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Effect of Age and Frequency of Injections on Immune Response to Hepatitis B Vaccination in Drug Users

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Abstract

Despite the high immunogenicity of the hepatitis B vaccine, evidence suggests that immunological response in drug users is impaired compared to the general population.

A sample of not-in-treatment adult drug users from two communities in Houston, Texas, USA, susceptible to hepatitis B virus (HBV), was sampled via outreach workers and referral methodology. Participants were randomized to either the standard multi-dose hepatitis B vaccine schedule (0, 1, 6 month) or to an accelerated (0, 1, 2 month) schedule. The participants were followed for one year. Antibody levels were measured at 2, 6 and 12 months after enrollment in order to determine the immune responses.

At 12 months, cumulative adequate protective response was achieved in 65% of the HBV susceptible subgroup using both the standard and accelerated schedules. The standard group had a higher mean antibody titer (184.6 vs 57.6 mIU/mL). But at six months, seroconversion at the adequate protective response was reached by a higher proportion of participants and the mean antibody titer was also higher in the accelerated schedule group (104.8 vs. 64.3 mIU/mL). Multivariate analyses indicated a 63% increased risk of non-response for participants 40 years or older ($p=0.046$). Injecting drugs more than once a day was also highly associated with the risk of non-response ($p=0.016$).

Conclusions from this research will guide the development of future vaccination programs that anticipate other prevalent chronic conditions, susceptibilities, and risk-taking behaviors of hard-to-reach populations.

Keywords

hepatitis B vaccine; immunogenicity; drug users; hepatitis B virus

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Introduction

Despite inclusion in comprehensive hepatitis B immunization strategies in the United States, injection drug users and other high risk adults with behavioral risk factors, particularly, men who have sex with men (MSM), heterosexual individuals with multiple sex partners continue to experience a high rate of hepatitis B transmission [1]. In fact, high risk adults – MSM, IDUs, those with multiple sex partners or a history of sexually transmitted disease – account for over 75% of all new cases of hepatitis B each year [2].

Injection drug users are susceptible to acquiring and transmitting hepatitis B virus because of their exposure to body fluids by sharing syringes and using drug preparation equipment together [3]. Injecting drug use is a leading risk factor for HBV infection in non-endemic countries such as the United States, where hepatitis B serologic markers have been identified in 51-88% of intravenous drug users who had entered or enrolled in drug abuse treatment programs [4, 5]. In a review of 25 studies published between 1966-1993, in which most of the participants were recruited through drug treatment centers, Levine et al. (1994) found that the reported seroprevalence of hepatitis B viral markers among asymptomatic IDUs ranged from 38.0% to 99.2% [6]. Outbreaks continue to occur among drug users and pose a significant threat not only to the health of infected individuals but to the health of others in the community including their sexual partners and household contacts [7].

Drug users continue to experience low vaccine coverage, with up to 84% of young IDUs and non-injection drug users (NIDU) reporting at least one missed opportunity for vaccination [8, 9]. This has led to modification of national guidelines to reflect a venue-based approach, in settings where there are a high proportion of adults with risks for HBV infection such as STD/HIV testing and treatment facilities, jails and prisons, healthcare settings serving IDUs and MSM, and drug treatment facilities [10]. NIDUs may contract hepatitis B through additional pathways including engagement in risky sexual behaviors (e.g., sex with an IDU) and are at risk for HBV as well as HIV/HCV infection by initiating or resuming injection practices [8, 11]. Although a majority of injection drug users typically begin injecting during late adolescence or early adulthood, a sizeable proportion will initiate drugs injection in later years [12].

Approximately 50-70% of drug users become infected with hepatitis B within five years of initiating injecting drugs, and among young IDUs who have recently initiated, the prevalence of past HBV infection is nearly twice that of NIDUs (37% versus 19%) [9].

Available research on immunological response in drug users is scarce. Evidence suggests that immunological response to hepatitis B vaccination may be compromised, both in terms of lower seroprotection and impaired levels of antibodies. Compared to the 95% efficacy in young healthy adults receiving three doses, suboptimal vaccine seroconversion rates of 58-76% have been observed in drug users, particularly with the application of accelerated vaccination protocols [13-18].

The current study is an analysis of the differences in immunological responses to a hepatitis B vaccine of not-in-treatment drug users participating in two different vaccine schedules and characteristics associated with an adequate immunological response to this vaccine. The 0, 1, 2-month accelerated schedule is hypothesized to boost short-term (≤ 1 year) immune protection, with a comparable or greater proportion demonstrating seroprotection after the second dose, making this schedule an appropriate choice for similar high risk individuals who are exposed to hepatitis B primarily through parenteral or sexual transmission [19]. Little is known of the durability of immune protection using accelerated vaccination schedules in this population. A meta-analysis, including immunocompetent participants without restriction on age, suggests that long-term protection with the completion of three or

four doses of monovalent hepatitis B vaccine extends for at least 20 years [20] (delineation between vaccine schedules was not reported).

Materials and Methods

Study Design and Population

A total of 1,260 not-in-treatment current drug users who screened negative for antibodies to HIV (anti-HIV), hepatitis B surface antigen (HBsAg) and antibodies to HBsAg (anti-HBs) were enrolled into a randomized enhanced behavioral and accelerated vaccine schedule intervention trial intended to increase hepatitis B vaccination acceptance and adherence during February 2005 to November 2007 in urban communities of Houston, Texas. All participants reported illicit drug use (cocaine, heroin, methamphetamine, and/or marijuana) in the 48 hours and drug use was confirmed by urine screening [21].

In order to examine the immune response to HepB vaccine in drug users, this analysis was carried out in the subgroup, 707 out of the 1,260. This subgroup included the hepatitis B susceptible participants, who did not have immunity from natural hepatitis B infection (presence of anti-HBs and/or anti-HBc), active infection (presence of HBsAg with anti-HBc) or previous vaccination (presence of anti-HBs only). The inclusion criteria for this subgroup were negative tests for HBsAg, hepatitis B core antibody (anti-HBc), and an anti-HBs titer that was negative or less than 10 mIU/mL. All members of this group also had to complete the three doses of HepB vaccine for their schedule group. Exclusion of anti-HBc positive participants limited the possibility of previous exposure, and resolved acute / latent (chronic) infection which could affect the analyses. It was determined to vaccinate all eligible participants with sub-protective levels for ethical reasons. This study was approved by the Committee for the Protection of Human Subjects at The University of Texas Health Science Center at Houston.

At enrollment, after explanation of the study and a signed informed consent, each study participant was enrolled into one of two vaccine schedule groups. Assignment to a schedule group was determined based on each participant's month of enrollment. A participant enrolling in an odd numbered month was assigned to the standard schedule group and received the HepB vaccine at months 0, 1, and 6, whereas participants enrolling in an even numbered month were assigned to the accelerated schedule group and received the vaccine at months 0, 1 and 2. The vaccine used for this study was the adult formulation of *Engerix-B*, a monovalent vaccine containing 20µg of hepatitis B surface antigen (GlaxoSmithKline, Philadelphia, PA.). Vaccine was administered intramuscularly in the deltoid muscle by a licensed vocational nurse or medical assistant at two study sites located in urban areas where recruitment took place. An interview was conducted at enrollment, and follow-up interviews of study participants occurred at months 6, 12, 18, and 24, with blood draws for viral markers.

Data Collection and Laboratory Methods

Instruments used in previous studies were used to create the enrollment and follow-up questionnaires for this study [21]. The content of the questionnaires included: socio-demographic attributes (age, gender, race/ethnicity, living arrangement, jail history of >24 hours), ever injection drug use (IDU/NIDU status), duration of IDU, times injected drugs in past 30 days, lifetime and number of times shared needles in past 30 days, frequency of specific drug use in past 48 hours and 30 days including cocaine, heroin, methamphetamine, marijuana, and alcohol (cocaine, heroin and methamphetamine use confirmed by urine drug screen (OnTrak Varian Testik, Palo Alto)), history of blood transfusion, occupational exposure to blood, drug treatment, sexually transmitted disease diagnoses, and sexual

behavior (number and type of partner in past 30 days, condom use, trading sex for money or drugs in past 30 days, and sexual orientation). All interviews were verbally administered and recorded electronically via computer administered personal interview (CAPI, Questionnaire Development System, Bethesda, Maryland).

Blood specimens collected at enrollment and follow-up for this study were tested for anti-HIV using the Abbott PPC Commander System, and for antibodies to hepatitis C (anti-HCV), anti-HBs, HBsAg, and anti-HBc using the Abbott AxSYM system (Abbott Laboratories, Chicago, IL), per study protocol.

Statistical analysis

Laboratory results were entered into a Microsoft Access database, questionnaire data were exported from QDS into SAS 9.1 (SAS Institute, Inc., Cary, NC), and all data analysis was performed using STATA 9.1 (STATA Corp., College Station, TX). Odds ratios were reported with 95% confidence intervals for relevant immune response factors and demographic variables. To evaluate potential associations between participant behaviors or characteristics and the post-vaccination protective responses (anti-HBs titers meeting specified thresholds at any return visit after baseline), univariate analyses were conducted to obtain odds ratios (ORs) and 95% confidence intervals to measure the strength of association between each dependent variable and independent variables. Biologically plausible or variables having evidence of potentially influencing immune protection (age, gender, HCV co-infection, current specific drug use) were included in the multivariable regression model. Variables considered in the multivariable model were vaccine schedule, living arrangements, trading money for sex, history of drug treatment, duration of injecting drugs, HCV co-infection, frequency of drug injection use, number of different drugs used in the past 30 days, current crack cocaine use, alcohol use, speedball (mix of heroine and cocaine) use and methamphetamine use. Along with reported factors (age and gender), independent variables having a p-value of <0.2 were included using forward stepwise multiple logistic regression. The final model consisted of adjusted odds ratios and 95% confidence intervals calculated for the variables with p-values ≤ 0.05 .

The generally accepted anti-HBs titer of ≥ 10 IU/mL was the cut-point for seroprotection. Geometric mean titers (GMT) were compared by variance analysis using the non-parametric Wilcoxon Rank Sum/Mann-Whitney U test. The mean titers for the follow-up sessions were presented with 95% confidence intervals. Antibody response was arbitrarily categorized into three levels: negative or <10 mIU/mL (non-response); between 10-100 mIU/mL (protective response); and >100 mIU/mL. Past or current hepatitis B infection was defined as a positive for HBsAg and/or anti-HBc, with or without anti-HBs.

Results

Baseline characteristics of the two vaccine schedule groups (accelerated versus standard) of the 707 hepatitis B susceptible subgroup are shown in Table 1, and were examined to assess the randomization process. A significant difference between the vaccine schedule groups was found for men who have sex with men (MSM).

Overall, the majority of the participants were African American (87%) and male (77%). The remaining consisted of whites (8%) and Hispanics (4%). Less than 10% were younger than 30 years, about a quarter of the population was between 30-39 years of age, and a substantial proportion (65%) were 40 years or older. The mean age was 43 years ($SD \pm 9.0$). Twenty percent of the sample was found to have antibodies to hepatitis C virus. Approximately 7% of the study population included men who have sex with men. Two-thirds of the population (65%) reported current alcohol use.

One-fifth (21%) of the population had a history of injection drug use, and only 5% disclosed injection of drugs in the past 30 days. One third of those who admitted to injecting in the past 30 days had shared needles or “works” (drugs preparation equipment) during that time. Almost half of the drug users with a positive injection drug use history had injected for less than one year, while 40% had injected for 5 or more years.

Seroprotection Rates

Overall, 65% (459/707) of the HBV susceptible individuals developed the minimal adequate protective response category of anti-HBs titers ≥ 10 mIU/mL by the 12 month visit [21].

Differences in the timing of the dose and protective response to vaccine occurred between the two groups (Figures 1A and 1B). The 12-month proportions were not significantly different; however, only 55% of accelerated schedule participants achieved adequate protective response while 63% of standard schedule participants had adequate protective response after completing their third dose at the 12-month visit.

Differences in the level of immune response with regard to antibody titers for the hepatitis B susceptible subgroup were recorded (Figure 2). At the 6 month visit, the anti-HBs GMT for the accelerated group was 104.8 mIU/mL (95% CI=84, 130.8), measured 4 months after three doses of vaccine; it was 64.3 mIU/mL (95% CI=50.6, 81.8) for the standard group only after two doses of vaccine. At the 12 month visit, the standard group had a higher anti-HBs GMT (measured six months after the last dose) of 184.6 mIU/mL (95% CI=139.6, 244.0), and the accelerated schedule titers decreased to 57.6 mIU/mL (95% CI=46.3, 71.6) (measured ten months after the last dose). Results from the Wilcoxon Rank-Sum tests confirmed that the distributions were not statistically different at 2 months, whereas the antibody titers were significantly different for the standard and accelerated schedules at both 6 and 12 months.

Factors Associated with Adequate Protective Response

In univariate analysis (chi-square test), the characteristics of drug users found significantly associated with an adequate protective immune response (negative or <10 mIU/mL vs. ≥ 10 mIU/mL) measured at 12 months were gender (p-value =0.049), number of drug types currently used (p-value=0.003), and crack cocaine use in the last 30 days (p-value =0.049) (Table 2). Biologically plausible, reported factors such age, IDU, and HCV status, were not associated with a protective response.

After adjustment in the multivariable analysis (Table 3), individuals aged 40 or older were less likely to achieve immune protection (OR=0.37, 95% CI 0.14-0.98, p=0.046), and individuals who reported injecting drugs more than one time per day were also less likely to achieve an adequate immune response (OR=0.36, 95% CI 0.15-0.82, p=0.016).

Discussion

Host factors that may affect hepatitis B vaccine response in the current study included age of 40 years or greater, and more than daily injection drug use. Immunological response to HepB is dictated by several host characteristics that influence the body's ability to mount an effective defense. In particular, immune response to the vaccine is dependent on the activity of T-cells and may be inhibited by conditions associated with impaired T-cell function [22]. Factors associated with failure to develop hepatitis B seroprotection include older age, lack of immunocompetence, smoking habits, and genetics [23-25]. Characteristics including male gender and higher body mass index (BMI) also appear to diminish HBV seroconversion [24, 26]. Although not significant, our findings also suggested that males were less likely than

females to develop seroprotection at 12 months, but this may be due to a disproportionate sample.

Participants aged 40 years or older demonstrated a 63% increased risk of non-response to vaccine ($p=0.046$) in this study, which is consistent with previous research. An accelerating decline in immune responses to vaccination appears to manifest after 40 years of age, with less than 90% of vaccinees gaining protection, and the proportion drops precipitously to 65-75% at 60 years of age [27]. It is recognized that immune function generally declines in healthy elderly individuals, irrespective of underlying disease or environmental exposures [28, 29]. The shift toward humoral immune dysfunction is evident in lowered seroconversion rates and geometric antibody concentrations in elderly populations [25]. A meta-analysis of 24 studies conducted from 1986-1999, composed primarily of health care workers, indicated an association between age and risk of non-response to HepB, regardless of the age cutoff value used [30]. For adults 40 years and older, immunologic response was influenced most by age, followed by gender, and least by BMI [31]. With over two-thirds of the sample over 40 years, there is a clear risk of impaired immunity with increased age.

A 64% increase in non-response was observed for those who injected drugs more than daily. This is the first report, to our knowledge, of injection frequency influencing the serological response, although it has been correlated with vaccine completion [14, 32, 33]. The suppressed immune function does not appear to be a result of confounding caused by the use of multiple drugs, but use of multiple drugs and multiple bacterial infections have been offered as possible explanations for poor immune response that may be unique to the drug user population [3]. It is unclear from our findings if any particular drug or combination of drugs may be responsible.

The current study did not demonstrate an association between vaccine response and hepatitis C virus status. In a sample of 1175 heroin drug users, factors including older age, two-month vaccine schedule (0, 1, 2 month), HCV and HIV seropositivity were associated with impaired immune response [16]. However, the role of HCV antibody remains controversial and other studies show conflicting results in both chronic HCV patients and intravenous drug users [17, 34]. For example, Minniti et al. (1999) vaccinated 110 intravenous heroin users on the 0-, 1-, 2-month accelerated schedule with a 10 µg dose and found that immunogenicity was not associated with anti-HCV seropositivity [15].

In the current study, the reported current use of particular drugs, including alcohol, were not associated with poor immune response. It may be that reporting the behaviors at the baseline visit did not reveal changes in alcohol consumption during the ensuing 12 months. However, the abuse of alcohol has been associated with impaired immunity in other research, with reported seroconversion rates ranging from 43-70% [35-39]. Available data from two randomized studies on the influence of high HBV vaccine dose in alcoholics is conflicting; however, alcoholic patients who received a high dose on the accelerated schedule (0, 1, 2 month) demonstrated improved serologic response [37, 38]. It may be that the effects of alcoholism on immune response, as evidenced by drinking during the study, may persist for several weeks after withdrawal from alcohol consumption. Factors associated with alcoholism, such as malnutrition, poor socioeconomic conditions, and liver disease may also contribute to impaired immune response [22].

Seroconversion occurred in 65% of participants by 12 months regardless of schedule. This is comparable to findings from existing HepB research in drug using populations [15, 18]. A number of studies have confirmed at least 70% adequate protective response by six months in drug users who have received 3 doses [14-16, 18, 40, 41].

Although the antibody titer values gradually drop for the accelerated group, the GMT values for both schedules were all well above the threshold for minimal protection. The cumulative proportions of those deemed protected were identical (65%) at 12 months. It remains to be seen whether these titer levels continue to drop beyond 12 months, and if so, the time at which the sample approaches the 10 mIU/mL level is instructive for the timing of booster doses. Long-term persistence of antibody response appears predictable on the accelerated schedule, with steady decreases between the follow-up sessions. Follow-up beyond 12 months to further characterize the decrease in persistence of antibody should be evaluated to see if a booster would be needed. In contrast, the surge in titer levels at the 12th month for the standard schedule is sudden and further analysis is required to evaluate the long-term trend. This surge, observed six months after completion of the series, may be due to the boosting effect of administration of the third dose, but no evidence of a similar gain is seen on the accelerated schedule.

The lower geometric mean titers obtained at 12 months with the accelerated schedule is a concern. The substantial increase in the seroprotection rate at six months [21] may be worth the trade-off against the imminent antibody titer decrease, especially considering that actual protection is mediated by immunological memory and very rarely have breakthrough infections been recorded. There is a need to focus on the degree of protection and to determine the extent of breakthrough and subclinical infections in drug users [40]. The suggestion of a fourth booster dose for the 0, 1, 2 schedule to mitigate rapidly declining antibody levels would be of benefit primarily for the detection of comorbidities such as HCV or HIV, as well as for informing the drug user of preventive behaviors to limit further bloodborne pathogen transmission to or from their peers and acquaintances in the community [42]. However, it is difficult to achieve this in a hard-to-reach population without deliberate selection of convenient settings for vaccine delivery. In this study, we used a community site that was easily accessible and local to the participants.

Limitations

The hepatitis B susceptible immune response subgroup was selected from the baseline enrollment population in order to obtain the largest possible sample size. Drug use behaviors, including current drug use (reported at the time of enrollment) were assessed on a limited scale after the baseline questionnaire. In our experience, however, we did not see drug use behaviors drastically change throughout the first 12 months of study. It is likely that longitudinal changes in drug or sexual habits, such as ceasing drug use activities, would have an impact on HepB immune response. Because this study is restricted to drug users, the findings may not be applicable to other populations such as clients of STD clinics or vaccination programs that are linked with primary health care services. IDUs may also have biologically plausible different characteristics than NIDU for non-response or impaired response to hepatitis B vaccine (commonly exhibiting anti-HBc in the absence of other HBV markers), but follow-up after a mean of 49 months in one study indicates that IDUs with isolated anti-HBc do not require vaccination [43]. The mean age of the participants was 43 years (SD+/- 9.0) and these findings cannot be generalized to younger drug users. Additionally, factors such as smoking habits and BMI were not measured and their effect on serological response could not be determined. Although anti-HBs titers <10 were included for the susceptible subgroup (only 2 participants had a non-zero titer value) and previous vaccination was not confirmed, the actual interim and final antibody titers relative to dose are similar to what is reported.

Conclusion

Much of the literature on hepatitis B vaccine has focused on immunocompetent adults and less is known about vulnerable populations, particularly the drug using community.

Completing the HepB series remains a priority for initiating drug users, particularly younger drug users. These results indicate that the accelerated schedule may confer early protective immunity for a risk group that may suppress their immune response and alter their susceptibility to hepatitis B through frequent risky drug and sexual behaviors. Investigation of hepatitis B vaccine and similar multi-dose/accelerated schedules should consider older age and injection frequency in the creation/adjustment of intervention programs and treatment plans when evaluating the problems of poor immune response to vaccinations in drug users and other mobile populations. The findings from this study may be of value to physicians who treat the small subset of initiating older (>40 years) injection drug users with more than daily injection frequency who may demonstrate reduced immunological response [12].

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Abbreviations

HepB	hepatitis B vaccine
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IDU	injection drug users, injecting drug use
NIDU	non-injection drug users
Anti-HBc	antibody to hepatitis B core antigen
HBsAg	hepatitis B surface antigen
Anti-HBs	antibody to hepatitis B surface antigen
Anti-HCV	antibody to hepatitis C virus
MSM	men who have sex with men
OR	odds ratio
CI	confidence interval

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Highlights

Question of immune response to HepB vaccine in drug users.

Cumulative adequate protective response was achieved in 65% of HBV susceptible subgroup using a 0, 1, 6 schedule and 0, 1, 2 schedule at 12 months.

Increased risk of non-response for participants 40 years or older ($p=0.046$) or injecting drugs more than once a day ($p=0.016$).

0, 1, 2 schedule had higher proportion of adequate immune response and higher mean antibody titers at 6 months.

Figure 1A. Proportional Trends in Immune Response Categories at 2-, 6-, and 12-Months (Standard Schedule)

Figure 1B. Proportional Trends in Immune Response Categories at 2-, 6-, and 12-Months (Accelerated Schedule)

Figure 2. Anti-HBs Geometric Mean Titers (GMT) at 2-, 6-, and 12-Months

Table 1
Baseline Demographics/Characteristics of HBV Susceptible Subgroup (Anti-HBc Negative, Anti-HBs Negative or <10 mIU/mL, 3-Dose Compliant Drug Users) (N=707)

Variables	Standard Schedule N (%)	Accelerated Schedule N (%)	Total N (%)
	342 (48)	365 (52)	707
Gender			
Male	259 (76)	284 (78)	543 (77)
Female	83 (24)	81 (22)	164 (23)
Race			
African American	303 (89)	313 (86)	616 (87)
Hispanic	12 (3.5)	18 (4.9)	30 (4.2)
Caucasian	26 (7.6)	33 (9.0)	59 (8.4)
Other	1 (0.3)	1 (0.3)	2 (0.3)
Age Group			
18-29	32 (9.4)	30 (8.2)	62 (8.8)
30-39	87 (25)	101 (28)	188 (27)
40-49	148 (43)	145 (40)	293 (41)
>=50	75 (22)	89 (24)	164 (23)
Marital Status^a			
Single	159 (47)	201 (55)	360 (51)
Married ^b	66 (19)	64 (18)	130 (18)
Living with same sex partner	7 (2.0)	4 (1.1)	11 (1.6)
Separated/Divorced/Widowed	110 (32)	96 (26)	206 (29)
Education^a			
Less than High School	10 (2.9)	21 (5.8)	31 (4.4)
High School	255 (75)	248 (68)	503 (71)
More than High School	77 (22)	96 (26)	173 (25)
Living Arrangements^a			
Own House/Apartment	107 (31)	92 (25)	199 (28)
Someone Else's Dwelling	211 (62)	237 (65)	448 (63)
Streets/Shelter	24 (7.0)	36 (9.9)	60 (8.5)
Anti-HCV			
No	275 (81)	292 (80)	567 (80)
Yes	66 (19)	73 (20)	139 (20)
Ever Injected Drugs^a			
No (NIDU)	281 (82)	280 (77)	561 (79)

Variables	Standard Schedule N (%)	Accelerated Schedule N (%)	Total N (%)
	342 (48)	365 (52)	707
Yes (IDU)	61 (18)	85 (23)	146 (21)
Drug Injection Duration			
0-1 years	26 (43)	41 (49)	67 (46)
2-4 years	8 (13)	12 (14)	20 (14)
5-10 years	13 (21)	16 (19)	29 (20)
>10 years	14 (23)	15 (18)	29 (20)
Drug Injection Frequency			
Less than Daily	34 (56)	40 (48)	74 (51)
Daily	6 (9.8)	10 (12)	16 (11)
More Than Daily	21 (34)	33 (40)	54 (38)
Shared Needles/Works (Last 30 Days)			
No	337 (98)	357 (98)	694 (98)
Yes	5 (1.5)	7 (1.9)	12 (1.7)
Injected Drugs (Last 30 Days)			
No	325 (95)	345 (95)	670 (95)
Yes	17 (5.0)	19 (5.2)	36 (5.1)
Drug Types Currently Used			
0	15 (4.4)	10 (2.7)	25 (3.5)
1	63 (19)	78 (21)	141 (20)
2	135 (39)	135 (37)	270 (38)
3 or more	129 (38)	142 (39)	271 (38)
Current Alcohol Use (Last 30 Days)			
No	121 (35)	128 (35)	249 (35)
Yes	221 (65)	237 (65)	458 (65)
Ever In Drug Treatment			
No	149 (44)	139 (38)	288 (41)
Yes	193 (56)	226 (62)	419 (59)
MSM^c			
No	324 (95)	333 (91)	657 (93)
Yes	16 (4.7)	31 (8.5)	47 (6.7)
Traded Sex For Money/Goods (Last 30 Days)			
No	65 (61)	66 (52)	131 (56)

Variables	Standard Schedule N (%)	Accelerated Schedule N (%)	Total N (%)
	342 (48)	365 (52)	707
Yes	41 (39)	60 (48)	101 (44)
Traded Money/Goods For Sex (Last 30 Days)			
No	86 (65)	93 (60)	179 (62)
Yes	46 (35)	63 (40)	109 (38)

^a
p<0.10

^b Married or living as married with someone of the opposite sex

^c
p<0.05

Table 2
Univariate Analysis of Characteristics with Cumulative 12-Month Immune Response in HBV Susceptible Subgroup Who Received 3 Doses of Vaccine

Variables	Total	Non-Protective Response ^a N (%)	Protective Response ^b N (%)	Odds Ratio 95% CI	P-value
Vaccine Schedule					
Standard (0, 1-, 6-month)	342	121 (35)	221 (65)	Ref	
Accelerated (0, 1-, 2-month)	365	127 (35)	238 (65)	1.03 (0.75-1.40)	0.870
Gender					
Male	543	201 (37)	342 (63)	Ref	
Female	164	47 (29)	117 (71)	1.46 (1.00-2.14)	0.049
Race					
African American	616	215 (35)	401 (65)	Ref	
Hispanic	30	11 (37)	19 (63)	0.93 (0.43-1.98)	
Caucasian	59	21 (36)	38 (64)	0.97 (0.56-1.70)	
Other	2	1 (50)	1 (50)	0.54 (0.03-8.61)	0.984
Age Group					
18-29	62	17 (27)	45 (73)	Ref	
30-39	188	62 (33)	126 (67)	0.77 (0.41-1.45)	
40-49	293	100 (34)	193 (66)	0.73 (0.40-1.34)	
≥50	164	69 (42)	95 (58)	0.52 (0.28-0.99)	0.133
Marital Status					
Single	360	118 (33)	242 (67)	Ref	
Married ^c	130	45 (35)	85 (65)	0.92 (0.60-1.41)	
Living with same sex partner	11	2 (18)	9 (82)	2.19 (0.47-10.32)	
Separated/Divorced/Widowed	206	83 (40)	123 (60)	0.72 (0.51-1.03)	0.210
Education					

Variables	Total	Non-Protective Response ^a N (%)	Protective Response ^b N (%)	Odds Ratio 95% CI	P-value
Less than High School	31	15 (48)	16 (52)	Ref	
High School	503	164 (33)	339 (67)	1.94 (0.94-4.02)	
More than High School	173	69 (40)	104 (60)	1.41 (0.66-3.04)	0.063
Living Arrangements					
Own House/Apartment	199	75 (38)	124 (62)	Ref	
Someone Else's Dwelling	446	146 (33)	302 (67)	1.25 (0.88-1.77)	
Streets/Shelter	60	27 (45)	33 (55)	0.74 (0.41-1.33)	0.110
Anti-HCV					
No	60	22 (37)	38 (63)	Ref	
Yes	439	135 (31)	304 (69)	1.31 (0.74-2.29)	0.335
Ever Injected Drugs					
No	561	198 (35)	363 (65)	Ref	
Yes	146	50 (34)	96 (66)	1.05 (0.71-1.54)	0.813
Drug Injection Duration					
0-1 years	67	20 (30)	47 (70)	Ref	
2-4 years	20	4 (20)	16 (80)	1.70 (0.51-5.73)	
5-10 years	29	14 (48)	15 (52)	0.46 (0.19-1.12)	
>10 years	29	12 (41)	17 (59)	0.60 (0.24-1.49)	0.138
Drug Injection Frequency					
Less than Daily	74	20 (27)	54 (73)	Ref	
Daily	16	5 (31)	11 (69)	0.81 (0.25-2.64)	
More Than Daily	54	25 (46)	29 (54)	0.43 (0.21-0.90)	0.074
Injected Drugs (Last 30 Days)					
No	670	236 (35)	434 (65)	Ref	
Yes	36	12 (33)	24 (67)	1.09 (0.53-2.21)	0.817
Drug Types Currently Used					

Variables	Total	Non-Protective Response ^a N (%)	Protective Response ^b N (%)	Odds Ratio 95% CI	P-value
(Last 30 Days)					
0	25	15 (60)	10 (40)	Ref	
1	141	60 (43)	81 (57)	2.02 (0.85-4.82)	
2	270	79 (29)	191 (71)	3.62 (1.56-8.41)	
3 or more	271	94 (35)	177 (65)	2.82 (1.22-6.53)	0.003
Currently Use Crack Cocaine (Last 30 Days)					
No	75	34 (45)	41 (55)	Ref	
Yes	632	214 (34)	418 (66)	1.62 (1.00-2.63)	0.049
Currently Use Heroin (Last 30 Days)					
No	244	244 (35)	448 (65)	Ref	
Yes	4	4 (27)	11 (73)	1.50 (0.47-4.75)	0.493
Currently Use Alcohol (Last 30 Days)					
No	249	98 (39)	151 (61)	Ref	
Yes	458	150 (33)	308 (67)	1.33 (0.97-1.84)	0.079
Currently Use Speedball (Last 30 Days)^d					
No	710	248 (35)	453(65)	Ref	
Yes	7	0 (0)	6 (100)	-----	0.096
MSM					
No	657	234 (36)	423 (64)	Ref	
Yes	47	13 (28)	34 (72)	1.45 (0.75-2.80)	0.270
Traded Sex For Money (Last 30 Days)					
No	131	40 (31)	91 (69)	Ref	
Yes	101	24 (24)	77 (76)	1.41 (0.78-2.54)	0.253
Traded Money For Sex					

Variables	Total	Non-Protective Response ^a N (%)	Protective Response ^b N (%)	Odds Ratio 95% CI	P-value
(Last 30 Days)					
No	179	73 (41)	106 (59)	Ref	
Yes	109	34 (31)	75 (69)	1.52 (0.92-2.51)	0.102
Ever In Drug Treatment					
No	288	111 (39)	177 (61)	Ref	
Yes	419	137 (33)	282 (67)	1.29 (0.94-1.77)	0.110

^aNon-protective response refers to an anti-HBs titer negative or <10 mIU/mL

^bProtective response refers to an anti-HBs titer of ≥10 mIU/mL

^cMarried or living as married with someone of the opposite sex

^dSpeedball is the use of heroin and cocaine together

Table 3
Multivariable Analysis of Characteristics Associated with Adequate Immune Response at 12 Months in HBV Susceptible Drug Users who received 3 dose vaccine

Variable	Negative or <10 mIU/mL N (%)	≥10 mIU/mL N (%)	OR (95% CI)	P value
Age In Years				
Less Than 40	79 (32)	171 (68)	Ref	
40 Or Older	169 (37)	288 (63)	0.37 (0.14-0.98)	0.046
Daily Injections				
Less Than Daily	42 (32)	91 (68)	Ref	
Daily	12 (29)	29 (71)	1.05 (0.29-3.80)	0.943
More Than Daily	55 (36)	96 (64)	0.36 (0.15-0.82)	0.016

Adjusted for vaccine schedule, gender, age, marital status, education level, living arrangements, trading money for sex, ever been in drug treatment, duration of injecting drugs, frequency of injecting drugs, types of drugs currently used, current crack cocaine use, current alcohol use, speedball, and methamphetamine use.