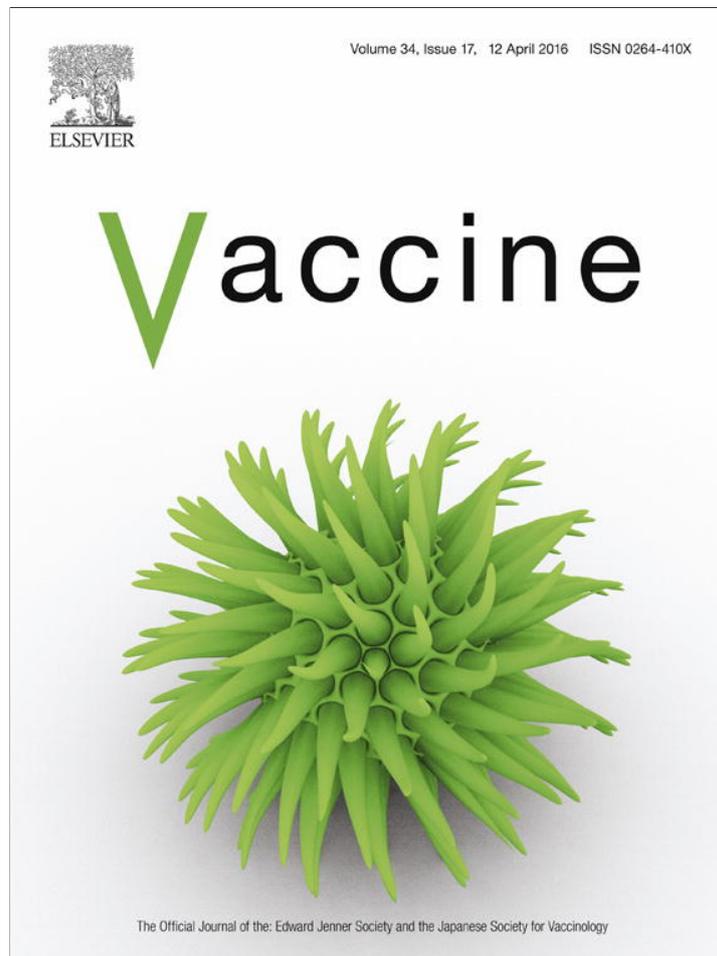


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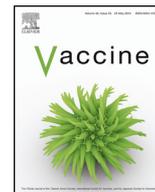
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Hepatitis B vaccination uptake and correlates of serologic response among HIV-infected and uninfected men who have sex with men (MSM) in Bangkok, Thailand



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ABSTRACT

Background: Vaccination against hepatitis B virus (HBV) is recommended for all HBV-susceptible men who have sex with men (MSM). There is limited information on correlates of immunity to HBV vaccination in this group. We present serologic response rates to hepatitis B vaccine and identify factors associated with impaired response among HIV-uninfected and HIV-infected Thai MSM.

Methodology: HBV-susceptible volunteers were offered hepatitis B vaccination at months zero, one, and six. We measured baseline (pre-vaccination) total serum IgG and IgG subclasses (all participants), baseline CD4 count, and plasma HIV-1 viral load (PVL) (HIV+ participants). HBV serologies were retested at 12 months. Serologic responses were compared between all groups in men receiving three vaccine doses. **Results:** 511/651 HIV-negative and 64/84 HIV-positive participants completed the three-dose series. Response rates in HIV-uninfected and -infected participants were 90.1% vs. 50.0% ($p < 0.0001$). Median pre-vaccination IgG was higher among non-responders than responders overall (1238.9.0 vs. 1057.0 mg/dL, $p = 0.003$) and among HIV-infected participants (1534.0 vs. 1244.5 mg/dL, $p = 0.005$), but not significantly among HIV-uninfected participants (1105.5 vs. 1054.3 mg/dL, $p = 0.96$). Pre-vaccination IgG1 and IgG3 levels were higher among HIV-positive than HIV-negative participants (median 866.0 vs. 520.3, and 105.8 vs. 83.1 mg/dL, respectively, $p < 0.0001$). Among HIV-infected participants, median CD4 count in non-responders was 378 cells/ μ L vs. 431 cells/ μ L in responders ($p = 0.20$). Median PVL in non-responders was 64,800 copies/mL vs. 15500 copies/mL in responders ($p = 0.04$). Participants with pre-vaccination plasma IgG >1550 mg/dL and PVL >10,000 copies/mL were almost always non-responsive ($p < 0.01$).

Conclusions: HIV infection was associated with poor vaccine responses. High plasma viral load, elevated pre-vaccination total serum IgG and elevated pre-vaccination IgG1 are associated with poorer response to vaccination among HIV-infected MSM. In this group, the combination of high PVL and pre-vaccination total IgG is highly predictive of vaccine failure.

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1. Introduction

Worldwide, an estimated 240 million people are chronically infected with the hepatitis B virus, and are at increased risk of

developing cirrhosis, hepatic decompensation, and hepatocellular carcinoma [1]. Transmission occurs vertically and horizontally through exposure to contaminated blood or other body fluids. Men who have sex with men (MSM) are at a considerably greater risk of HBV infection than the general population, with seroprevalence rates ranging from 19% to 50.8% in various studies around the world [2–6]. While 95% of healthy adults will experience transient disease after HBV infection, 25% of HIV-infected individuals will go on to develop chronic HBV infection; among co-infected individuals, all-cause and liver-related mortality are significantly higher

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than with either infection alone [7–9]. The CDC now recommends routine serological testing for HBV in MSM, and vaccination of susceptible individuals [10]. However, despite the availability of a well-tolerated HBV vaccine regimen, vaccination rates among susceptible MSM have remained low [2,11–13].

Among HIV-infected MSM, behavioral and socioeconomic barriers to HBV vaccination are compounded by poor responses due to immune dysfunction. HIV-infected individuals are significantly less likely to develop protective antibody titers after HBV vaccination, with response rates ranging from 24% to 64% [14–22], compared with expected rates of approximately 90% among healthy individuals. While the causes of impaired adaptive humoral responses in HIV-infected individuals are incompletely understood, studies implicate several mechanisms, including a direct effect of HIV-1 on B cell function [23,24] and dysregulation of T helper cell function, particularly during the interaction between follicular T helper cells and B cells at the germinal center within B cell follicles [25], resulting in persistent pathologic stimulation of naive B lymphocytes. Accordingly, impaired B cell immunity has been correlated with high HIV viremia, decreased numbers of circulating memory B cells, elevated numbers of activated naive B cells, and hypergammaglobulinemia representing inappropriate expression of non-specific IgG [26–28].

Thus, despite an imperative need for effective hepatitis B prevention measures particularly among HIV-infected MSM, behavioral and biological factors limit the effectiveness of current hepatitis B vaccination programs. Because sexual exposure is a major route of transmission for both HBV and HIV-1 infection in Thailand, the risk of HBV coinfection is a significant health concern for Thai MSM and other adults at risk of HIV infection. However, there is presently limited information on uptake of the 3-dose intramuscular HBV vaccine, vaccine series completion rates, serologic response, and correlates of immunogenicity among HIV-infected and HIV-uninfected MSM in Thailand. Here we present findings on response to implementation of an HBV vaccination program in a cohort of HIV-infected and -uninfected Thai urban MSM [29].

2. Methods

2.1. Study population

This study was conducted with approval of the Institutional Review Board of the US Centers for Disease Control and Prevention and the Ethics Review Committee of the Thai Ministry of Public Health, and with informed consent of all participants. Participants were enrolled between April 2006 and November 2010. Eligibility criteria included being a Thai male, age 18 years or older, with a history of insertive or receptive oral or anal sex with another man in the last six months, and residence in Bangkok or neighboring provinces, as previously described [29]. We recruited MSM from numerous sources, including HIV voluntary counseling and testing services provided at the study clinic, venues where MSM congregate for socializing and seeking sexual partners, the Internet, referral by community-based organizations (Rainbow Sky Association, Bangkok Rainbow Organization, Sex Worker in Group, and Poz Home Center), and word of mouth.

2.2. Study procedures

After providing informed consent, participants received HIV pre-test counseling, HIV risk-reduction counseling, and underwent baseline serological testing for HBV and HIV. Participants were considered previously HBV-infected if either HBsAg, or anti-HBc was detected, immune by prior vaccination if anti-HBs alone was detected, and HBV-susceptible if no HBV markers were

present. HBV-susceptible participants were offered hepatitis B vaccination. Recombinant Hepatitis B surface antigen (Engerix-B® 20 mcg, GlaxoSmithKline) was stored at 4°C continuously until use, and administered by intramuscular injection with a 26-gauge needle in the left or right deltoid muscle at 0, 1, and 6 months. Serum was collected from participants at 12 months after the initial vaccination for evaluation of HBV infection status and response to hepatitis B vaccination. Vaccine lot numbers used in this study were: AHBVB128AE, AHBVB150AO, AHBVB213BE, AHBVB264BC, AHBVB277AO, AHBVB339AI, AHBVB356AG, AHBVB434AB, AHBVB527AJ, AHBVB629FC, AHBVB713AF.

2.3. Laboratory methods

Participants were screened for HIV infection at baseline using OraQuick (OraSure Technologies Inc., Beaverton, Oregon, USA) on oral fluid, and if reactive, confirmed with three rapid blood tests (Determine™ HIV 1/2, Inverness Medical Japan, Chiba, Japan; DoubleCheck™ II HIV 1&2, Origenics Ltd., Inverness Medical Innovations, Yavne, Israel; Capillus™ HIV-1/HIV-2, Trinity Biotech, Jamestown, NY, USA; [after 11/2008 replaced by Core™ HIV1/2, Birmingham, UK]). Hepatitis B surface antigen (HBsAg) and antibody to hepatitis B surface antigen (anti-HBs) were determined qualitatively using a hemagglutination assay (Serodia, FUGIREBIO Inc., Tokyo Japan), or one of two enzyme immunoassays (Murex, Abbott Diagnostics, Kyalami, South Africa, or Monolisa, Bio-Rad, Marnes-la-Coquette, France) depending on kit availability. Antibody to hepatitis B core antigen (anti-HBc) were determined using a competitive enzyme immunoassay (ETI-AB-COREK PLUS, DiaSorin, Saluggia, Italy) or one of two enzyme immunoassays (Murex, Abbott Diagnostics, Kyalami, South Africa, or Monolisa, Bio-Rad, Marnes-la-Coquette, France). Anti-HBs titers were measured semi-quantitatively as <10 IU/L (non-responder), 10–100 IU/L, and >100 IU/L. Serum IgG subclass levels were determined by enzyme immunoassay (Human IgG1 Ready-SET-Go!®, Human IgG2 Ready-SET-Go!®, etc., eBioscience, San Diego, CA, USA). All kits were used according to manufacturer instructions.

2.4. Data analysis

Vaccine-mediated immunity (i.e., a “protective response”) was defined as an anti-HBs titer ≥ 10 IU/L in the absence of other HBV serologic markers. Evidence of active or prior infection was defined as presence of HBsAg, anti-HBc or both. Participants who were HBV susceptible at enrollment who developed serological markers of new HBV infection occurring between first and final vaccination were excluded from analyses of vaccine response. Associations between protective response and continuous variables were evaluated using the Wilcoxon rank-sum test and associations between continuous variables were tested by Spearman rank correlation coefficient using two-tailed analyses. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina, USA).

3. Results

3.1. Demographics and pre-vaccination serostatus

Between 2006 and 2010, we enrolled 1744 HIV-infected and HIV-uninfected otherwise healthy Thai male volunteers into the cohort, among whom 1372 (79%) were determined to be HIV uninfected (mean age 27 years, range 18–56) and 372 (21%) were HIV infected (mean age 27 years, range 18–50; median CD4 count 412/mm³, range 13–1712; median PVL 4.57 log₁₀ copies/mL, range 0–6.30). Among HIV-uninfected participants, two did not

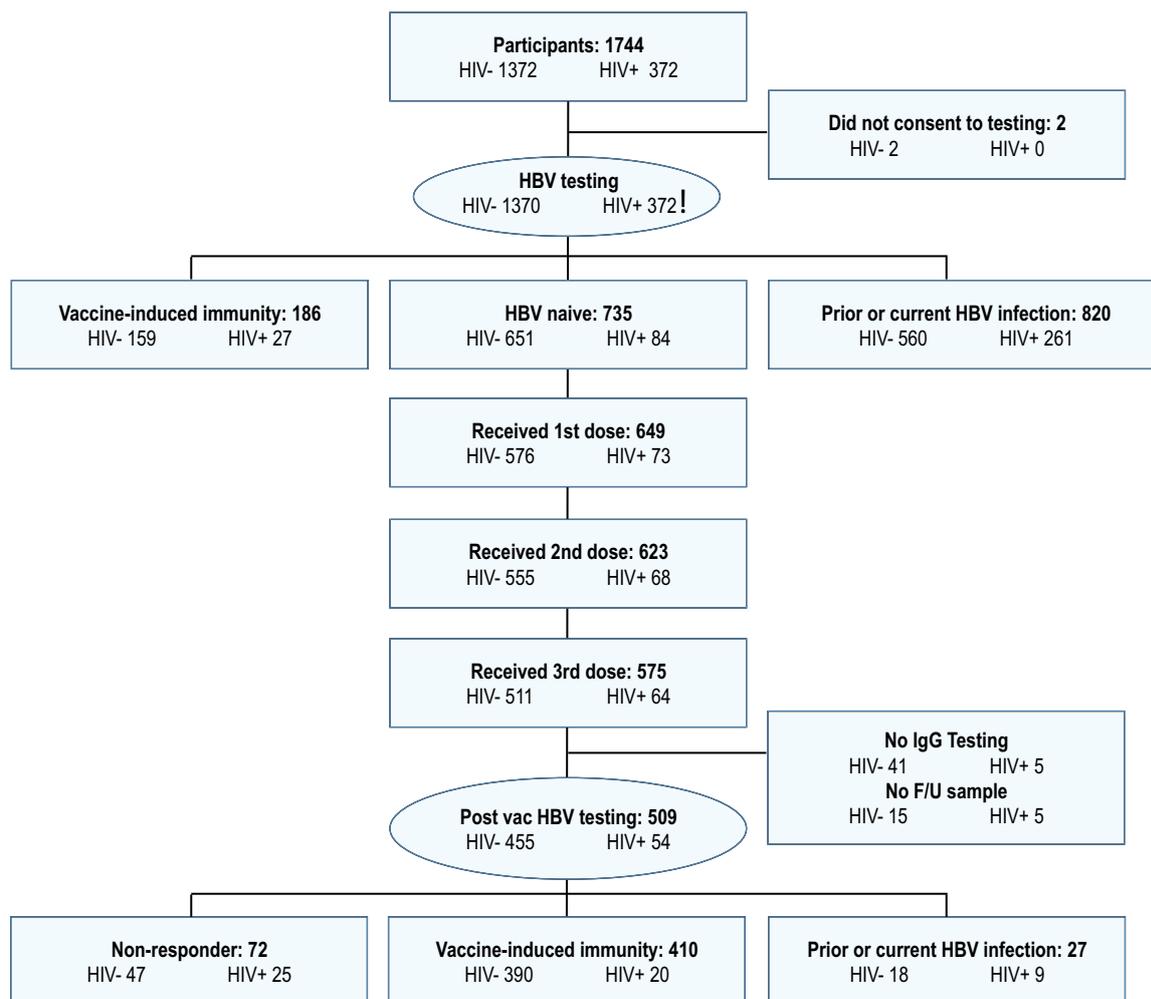


Fig. 1. Enrollment, baseline immune status, vaccine acceptance, and vaccine response among 1744 MSM study participants. (§) Four HIV-infected participants contributing to the analysis were receiving antiretroviral therapy at some time between initial vaccination and assessment of vaccine response at 12 months.

have baseline blood collection; thus HBV serological results were obtained for 1370 participants. Of these, 651 (47.5%) were susceptible to HBV infection, 159 (11.6%) had HBV vaccine-induced immunity, and 560 (40.9%) had serologic evidence of prior or current HBV infection. Among HIV-infected participants, 84 (22.6%) were susceptible to HBV infection, 27 (7.2%) had HBV vaccine-induced immunity, and 261 (70.2%) had serologic evidence of prior or current HBV infection (Fig. 1).

3.2. Uptake of HBV vaccination, and series completion

Among 651 HIV-uninfected HBV-susceptible participants, 576 (88.5%) consented to and received the first vaccine dose. Among 84 HIV-infected HBV-susceptible participants, 73 (86.9%) consented to and received the first vaccine dose. Reasons for not initiating the three-dose vaccination series included loss to follow up ($n=56$), claim of prior HBV vaccination ($n=13$), participant refusal with no specific reason given ($n=16$), and concern regarding yeast allergy ($n=1$). Among 649 participants who agreed to receive vaccination, 575 (88.6%) completed the three-dose series, including 511/576 (88.7%) of HIV-uninfected and 64/73 (87.7%) of HIV-infected participants ($p=0.769$) (Fig. 1). The mean age of participants failing to complete the three-dose vaccination series was lower than the mean age of those completing the series (23 vs. 26 years, $p<0.0001$).

3.3. Overall response to vaccination

Of 575 participants completing the third vaccination, 555 returned at 12 months for follow-up serological testing. The overall response rate in this group was 81.6%. However, 30 participants eligible for vaccination at entry showed evidence of natural infection at 12 months. Excluding these individuals, the overall response rate was 86.3%. There was no significant correlation between age and anti-HBs titer (i.e., <10 , $10-100$, and >100 IU/L, $p=0.49$) or rate of protective response ($p=0.47$).

3.4. Effect of HIV status on vaccine response

Protective responses to vaccination occurred in 428/475 (90.1%) of HIV-uninfected participants, and were significantly more frequent than in HIV-infected participants, among whom protective responses occurred in 25/50 (50.0%) participants ($p<0.0001$). Similarly, stratified antibody titers (non-responder, $10-100$, and >100 IU/L) were higher among HIV-uninfected participants than among HIV-infected participants. In the HIV-uninfected group 62/475 (13.1%) had anti-HBs titers between 10 IU/L and 100 IU/L and 366/475 (77.1%) with anti-HBs greater than 100 IU/L while in the HIV-infected group 12/50 (24.0%) had anti-HBs titers between 10 IU/L and 100 IU/L and 13/50 (26.0%) with anti-HBs greater than 100 IU/L ($p<0.0001$) (Fig. 1). Among HIV-infected individuals, there

Table 1

Pre-vaccination plasma viral load, CD4 count and plasma IgG levels among HIV-positive and HIV-negative study participants. HIV plasma viral load presented as log₁₀ copies/mL (median and range), CD4 count per mm³, median, range), IgG levels presented as mg/dL.

Group	All			HIV-positive			HIV-negative		
	Responders	Non-responders	<i>p</i>	Responders	Non-responders	<i>p</i>	Responders	Non-responders	<i>p</i>
Total IgG	1057.0	1238.9	<i>p</i> = 0.003	1244.5	1534.0	<i>p</i> = 0.005	1054.3	1105.5	<i>p</i> = 0.96
IgG1	532.0	683.7	<i>p</i> = 0.003	813.4	1139.5	<i>p</i> = 0.009	526.0	524.0	<i>p</i> = 0.56
IgG2	350.0	365.5	<i>p</i> = 0.86	269.2	242.4	<i>p</i> = 0.67	352.9	399.4	<i>p</i> = 0.16
IgG3	83.7	90.5	<i>p</i> = 0.18	112.0	92.1	<i>p</i> = 0.93	83.1	84.0	<i>p</i> = 0.94
IgG4	50.5	46.4	<i>p</i> = 0.38	43.0	48.0	<i>p</i> = 0.20	50.5	44.0	<i>p</i> = 0.17
CD4	NA	NA	NA	431 (63–1055)	378 (226–698)	0.07	NA	NA	NA
HIV-1 RNA	NA	NA	NA	4.19 (2.37–5.86)	4.81 (1.67–5.59)	0.04	NA	NA	NA

was a nonsignificant trend towards higher baseline median CD4 count among those with protective responses after vaccination (431 vs. 378 cells/mm³, *p* = 0.07), but no clear correlation between CD4 count and antibody titers in stratified analyses (*p* = 0.25). There was a significant correlation between lower baseline median plasma HIV-1 viral load and protective response following vaccination (4.19 vs. 4.81 log copies/mL, *p* = 0.04) and a non-significant trend towards higher titers with lower viral loads in stratified analyses (*p* = 0.06) (Table 1).

3.5. Relationship between HIV status and pre-vaccination IgG levels

Pre-vaccination total IgG, IgG1, and IgG3 levels were all significantly higher among HIV-positive than HIV-negative participants (median 1373.6 vs 1038.2, 866.0 vs. 520.3, and 105.8 vs. 83.1 mg/dL, respectively, *p* < 0.001). By contrast, pre-vaccination IgG2 levels were significantly depressed in HIV-positive individuals (median 274.7 vs. 355.0 mg/dl *p* < 0.001). There was no significant difference between IgG4 levels in HIV-positive vs. HIV-negative participants (Fig. 2).

3.6. Relationship between pre-vaccination total IgG levels and vaccine response

Among 555 participants completing the three-dose vaccination series, 509 had samples available for measurement of pre-vaccination total serum IgG. Among HIV-infected individuals, IgG levels correlated with HIV-1 plasma viral load (Spearman rank correlation 0.32, *p* = 0.017) but did not correlate with CD4 count (Spearman rank correlation 0.08, *p* = 0.56). IgG levels were significantly lower in vaccine responders than in vaccine non-responders, both in the entire cohort (1057.0 vs. 1238.9 mg/dL, *p* = 0.003) and among HIV-infected participants (1244.5 vs. 1534.0 mg/dL, *p* = 0.005) (Table 1). Among HIV-uninfected participants, IgG levels were slightly but not significantly lower among responders

than non-responders (1054.3 vs. 1105.5 mg/dL, *p* = 0.96). When HIV-infected participants were stratified by pre-vaccination serum IgG levels (IgG > or ≤ 1550 mg/dl) and HIV viral load (PVL > or ≤ 10⁴ copies/mL), those with elevated IgG levels and elevated PVL had a significantly lower response rate to vaccination (12/14, 86%) than the other three groups (Fig. 3) (*p* < 0.01).

3.7. Relationship between pre-vaccination IgG subclasses and vaccine response

Only pre-vaccination IgG1 levels differed significantly between vaccine responders and non-responders; IgG1 levels were significantly lower for responders than for non-responders in the cohort as a whole (532.0 vs 683.7 mg/dL, *p* = 0.003) and among HIV-positive participants (813 vs 1139 mg/dL, *p* = 0.01), but not among HIV-negative participants (526 vs. 524 mg/dL, *p* = 0.56) (Fig. 4). The remaining IgG subclasses did not differ between responders and non-responders (Table 1).

4. Discussion

We have examined baseline HBV serostatus, hepatitis B vaccine uptake, series completion, and correlates of protective immunity following hepatitis B vaccination in a cohort of 1744 MSM in Bangkok, Thailand. Among HBV-susceptible participants, vaccination uptake and series completion were high in comparison with other studies of MSM reporting uptake rates of 51%–62% [30,31]. The most common reason for failure to receive the vaccine series was complete loss to clinical follow-up, and thus possibly not directly related to a reluctance to receive hepatitis B vaccination. Protective responses to vaccination were significantly less frequent among HIV-infected than among HIV-uninfected participants, consistent with prior studies in developed settings, East Africa, and Asia, which reported rates of approximately 33–66% and 80–90% in these two groups, respectively [14–16,20,22,32]. There was a trend towards higher response rates among those with lower plasma

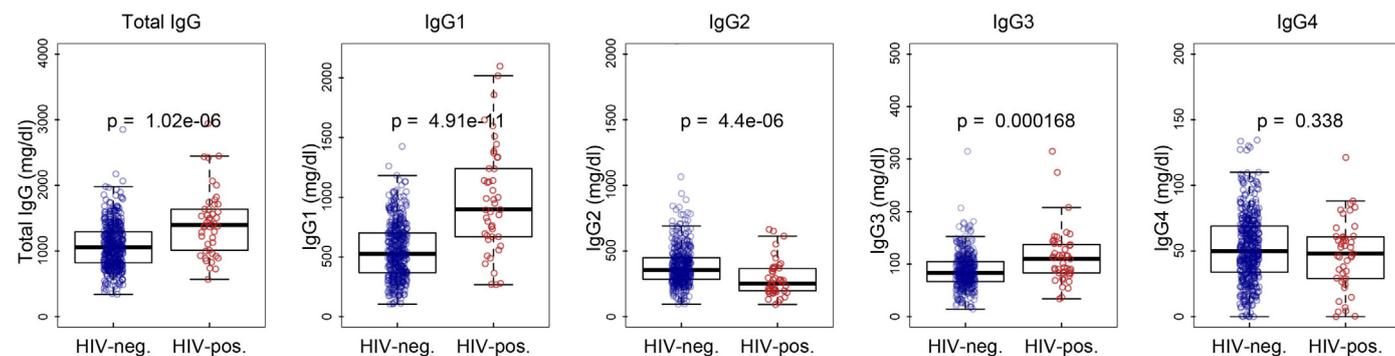


Fig. 2. Relationship between HIV status and pre-vaccination serum total IgG and IgG subclass levels. Total IgG, IgG1, and IgG3 levels were significantly higher in HIV-infected participants than in HIV-negative participants. IgG2 levels were significantly lower in HIV-infected participants. IgG4 levels did not vary by HIV status.

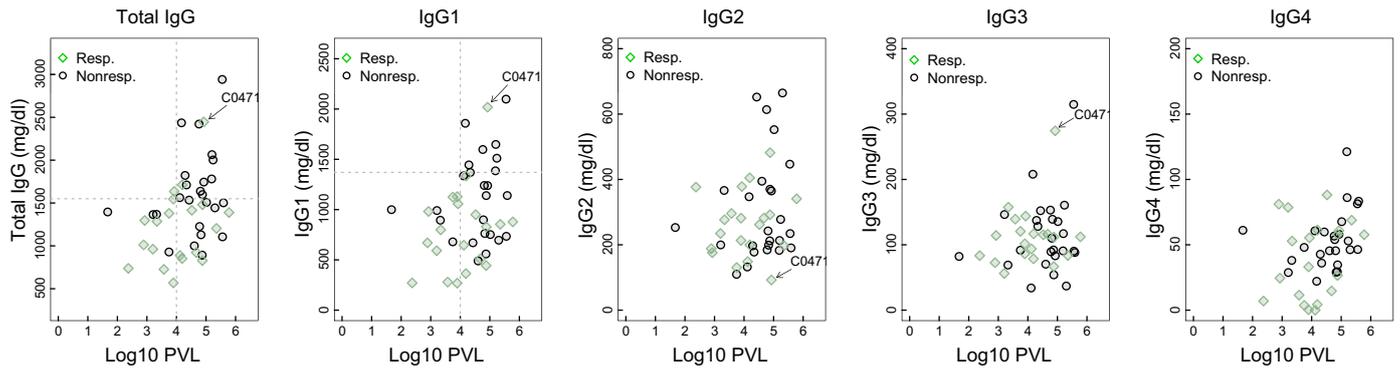


Fig. 3. Relationship between pre-vaccination serum IgG subclass levels and vaccine response. Pre-vaccination total serum IgG and IgG subclass levels (mg/dl) vs. plasma HIV-1 viral load (\log_{10} copies/ml) for participants with protective anti HBs titers (responders, green diamonds) and lack of protective response (non-responders, black circles) following completion of three-dose HBV vaccine series. Participants with IgG > 1550 mg/dl and PVL > 10,000 copies/ml (right upper quadrant, dotted lines) are all non-responders, with the exception of two outlying individuals ($p < 0.01$) (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

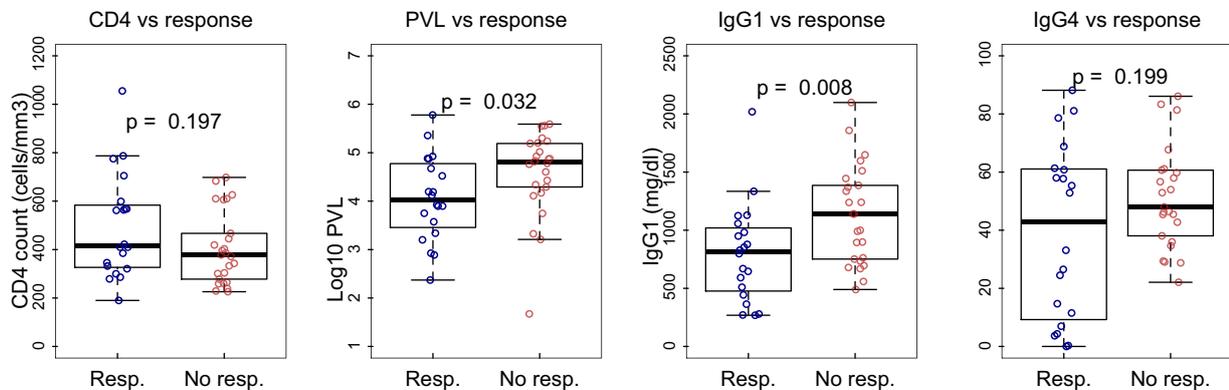


Fig. 4. Relationship between CD4 count, plasma viral load, baseline IgG1 and baseline IgG4 and response to vaccination among HIV-positive individuals. Among HIV-infected participants, HIV plasma viral load and baseline IgG1 were significantly lower among responders than non-responders ($p = 0.032$ and 0.008 , respectively) while CD4 count and IgG4 did not significantly differ between responders and non-responders.

HIV viral loads, but no association with baseline CD4 T cell count (Table 1). While these findings are in agreement with past studies [21,33], we did not find a significant correlation between age and vaccine response, as has been previously reported [34].

We observed a significant inverse relationship between pre-vaccination total serum IgG levels and likelihood of a protective response at 12 months after initial vaccination. This relationship was seen in the cohort as a whole and among HIV-infected participants, but was not apparent in HIV-negative participants. Notably, while there were responders at every plasma viral load level, HIV-infected participants with plasma viral load levels in excess of 10,000 copies/ml and pre-vaccination serum IgG levels above 1550 mg/dL were almost always non-responders (Fig. 3). Total pre-vaccination IgG levels were weakly correlated with plasma viral load, and pre-vaccination serum IgG and PVL therefore appear to be additive predictors of immunological response to vaccination. There was no relationship between IgG levels and CD4 count.

Two previous studies have shown that HIV infection may be associated with changes in IgG subclass regulation, characterized by elevations of IgG1 and IgG3 levels [35,36]. To further understand the role of pre-vaccination IgG levels in shaping immune responses to vaccination, we measured individual IgG subclass components of pre-vaccination total IgG. IgG1 and IgG3 were both significantly elevated in HIV-positive individuals, but IgG2 levels were lower in those with HIV infection. Immunization response failure has previously been linked to IgG2 deficiency in a number of smaller studies [37,38]. We saw no relationship between vaccine responses and

IgG2 levels, but in contrast observed that elevated IgG1 levels were strongly associated with a failure to mount protective immune responses to HBV immunization in HIV-positive individuals. We are unaware of any previous reports of such a relationship. Impairment of humoral responses in HIV infection may be partly the result of distraction and misdirected rather than deficient IgG production.

Several limitations should be considered here; some participants became infected with HBV sometime during the vaccination series. Because the timing of infection is not known, excluding these participants or categorizing them as non-responders may both introduce some bias. However the number of incident cases of HBV infection was modest, and did not affect the primary outcomes observed. In addition, during the course of the study, several serological testing kits were used, and it is possible that differences in sensitivity between kits may have introduced some variability into the results. Finally, there were relatively few HIV-infected participants and participants older than age 40 years, which limited our power to detect the effects of CD4 level and age on immunogenicity. The associations seen in this limited group would be best confirmed and understood in larger prospective trials.

Since the discovery of HBV 50 years ago, vaccination remains the best way to prevent HBV transmission, and vaccination programs have been shown to be effective in many groups and many countries [39–42]. Our results suggest that appropriately implemented vaccination campaigns can achieve a high level of coverage and interrupt sexual transmission of HBV in MSM. However the poor responses seen in HIV-infected individuals are problematic

and may require novel approaches such as augmented dosing regimens antigen, intradermal injection, and the use of adjuvants to improve immunogenicity in this group [40–42]. Among HIV-infected persons, elevated IgG levels are presumably associated with impaired antibody responses after vaccination because they are markers of underlying immune dysregulation caused by persistent virally-mediated antigenic stimulation.

Summary

Response to HBV vaccination is inconsistent and suboptimal in some groups. Elevated plasma IgG is associated with poor response to vaccination. In HIV-infected MSM, the combination of high PVL and pre-vaccination total IgG is highly predictive of vaccine failure.

Disclaimer

The findings and conclusions presented in this paper are those of the authors and do not necessarily represent the views of the U.S. Centers for Disease Control and Prevention.

Disclosure

The authors report no conflicts of interest. All authors have approved the final article

Author roles

Study design: BR, MEC; study procedures: WC, PW, JT, SC; data analysis: WC, PW, SP, MEC; data interpretation: WC, JMM, MEC; approval of final manuscript: WC, BR, THH, PW, JT, SC, SP, JMM, FvG, MEC.

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