, Tauillii S, Margolis HS, Mahoney FJ. Long term antibody response to hepatitis B vaccination beginning at birth and to subsequent booster vaccination. *Pediatr Infect Dis J.* 2003; 22:157–63. [PubMed: 12586980]
24. Ozaki T, Mochizuki H, Ichikawa Y, Fukuzawa Y, Yoshida S, Morimoto M. Persistence of hepatitis B surface antibody levels after vaccination with a recombinant hepatitis B vaccine: a 3-year follow-up study. *J Oral Sci.* 2000; 42:147–50. [PubMed: 11111325]
25. Poovorawan Y, Theamboonlers A, Hirsch P, et al. Persistence of antibodies to the surface antigen of the hepatitis B virus (anti-HBs) in children subjected to the Expanded Programme on Immunization (EPI), including hepatitis-B vaccine, in Thailand. *Ann Trop Med Parasitol.* 2000; 94:615–21. [PubMed: 11064763]
26. Chadha MS, Arankalle VA. Ten-year serological follow up of hepatitis B vaccine recipients. *Indian J Gastroenterol.* 2000; 19:168–71. [PubMed: 11059182]
27. Seto D, West DJ, Ioli VA. Persistence of antibody and immunologic memory in children immunized with hepatitis B vaccine at birth. *Pediatr Infect Dis J.* 2002; 21:793–5. [PubMed: 12233715]

28. Boxall EH, Sira A, El-Shuhkri N, Kelly DA. Long-term persistence of immunity to hepatitis B after vaccination during infancy in a country where endemicity is low. *J Infect Dis.* 2004; 190:1264–9. [PubMed: 15346336]
29. Duval B, Gilca V, Boulianne N, et al. Comparative long term immunogenicity of two recombinant hepatitis B vaccines and the effect of a booster dose given after five years in a low endemicity country. *Pediatr Infect Dis J.* 2005; 24:213–8. [PubMed: 15750456]
30. Samandari T, Fiore AE, Negus S, et al. Differences in response to a hepatitis B vaccine booster dose among Alaskan children and adolescents vaccinated during infancy. *Pediatrics.* 2007; 120:e373–81. [PubMed: 17636112]
31. Choudhury, S.; Hodes, D.; Peters, V. Antibody response to booster doses of hepatitis B vaccine in HIV-infected children [abstract I27]. Program and abstracts of the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy (Orlando); Washington, DC: American Society for Microbiology; 1994. p. 34
32. Zaccarelli-Filho CA, Ono E, Machada DM, et al. HIV-1 infected children on HAART: immunologic features of three different levels of viral suppression. *Cytometry B Clin Cytom.* 2007; 72:14–21. [PubMed: 17041945]
33. Banatvala J, Van Damme P, Oehen S. Lifelong protection against hepatitis B: the role of vaccine immunogenicity in immune memory. *Vaccine.* 2000; 19:877–85. [PubMed: 11115711]
34. Watson B, West DJ, Chilkatowsky A, Piercy S, Ioli VA. Persistence of immunologic memory for 13 years in recipients of a recombinant hepatitis B vaccine. *Vaccine.* 2001; 19:3164–8. [PubMed: 11312012]
35. Anamnestic response to administration of purified non-adsorbed hepatitis B surface antigen in healthy responders to hepatitis B vaccine with long-term non-protective antibody titres. *Vaccine.* 2002; 20:3725–30. [PubMed: 12399201]
36. Jongjirawisan Y, Ungulkraiwit P, Sungkanuparph S. Isolated antibody to hepatitis B core antigen in HIV-1 infected patients and a pilot study of vaccination to determine the anamnestic response. *J Med Assoc Thai.* 2006; 89:2028–34. [PubMed: 17214053]
37. Gandhi RT, Wurcel A, Lee H, et al. Response to hepatitis B vaccine in HIV-1–positive subjects who test positive for isolated antibody to hepatitis B core antigen: implications for hepatitis B strategies. *J Infect Dis.* 2005; 191:1435–41. [PubMed: 15809901]
38. Working Group on Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-Exposed and HIV-Infected Children. Guidelines for prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. [10 February 2009]. Available at: <http://aidsinfo.nih.gov>
39. Pasricha N, Datta U, Chawla Y, et al. Poor responses to recombinant HBV vaccination in patients with HIV infection. *Trop Gastroenterol.* 2005; 26:178–82. [PubMed: 16737046]
40. Hart M, Steel A, Clark SA, et al. Loss of discrete memory B cell subsets is associated with impaired immunization responses in HIV-1 infection and may be a risk factor for invasive pneumococcal disease. *J Immunol.* 2007; 178:8212–20. [PubMed: 17548660]
41. Soriano V, Puoti M, Bonacini M, et al. Care of patients with chronic hepatitis B and HIV co-infection: recommendations from an HIV-HBV international panel. *AIDS.* 2005; 19:221–40. [PubMed: 15718833]
42. Levin MJ, Gershon AA, Weinberg A, et al. Immunization of HIV-infected children with varicella vaccine. *J Pediatr.* 2001; 139:305–10. [PubMed: 11487761]
43. Berkelhamer S, Borock E, Elsen C, Englund J, Johnson D. Effect of highly active antiretroviral therapy on the serological response to additional measles vaccination in human immunodeficiency virus-infected children. *Clin Infect Dis.* 2001; 32:1090–4. [PubMed: 11264038]
44. Weinberg A, Gona P, Nachman SA, et al. Antibody responses to hepatitis A virus vaccine in HIV-infected children with evidence of immunologic reconstitution while receiving highly active antiretroviral therapy. *J Infect Dis.* 2006; 193:302–11. [PubMed: 16362896]
45. Wang C, Tang J, Song W, Lobashevsky E, Wilson CM, Kaslow RA. HLA and cytokine gene polymorphisms are independently associated with responses to hepatitis B vaccination. *Hepatology.* 2004; 39:978–88. [PubMed: 15057902]

46. Sasaki MG, Foccacia R, de Messias-Reason IJ. Efficacy of granulocyte-macrophage colony-stimulating factor (GM-CSF) as a vaccine adjuvant for hepatitis B virus in patients with HIV infection. *Vaccine*. 2003; 21:4545–9. [PubMed: 14575766]

Figure 1.

Proportion of P1024 subjects with protective concentrations (≥ 10 mIU/mL) of antibody to hepatitis B surface antigen (anti-HBs). Percentages are depicted at each P1024 study visit, for all subjects and by immune stratum (stratum 1, pre-highly active antiretroviral therapy [HAART] nadir CD4 cell percentage <15% and screening CD4 cell percentage <15%; stratum 2, pre-HAART nadir CD4 cell percentage <15% and screening CD4 cell percentage 15%; stratum 3, pre-HAART nadir CD4 cell percentage 15% to <25% and screening CD4 cell percentage 15%; and stratum 4, pre-HAART nadir CD4 cell percentage ≥ 25% and screening CD4 cell percentage ≥ 25%). Hepatitis B virus vaccine booster was given at week 0.

Figure 2.

Proportion of P1024 subjects with protective concentrations (≥ 10 mIU/mL) of antibody to hepatitis B surface antigen (anti-HBs) as a function of plasma human immunodeficiency virus (HIV) load at study entry. Differences among HIV load groups were present at weeks 8, 48, and 96 ($P = .03$, Fisher exact test). Pairwise comparisons demonstrated significant differences at each of these time points ($P = .03$) between subjects with an HIV load ≤ 400 copies/mL versus >5000 copies/mL but not between subjects with an HIV load ≤ 400 copies/mL versus 401–5000 copies/mL or between subjects with an HIV load 401–5000 copies/mL versus >5000 copies/mL. Hepatitis B virus vaccine booster was given at week 0.

Figure 3.

Median concentrations of antibody to hepatitis B surface antigen (anti-HBs) in P1024. Subjects are divided according to the presence or absence of protective antibody concentrations (≥ 10 mIU/mL) at entry and immune stratum (see figure 1). Higher median antibody concentrations at weeks 8, 48, and 96 were seen in subjects with baseline antibody concentrations ≥ 10 mIU/mL, and among these subjects the median concentration in stratum 4 was higher than that in strata 2 and 3 at weeks 8, 48, and 96. Although median antibody concentrations among subjects with baseline antibody concentrations < 10 mIU/mL did not exceed 10 mIU/mL at any of the subsequent time points, the median concentration in stratum 4 was higher than that in strata 2 and 3 at week 8 (7.2 mIU/mL in stratum 4 vs 2.5 mIU/mL in strata 2 and 3) and week 48 (5.3 mIU/mL in stratum 4 versus 2.5 mIU/mL in strata 2 and 3) but not at week 96 (2.5 mIU/mL in strata 2–4). Stratum 1 is not included because of the small number of subjects in each subgroup. Hepatitis B virus vaccine booster was given at week 0. Ab, anti-HBs.

Table 1
Characteristics of P1024 Hepatitis B Virus (HBV) Vaccine Recipients

Characteristic, parameter	All strata (n = 204)	Stratum 1 (n = 10)	Stratum 2 (n = 56)	Stratum 3 (n = 78)	Stratum 4 (n = 62)	p ^a
Age						
Median, years	9.1	13.9	10.1	9.4	5.5	<.001
7 years	66	80	77	72	47	.002
Male sex	46	60	50	41	47	.57
Race/ethnicity						.79
White Non-Hispanic	12	0	14	12	13	
Black Non-Hispanic	58	50	59	60	53	
Hispanic	30	50	27	28	32	
Asian/Pacific Islander	1	0	0	0	2	
CDC clinical classification						.01
N (nonsymptomatic)	11	0	4	13	16	
A (mildly symptomatic)	33	20	34	28	40	
B (moderately symptomatic)	37	40	30	43	34	
C (severely symptomatic)	20	40	32	16	8	
Pre-HAART nadir CD4 cell percentage						NA
Median	19	6	10	19	31	
<15%	33	100	100	0	0	
15% to <25%	37	0	0	100	0	
25%	30	0	0	0	100	
Screening CD4 cell percentage						NA
Median	34	14	29	36	39	
CDC immunologic classification III (<15%)	5	100	0	0	0	
CDC immunologic classification II (15% to <25%)	11	0	25	10	0	
CDC immunologic classification I (≥25%)	84	0	75	90	100	
Entry HIV RNA level						<.001
400 copies/mL	61	30	45	64	76	
401–5000 copies/mL	18	0	18	24	16	
>5000 copies/mL	20	70	38	12	8	

Characteristic, parameter	All strata (n = 204)	Stratum 1 (n = 10)	Stratum 2 (n = 56)	Stratum 3 (n = 78)	Stratum 4 (n = 62)	P ^a
Interval from last prior HBV vaccine to entry						
Median, years	4.8	3.8	5.2	4.8	4.4	.23
Interval 2 years	13	30	12	16	8	.20
No. of HBV vaccines before entry						.28
3	91	90	96	91	87	
4–5	9	10	4	9	13	

NOTE. Data are percentage of subjects, unless otherwise indicated. Immunologic strata were as follows: stratum 1, pre-HAART nadir CD4 cell percentage <15% and screening CD4 cell percentage <15%; stratum 2, pre-HAART nadir CD4 cell percentage <15% and screening CD4 cell percentage 15% to <25% and screening CD4 cell percentage 15% to <25%; and stratum 4, pre-HAART nadir CD4 cell percentage 25% and screening CD4 cell percentage 25%. CDC, Centers for Disease Control and Prevention; HAART, highly active antiretroviral therapy; NA, not applicable (immunologic groups were defined by pre-HAART nadir CD4 cell percentage and screening CD4 cell percentage).

^aFisher exact test for categorical variables and Kruskal-Wallis test for continuous variables.

Table 2
Serologic Status Before and After Hepatitis B Virus Vaccination in P1024, Overall and as a Function of Immune Stratum

End point, study time point ^d	All strata combined	Stratum 1	Stratum 2	Stratum 3	Stratum 4
Percentage with an anti-HBs concentration ≥ 10 mIU/mL (no. of subjects evaluated)					
Week 0	24.5 (204)	10.0 (10)	21.4 (56)	19.7 (76)	35.5 (62)
Week 8	45.6 (204) ^b	20.0 (10)	37.5 (56) ^b	39.5 (76) ^b	64.5 (62) ^{b,c}
Week 48	37.6 (201) ^b	10.0 (10)	27.3 (54) ^b	30.3 (76) ^b	60.7 (61) ^c
Week 96	37.9 (195) ^d	14.3 (7)	30.2 (53) ^d	28.0 (75)	60.0 (60) ^{c,d}
Antibody concentration among all subjects, median (IQR), mIU/mL ^e					
Week 0	2.5 (2.5–8.7)	2.5 (2.5–2.5)	2.5 (2.5–6.3)	2.5 (2.5–5.2)	2.5 (2.5–32.0)
Week 8	7.5 (2.5–143.6)	2.5 (2.5–9.4)	2.5 (2.5–32.8)	3.8 (2.5–70.9)	95.8 (2.5–774.8)
Week 48	2.5 (2.5–36.4)	2.5 (2.5–2.5)	2.5 (2.5–11.6)	2.5 (2.5–18.4)	24.7 (2.5–188.2)
Week 96	2.5 (2.5–37.0)	2.5 (2.5–2.5)	2.5 (2.5–13.0)	2.5 (2.5–16.5)	16.2 (2.5–247.1)
Antibody concentration among subjects with an anti-HBs level ≥ 10 mIU/mL at week 8, median (IQR), mIU/mL ^f					
Week 0	11.0 (2.5–72.6)	NA ^f	16.4 (2.5–40.9)	7.0 (2.5–76.6)	11.0 (2.5–126.2)
Week 8	190.0 (50.2–1184.9) ^g	NA ^f	224.7 (13.7–398.5) ^g	95.0 (46.7–648.9) ^g	303.4 (107.1–2038.9) ^{g,h}
Week 48	53.3 (10.6–307.2) ^g	NA ^f	25.2 (7.1–137.8) ^g	33.7 (7.3–249.1) ^g	122.6 (25.1–712.1) ^{g,h}
Week 96	41.0 (9.8–222.7) ^{g,i}	NA ^f	25.2 (4.6–105.8) ^{g,i}	33.5 (2.5–140.6) ^g	79.0 (13.8–600.7) ^{g,h,i}

NOTE. Anti-HBs, antibody to hepatitis B surface antigen; IQR, interquartile range; NA, not applicable.

^aWeek 8, 48, and 96 serological results were included if they were obtained within windows of ± 4 , ± 8 , and ± 12 weeks, respectively.

^b $P = .05$ (McNemar test) for the comparison of the proportion of subjects with an anti-HBs concentration ≥ 10 mIU/mL vs the previous time point.

^c $P = .003$ (Fisher exact test) for the difference among immune strata. Pairwise comparisons between stratum 4 and other strata were statistically significant ($P = .04$), but pairwise comparisons among strata 1–3 were not.

^d $P = .001$ (McNemar test) for all strata combined and stratum 4 and $P = .03$ (McNemar test) for stratum 2 for the comparison of the proportion with an anti-HBs concentration ≥ 10 mIU/mL at week 96 vs week 0.

^eWithin-subject comparisons are not reported for all subjects because of the large number with values below the lower level of quantitation for the assay.

^fExcluding stratum 1, for which only 2 subjects had an anti-HBs concentration ≥ 10 mIU/mL at week 8. High proportions (87%–96%) of the 111 subjects with an anti-HBs concentration < 10 mIU/mL at week 8 had levels below the lower level of quantitation at each time point.

$^gP < .02$ (Wilcoxon rank-sum test) for the comparison of within-subject change in antibody concentration from the previous time point.

$^hP = .04$ (Wilcoxon test) for the comparison of antibody concentrations between stratum 4 and strata 2 and 3 combined.

$^iP = .001$ (Wilcoxon rank-sum test) for all strata combined and stratum 4 and $P = .04$ (Wilcoxon rank-sum test) for stratum 2 for the comparison of within-subject change in antibody concentration from week 0 to week 96.

Table 3
Univariate Logistic Regression Analyses of Immunologic Memory Identified in P1061s

Variable ^a	Anti-HBs level 10 mIU/mL at entry or week 1 ^b		4-fold rise in antibody concentration between entry and week 1 ^b	
	OR	P	OR	P
Previous HBV vaccine within 4 years of P1024 entry	6.21	.001 ^c	NS	NS
Immunologic strata	3.20 ^d	.04	6.30 ^d	.02
Pre-HAART nadir CD4 cell percentage	1.41 ^e	.02	1.37 ^e	.04
CD4 cell percentage at P1061s entry	1.54 ^e	.02	1.58 ^e	.02
CD19 cell percentage at P1024 entry	1.66 ^f	.01	1.46 ^f	.05
CD19 cell percentage at P1061s entry	1.46 ^f	.05	NS	NS
HIV load 400 copies/mL at P1024 entry	8.05 ^g	.003 ^c	2.93 ^g	<.001 ^c
HIV load 400 copies/mL at P1061s entry	3.07 ^g	.03	3.59 ^g	.04
P1024 entry antibody concentration 10 mIU/mL	30.62 ^h	.002 ^c	NS	NS
P1024 week 8 antibody concentration 10 mIU/mL	19.50	<.001 ^c	7.86	.003 ^c
P1024 4-fold rise in antibody concentration from entry to week 8	11.39	<.001 ^c	13.95	<.001 ^c
P1061s entry antibody concentration 10 mIU/mL	NA	NA	NS	NS

NOTE. Anti-HBs, antibody to hepatitis B surface antigen; HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; HIV, human immunodeficiency virus; NA, not applicable; NS, not significant; OR, odds ratio.

^a Age, race, sex, duration of P1024 entry HAART regimen, whether subjects were receiving HAART at P1061s entry, and CD4 cell percentage at P1024 entry were additional variables included in univariate analyses that were not significant for a P1061s antibody concentration 10 mIU/mL at entry or week 1 or for a 4-fold rise in antibody concentration between entry and week 1.

^b Sixty-six subjects had adequate data from both P1024 and P1061s for inclusion in analyses of predictors of memory.

^c Statistically significant after applying the Bonferroni correction for multiple comparisons.

^d For immune stratum 3 or 4 vs immune stratum 1 or 2, according to original P1024 stratum assignment.

^e OR for every 5% increase in CD4 cell percentage.

^f OR for every 5% increase in CD19 cell percentage.

^g HIV load 400 copies/mL vs HIV load of 401–5000 copies/mL and >5000 copies/mL combined (categories were combined because of small numbers in the latter 2 groups).

^h 95% confidence interval, 3.7–253.3.