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Responses to Hepatitis A Virus Vaccine in HIV-Infected Women: Effect of Hormonal Contraceptives and HIV Disease Characteristics

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Introduction

HIV-infected individuals respond poorly to vaccines including the hepatitis A virus (HAV) vaccine[1-6]. Previous studies enorlled mostly men and although vaccine immunogenicity does not generally vary with sex[7-10], some exceptions exist[11-14].

Female sex hormones, estrogen and progesterone, have been implicated in down regulation of inflammatory and anti-infective immune responses[15,16], including increased HIV acquisition and transmission during pregnancy and in women receiving hormonal contraceptives (HC)[17-22].

In vitro supplementation of estrogen and progestin attenuates antiviral and autoimmune cell-mediated responses, particularly in the context of HIV infection [23-25]. Furthermore, cell-mediated immunity decreases during the menstrual cycle reaching a nadir at the peak of estrogen and progesterone secretion [26]. Collectively, these data indicate that female hormones may depress T-cell mediated immunity.

Less is known about the effect of female hormones on antibody production. Virtually all antiviral and some antibacterial responses are T-cell dependent and may be affected by downregulation of T-cell immunity. We evaluated the effect of hormonal contraception

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(HC) and of CD4 cell numbers and plasma HIV RNA load on antibody responses to HAV vaccine of HIV-infected women.

Methods

The study used archived samples collected between Nov 1994 and Feb 2010 from women enrolled in the prospective observational Women's Interagency HIV Study (WIHS)[27,28]. There are two recommended schedules of immunization against HAV (2 or 3 doses separated by 6 or 2 months, respectively) with FDA-licensed vaccines from two manufacturers, but the antibody responses after the last dose of vaccine are similar in immunocompetent hosts, regardless of product or administration regimen[29-33]. In this study, we made no distinction between products or regimens.

Quantitative HAV antibodies measurements were performed according to the manufacturer's instructions using a pseudo-competitive enzyme immunoassay kit (Mediagnost) with a dynamic range of 10 to 50 mIU/ml. Samples with titers >50 mIU/ml were diluted until a measurement within the dynamic range of the test was obtained.

Peak antibody titer was defined as the highest measurement observed after vaccination was reported. Antibody measurements were truncated at 20 mIU/ml, which is the threshold for vaccine-induced protection and for seropositivity. Samples with <20 mIU/ml were ascribed an arbitrary value of 10 mIU/ml. Response on the continuous scale was defined as Log_{10} of the ratio of peak/baseline antibody concentration. Response was also analyzed as a dichotomous outcome. In HAV-seronaive subjects (baseline <20 mIU/ml), a peak antibody titer ≥ 20 mIU/ml defined response. In HAV-experienced subjects (baseline titer ≥20 mIU/ml), response was defined by ≥2-fold increase in antibody concentration at peak compared with baseline. Subjects were defined as HC recipients if they reported HC at baseline and subsequent visit. Subjects with discrepant HC reports at the two above-mentioned visits were excluded from the analysis.

Differences between HC and non-HC recipients were analyzed using two-sample t-test or chi-square in SAS 9.2 (SAS Institute). Multivariate analyses used logistic regression.

Results

Among 373 women who met inclusion criteria, 36 (10%) used HC at the time of vaccination, including 18 on oral contraceptives, 17 on depo-medroxyprogesterone acetate and one with alternate use of both methods. Women who used HC were younger than those who did not (means±SD of 37±6 vs. 42±8 years; $p<0.001$). Other characteristics were similar including race and ethnicity (14% white, 31% Hispanics and 56% black); mode of HIV acquisition (21% intravenous drug use; 47% heterosexual; 2% transfusion; 19% unknown); CD4 cells/μl (mean±S.D.=478±265); plasma HIV RNA< 400 copies/ml (47%); use of HAART (78%) and HAV-seropositivity before vaccination (57%).

Baseline antibody titers were similar in HC and non-HC recipients [GM (95% GMCI) of 197.7 (88.2, 443.0) and 135.6 (105.3, 174.4) mIU/ml, respectively; $p=0.37$]. The magnitude of the peak antibody titer was also similar in the 2 groups: 504.8 (252.1, 1010.7) and 324.1 (254.9, 412.2) mIU/ml for HC and non-HC, respectively ($p=0.22$). Overall, 44% of the 36 HC and 39% of the 337 non-HC recipients responded to vaccination. Among 162 baseline-HAV-naïve participants (titers <20 mIU/ml), 62% of the 13 HC and 51% of the 149 non-HC recipients were responders. Among 211 baseline seropositive participants, 30% had a booster response to vaccination, including 35% of 23 HC recipients and 30% of 188 non-HC participants.

Overall, the geometric mean fold-rise (GMFR) in HAV antibody titers after vaccination was 2.4 (95% CI of 2.1, 2.8). Among the subset of women who showed a ≥2-fold increase in HAV antibody concentrations after vaccination, the GMFR was 8.7 (95% CI of 7.1, 10.7). The GMFR did not significantly differ between HC and non-HC recipients overall (p=0.78) or between HC and non-HC responders (p=0.75).

The table shows the predictors of HAV response investigated in this study. In the univariate analysis, white race, plasma HIV RNA <400 copies/ml, higher CD4 cells/μl and baseline antibody titers <20 mIU/ml (HAV seronaive) were significantly associated with an antibody response to the vaccine. A multivariate analysis, which included the variables significantly associated with antibody response in the univariate analysis and HC use, showed that CD4 cells, undetectable HIV RNA and baseline HAV-seronaive were independently associated with response.

Discussion

This study did not detect significant differences between HC and non-HC recipients with respect to antibody responses to HAV immunization. Given the actual proportion of subjects on HC therapy, which was lower than expected [34], and the 39% rate of response of the non-HC recipients, our study had 80% power to detect differences lower than 16% or higher than 66%. However, the observed rate of response among HC recipients was 44%. The significant overlap both in antibody concentrations and proportion of responders between the 2 groups strongly suggests that HC therapy does not interfere with antibody responses to HAV vaccine in HIV-infected women.

The overall rate of antibody response to HAV vaccination of 52% in HAV-seronaive HIV-infected women was considerably lower than the 100% rate previously reported in immunocompetent adults[35-37], which is in agreement with other studies of HIV-infected individuals[1-5]. We and others showed that increasing the number of doses and/or antigen content improves the response of HIV-infected children and adults to hepatitis A vaccine[1,38]. However, in the absence of a formal recommendation to increase the number doses of HAV vaccine, HIV-infected individuals may continue to be immunized in a suboptimal fashion.

The proportion of baseline HAV-seropositive subjects of 57% in this study was higher than the 32% seroprevalence previously reported among US adults[39]. This finding is in accordance with our previous observation that HIV-infected children without a history of HAV vaccination or wild type infection also had a higher rate of HAV seroprevalence than expected[1]. In view of this high HAV seroprevalence among HIV-infected individuals, the substantial cost of vaccination, and the poor boosting effect of HAV vaccine in seropositive HIV-infected women, it is reasonable to screen these individuals for existing antibodies before initiating an HAV immunization regimen.

The HIV disease-associated factors contributing to the low antibody response to vaccination were a decreased number of CD4 cells and detectable plasma HIV viral load, which is in agreement with previous findings[1,2,40]. The corollary of this observation is that in HIV-infected individuals who are not at an immediate risk of HAV infection (such as travel in an endemic area) or of developing exceedingly severe disease (such as underlying hepatitis B or C chronic infections), it may be acceptable to delay immunization if an increase of CD4 cells and/or decrease in viral load is anticipated in the near future, such as in patients who have recently started a new HAART regimen.

In conclusion, antibody responses to HAV immunization were equally low in HIV-infected women receiving HC or not. More potent vaccination regimens, with increased antigen content or number of doses are needed to adequately immunize HIV-infected women.

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Table

Determinants of antibody response to HAV immunization

Label	Value	Unadjusted				Adjusted	
		HAV Antibody Response[#]		OR (95% CI)[&]	p-value	OR (95% CI)[&]	p-value
		No (N=225)	Yes (N=148)				
Hormonal Contraception	no HC	205(91.1)	132(89.2)		0.66	-ref-	
	Depo or OCP	20(8.9)	16(10.8)	-ref-		1.3 (0.6, 2.6)	0.54
Age	Mean±SD	41.6± 7.6	41.7± 8.2	1.24 (0.6, 2.5)	0.95		
Race/Ethnicity*	White	24 (11)[$]	29 (20)		0.004		
	Hispanic	83 (37)	31 (21)				
	African-American	112 (50)	84 (57)	-ref-			
	Other	6 (3)	4 (3)	0.3 (0.2, 0.6)			
Exposure	Intravenous drug use	45 (20)	35 (24)	0.6 (0.3, 1.1)	0.30		
	Heterosexual	106 (47)	70 (48)	0.6 (0.1, 2.2)			
	Transfusion	8 (4)	1 (1)				
	No identified risk	65 (29)	41 (28)	-ref-			
Group	Prevalent case	98 (44)	61 (41)	0.8 (0.5, 1.5)	0.67		
	Incident case	127 (56)	87 (59)	0.2 (0.02, 1.4)			
HIV RNA*	<400 copies/ml	78 (35)	68 (46)	0.8 (0.5, 1.5)	0.03	1.7 (1.0, 2.6)	0.04
	≥400 copies/ml	147 (65)	80 (54)			-ref-	
HAART	No	54 (24)	27 (18)	-ref-	0.20		
	Yes	171 (76)	121 (82)	1.1 (0.7, 1.7)			
CD4 cells/il*	Mean±SD	450±250	519±281		0.02	1.1 (1.0, 1.2)	0.04
CD8 cells/il	Mean±SD	878±429	860±352	1.6 (1.0, 2.4)	0.67		
Baseline HAV antibodies*	**<20 mIU**	78 (35)	84 (57)	-ref-	<0.001	2.9 (1.9,4.6)	<0.001
	≥20 mIU	147 (65)	64 (43)	0.7 (0.4, 1.2)		-ref-	

[#]Antibody response was defined by a ≥2-fold increase between baseline and peak antibody concentrations or by conversion from <20 to ≥20 mIU/ml.

[&]Odds ratio (95% confidence interval)

[$]Number (%)

* Indicates factors that were significantly associated with antibody response to HAV vaccine in the univariate analysis.

Bold-facing underscores factors that remained significant in the multivariate analysis, which considered all significant factors identified by the univariate screen (see statistical methods) in model selection and HC use.