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Clinical Study

Predictors of humoral response to recommended vaccines in HIV-infected adults

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ABSTRACT

Humoral response to vaccination has been found to be inadequate in individuals infected with the human immunodeficiency virus (HIV). We retrospectively assessed antibody responses to three routinely recommended vaccines, against hepatitis B, hepatitis A and *S. pneumoniae*, in HIV-infected individuals. Data regarding age at HIV diagnosis, years of infection, sex, nationality, HIV mode of transmission, CD4 cell count, nadir CD4 count, plasma viral load, HIV stage, insurance status, educational level and treatment with Highly Active Antiretroviral Therapy (HAART) were collected. Univariate and multivariate analysis was performed in order to detect factors associated with response to vaccination. 437 patients were assessed for hepatitis B, 627 patients for hepatitis A and 66 patients for *S. pneumoniae* serologic vaccine responsiveness. Regarding hepatitis B and hepatitis A, education level and insurance status were the only predictors of response. As for *S. pneumoniae* vaccination HAART and control of viremia were correlated with better response to vaccination.

1. Introduction

Vaccination is one of the cornerstones of public health, since it is one of the most cost-effective methods of preventing infectious diseases. In human immunodeficiency virus (HIV) positive patients its importance is magnified due to their susceptibility to various infectious pathogens and due to shared modes of transmission of HIV with other viruses. In defiance of highly active antiretroviral therapy (HAART), seropositive patients remain at high risk for several diseases, such as pneumococcal disease [1]. Presently, vaccination against hepatitis B virus, hepatitis A virus and *S. pneumoniae* is recommended in HIV-infected patients [2]. Several studies have tried to assess the humoral responses to immunization against hepatitis B virus [3–6], hepatitis A virus [7,8] or *S. pneumoniae* [9–12] in the HIV setting, with conflicting results.

Immune responses to most vaccines have been shown to be impaired in patients with HIV infection [13,14]. However, apart from the primary response to vaccination, which has been widely documented [15,16], long-term persistence of protective immune response has been studied more recently. [17]. Timing of administration of boosting doses is currently based on data derived from healthy controls, even though antibody decay patterns may be different in HIV-infected individuals. Strategies to increase efficacy of hepatitis B vaccination have been implemented and include revaccination with higher dose (40 mcg) [18], higher number of injections [4,19], or an accelerated vaccination schedule [20,21]. It is therefore crucial to not only investigate predictors of antibody response but also to study how seroprotection decreases over time among HIV patients. In the current study, we reviewed data on humoral responses to three different vaccines administered routinely to HIV patients (against hepatitis B, hepatitis A and *S. pneumoniae*). To assess seroconversion, we measured antibody concentrations post vaccination, as these can be routinely assessed with standardized methods [17] and have been used in most vaccine efficacy trials.

2. Methods

2.1. Study population

We performed a twelve-year (January 2002–January 2014) retrospective, cross sectional study of all HIV infected adults followed in the Infectious Diseases (ID)/HIV Unit of the First Internal Medicine Department of the University General Hospital AHEPA, in Thessaloniki, Greece. A total number of 1210 HIV-infected patients were assessed for

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Table 1
Univariate analysis HAV antibodies.

	HAV antibodies < 20 (N = 121, 19.3%)	HAV antibodies > 20 (N = 506, 80.7%)	Total population (N = 627, 100%)	p-value
Age at infection [years]				
Median (range)	32.70 (18–66)	32.85 (15–75)	32.85 (15–75)	0.509
Mean (SD)	35.12 (10.07)	34.536 (10.01)	34.51 (10.02)	0.455
Years of infection [years]				
	5.16 (0.3–24.5)	6.51 (0.3–24.54)	6.33 (0.3–24.5)	**0.033**
Mean (SD)	7.12 (5.94)	7.91 (5.59)	7.76 (5.66)	0.169
Sex [N (%)]				
Male	104 (86,0%)	430 (85,0%)	534 (85.2%)	0.887
Female	17 (14.0%)	76 (15,0%)	93 (14.8%)	
Nationality[N (%)]				
Greek	111 (91.7%)	476 (94.1%)	587 (93.6%)	0,406
Other	10 (8.3%)	30 (5.9%)	40 (6.4%)	
HAART [N (%)]				
No	21 (17.4%)	111 (21,9%)	132 (21.1%)	0.321
Yes	100 (82.6%)	395 (78,1%)	495 (78.9%)	
HIV risk factor [N (%)]				
MSM	95 (78.5%)	386 (76.3%)	481 (76,7%)	0,943
Heterosexual sex	19 (16,0%)	84 (16,6%)	103 (16.4%)	
IVDU	1 (0,8%)	6 (1,2%)	7 (1.1%)	
Other	6 (5.0%)	30 (5.9%)	36 (5.7%)	
Nadir CD4 cell count (log10)				
Mean (SD)	2.43 (0.44)	2.38 (0.43)	2.39 (0.43)	0.308
CD4 cell count (log10)				
Mean (SD)	2.70 (0.34)	2.70 (0.27)	2.70 (0.28)	0.984
Plasma viral load (log10)				
Mean (SD)	4.32 (1.08)	4.15 (1.14)	4.18 (1.13)	0.147
CDC [N (%)]				
A	83 (68.6%)	310 (61.3%)	393 (62,7%)	0.296
B	28 (23.1%)	137 (27.1%)	165 (26.3%)	
C	10 (8.3%)	59 (11,7%)	69 (11.0%)	
Insurance [N (%)]				
Yes	18 (14.9%)	377 (74.5%)[a]	395(63.0%)	< **0.0005**
No	79 (65.3%)	34 (6.7%)[b]	113 (18.0%)	
Social welfare	24 (19.8%)	95(18.8%)	119 (19.0%)	
Education [N (%)]				
Primary	94 (77.7%)	154 (30.4%)[c]	248 (39.6%)	< **0.0005**
High School	25 (20.7%)	217 (42.9%)[d]	242 (38.6%)	
University	2 (1.7%)	135 (26.7%)[e]	137 (21.9%)	
CD4 cell count N(%)				
Less than 350	22 (19.5%)	107 (21.5%)	129 (21.1%)	0.703
More than 350	91 (80.5%)	391 (78.5%)	482 (78.9%)	
Plasma viral load N(%)				
Less than 10,000	94 (77.7%)	400 (79.1%)	494 (78.8%)	0.712
More than 10,000	27 (22.3%)	106 (20.9%)	133 (21.2%)	
Nadir CD4 cell count N(%)				
Less than 200	23 (20.5%)	136(28.0%)	159 (26.9%)	0.123
More than 200	89 (79.5%)	349 (72.0%)	438 (73.4%)	
Time of vaccination N(%)				
Before 2010	59 (48.8%)	308 (60.9%)	367 (58.5%)	**0.018**
After 2010	62 (51.2%)	198 (39.1%)	260 (41.5%)	

All quantitative data are presented as mean ± SD, *median (IQR), VL: HIV RNA viral load, HAART: Highly Active Antiretroviral Therapy, NA = not applicable, HCV: Hepatitis C infection, HBV: Hepatitis B infection, CDC: Centre For Disease Control; MSM: Men having sex with men; IVDU: Intravenous Drug Users. Statistical significance: $p < 0.05$.

[a] $p < 0,0005$.
[b] $p < 0,0005$.
[c] $p < 0,0005$.
[d] $p < 0,0005$.
[e] $p < 0,0005$.

vaccination status against hepatitis B virus, hepatitis A virus and *S. pneumoniae.* Patients who had at least one visit per year and two years of follow up at the ID/HIV Unit were included. Exclusion criteria for vaccine qualification included patients seropositive for HBsAb, HBsAg, HBeAb and isolated HBcAb, patients with a very low CD4 count at the time of vaccination (below 200cells/mm^3), current use of immunosuppresants, chemotherapy or corticosteroids, patients who were lost to follow up and patients who had natural immunity or previous history of vaccination, proven with serological testing. Demographic data were collected, including age at infection, years of infection, sex, nationality (Greek or other), HIV mode of transmission (male to male sexual contact, heterosexual contact, injecting drug use, other), nadir CD4 count, current CD4 cell count (cell count within three months before first dose of vaccination),plasma viral load at the time of initiation of vaccination, HIV disease stage according to CDC (A, B, C), insurance status (insured, uninsured or receiving social welfare), educational level (primary, high school or university) and treatment with Highly Active Antiretroviral Therapy (HAART). HAART was defined as three or more antiretroviral drugs, including at least one protease inhibitor or non-nucleoside reverse transcriptase inhibitor plus two other agents (including integrase inhibitors).