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Prevalence and titre of antibodies against Hepatitis A virus in HIV-infected men having sex with men in Greece

Prevalenza e titolo anticorpale anti-epatite A in maschi omosessuali con infezione da HIV in Grecia

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INTRODUCTION

During the last decade, a rise in the incidence of HIV infection as well as of syphilis and gonorrhoea was observed. This rise mainly concerns men having sex with men (MSM) and was clearly attributed to the resurgence of high-risk sexual behaviour.

Hepatitis A, like other bowel infections, may be transmitted by sexual intercourse and it is mainly associated with specific sexual behavior [1]. Acute hepatitis A outbreaks have been reported among MSM. Vaccination of MSM against Hepatitis A virus (HAV) is recommended [2]. Special care is required in MSM with HIV-infection. HIV-patients affected by HAV are hospitalized for prolonged periods of time and are at risk of serious complications including fulminant hepatitis [3].

In countries with low HAV endemicity, childhood morbidity is reduced and the likelihood of experiencing the disease during adulthood is increased. In Greece, during the last decades, the prevalence of HAV decreased with the improvement of socio-economic conditions [4]. Middle-aged and elderly patients usually have anti-HAV antibodies, because of a previous in-

fection, while younger adults belonging to high risk groups may develop immunity after vaccination. It is important to record Sexually Transmitted Diseases (STDs) among MSM and mainly HIV-infected patients not only for epidemiological reasons but also in order to organize prevention [5]. Usually, in the studies concerning STDs, HAV is not mentioned. Therefore, there is insufficient evidence on HAV immunity in specific population groups [6].

So, it would be of interest, as it is the aim of this study, to ascertain the immune status on Hepatitis A of HIV-infected MSM patients.

PATIENTS AND METHODS

The study included HIV-infected MSM attending the HIV clinic of the "A. Syggros" Hospital (Athens, Greece). During the period 2007-2011, patients were evaluated for anti-HAV antibodies, in order to plan their vaccination, even if they had undergone evaluation in the past. Patients already vaccinated against HAV were excluded from the study. This study was reviewed and approved by the Ethics Committee of the "A. Syggros" Hospital.

Anti-HAV antibodies were detected by a qualitative test (Architect[®] HAVAb-IgG and IgM; Abbott Wiesbaden; Germany).

The vaccination against HAV was recommended to patients with negative anti-HAV antibod-

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ies test and CD4 T-cell count >200 cells/mm³. They received 2 doses of either Havrix (1440 EL.U per dose, GlaxoSmithKline) or Vaqta (50 U per dose, Merck & Co), 6-12 months apart. The two brands of HAV vaccine are recommended as equivalent and interchangeable. One month after the administration of the second dose of the vaccine, the titer of anti-HAV antibodies was measured by a commercial enzyme-linked fluorescent assay method (VIDAS Anti-HAV Total, bioMérieux, France) which has a cut-off limit of ≥ 20 mIU/ml. The same method was used to determine the concentration of the anti-HAV antibodies in unvaccinated immune patients of a similar age with vaccinated patients. These patients probably had immunity due to asymptomatic infection in the childhood. Statistical analyses were conducted using the package PASW Statistics 18. Logistic regression models were used to evaluate factors associated with the initial detection of anti-HAV antibodies. Factors evaluated included age, ethnicity, co-infection with hepatitis B or C and the history of Sexually Transmitted Diseases (STDs). Patients with at least one diagnosis of early syphilis or gonorrhoea, which are high risk indicators, were considered as having STD.

RESULTS

The study included 897 HIV-infected MSM, 35.7% (320/897) of which had anti-HAV antibodies (Figure 1). The mean age (\pm Standard Deviation, SD) of total study population was 41.30 ± 9.88 years (Table 1).

Most of the patients (92.5%) were Greek. Patients of foreign descent (67/897, 7.5%) came from countries with high HAV endemicity (Africa, Asia, Eastern Europe) and their mean age (\pm SD) was 36.61 ± 9.18 years. The majority of patients of foreign descent (53/67.79%) were immune to HAV.

In the Greek patients, the presence of antibodies in those aged ≥ 40 years was statistically significant compared to younger patients ($p < 0.05$). On the contrary, in patients of foreign descent the anti-HAV antibody count did not vary statistically significantly between patients older than 40 years of age and younger patients ($p = 0.6$).

Thirty one percent (31.0%) of all patients had a history of STD (early syphilis or gonorrhoea) while only 6.9% had concomitant hepatitis B or C virus infection.

Among immune patients, only 8 experienced acute HAV during their adult life.

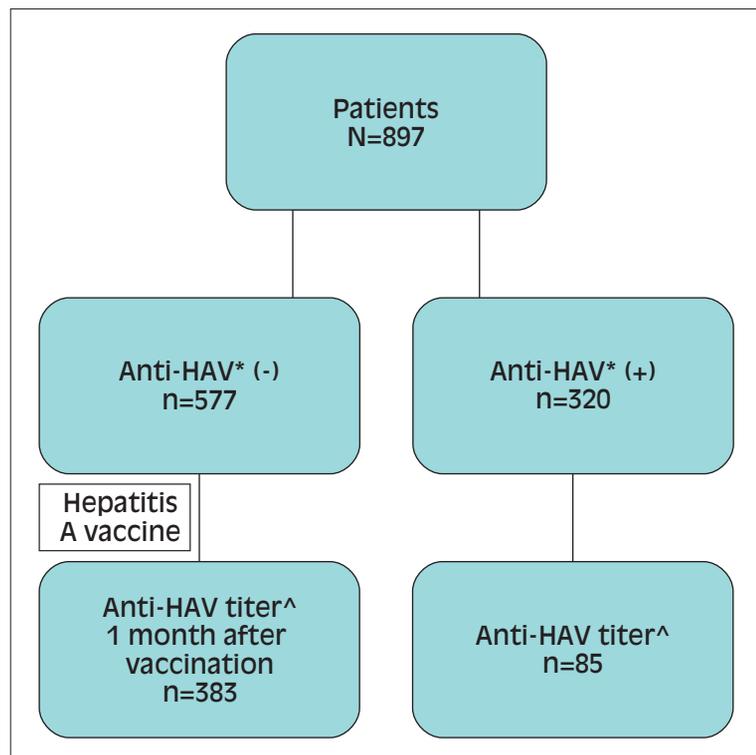


Figure 1 - Study flow diagram.
 Note: *Antibodies to Hepatitis A virus measured by a qualitative method (Architect[®] HAVAb-IgG and IgM; Abbott Wiesbaden; Germany). ^Antibodies to Hepatitis A virus measured by a quantitative method (VIDAS Anti-HAV Total, bioMérieux, France).

Table 1 - Patients characteristics at the time of anti-HAV detection.

		<i>n (%)</i>
Anti-HAV	Positive	320 (35.7)
	Negative	577 (64.3)
Sexually Transmitted Diseases	Yes	279 (31.0)
	No	618 (69.0)
Hepatitis B/C co-infection	Yes	53 (5.9)
	No	844 (94.1)
Antiretroviral therapy	Yes	615 (68.6)
	No	282 (31.4)
Origin	Foreigners [†]	67 (7.5)
	Greek	830 (92.5)
CD4 T-cells (cells/mm ³)	281.00 (219) ^{^^}	
Age (years)	41.30 (±9.88) [^]	
Note: *Anti-HAV: Antibodies to Hepatitis A virus. †Patients of foreign descent come from countries with high HAV endemicity (Africa, Asia, Eastern Europe). ^^Median (Interquartile Range). ^Mean (± Standard Deviation).		

The univariate analysis (Table 2) showed that ethnicity is statistically significant for the presence of antibodies. The statistically significant age difference between patients with anti-HAV antibodies and patients with no antibodies was also shown ($p < 0.001$). Patients with anti-HAV antibodies were older than patients without these antibodies.

A multiple logistic variation model was created and it was well adjusted to the available data. Nagelkerke R^2 equals 0.267, while the correct classification rate is 73.3%. The multivariate

analysis showed that only age ($p < 0.001$) and ethnic origin had a statistically significant effect on the presence of antibodies (Table 3). In addition, age has been shown to be a quite sensitive (68.4%) and specific (64.2%) marker and patients were separated by the 36.5 years cut-off point. The ROC curve is presented in Figure 2. The area under the ROC curve is 0.695 (95% CI 0.630- 0.761) which shows quite satisfactory diagnostic accuracy. Of the 577 patients, who were not immune to hepatitis A virus, 383 received the hepatitis A virus vaccine (Figure 1). Two hundred ninety-one patients developed antibodies against the HAV after completing the vaccination (response rate: 76%). Vaccinated patients had a mean age (\pm SD) of 40.20 ± 9.58 years. The Geometric Mean Titres of anti-HAV antibodies were 305 mIU/ml (95% CI 255-361 mIU/ml). In a group of 85 patients with immunity due to past infection and a mean age (\pm SD) of 39.49 ± 8.85 years, the geometric mean titre was 7105 mIU/ml (95% CI, 3.650-11.965 mIU/ml). Only 5 individuals had an antibody concentration lower than 1000 mIU/ml, while 22 individuals had an antibody titre higher than 10000 mIU/ml.

DISCUSSION

Epidemiological studies conducted in Greece in the late 70's, showed that 80% of the population had anti-HAV antibodies [7]. In the 80's, less than 10% of the children had immunity to hepatitis A virus [8]. Evidence collected during the last twenty years show that immunity re-

Table 2 - Univariate analysis for factors associated with the detection of anti-HAV antibodies in HIV-infected men having sex with men in Greece.

		<i>Anti-HAV* (n)</i>		<i>p-value</i>	<i>OR (95% CI)</i>
		<i>Negative</i>	<i>Positive</i>		
Sexually transmitted diseases	Yes	173	106	0.364	0.873 (0.651;1.171)
	No	404	214		
Hepatitis B/C coinfection	Yes	34	19	0.978	0.992 (0.556; 1.770)
	No	543	301		
Origin	Foreigners [†]	14	53	<0.001	0.125 (0.068; 0.230)
	Greek	563	267		
Age (years) [^]		38.97 (±8.40)	45.54 (±10.92)	<0.001	
Note: *Anti-HAV: antibodies to Hepatitis A virus. †Patients of foreign descent come from countries with high HAV endemicity (Africa, Asia, Eastern Europe). ^Mean (± Standard Deviation).					

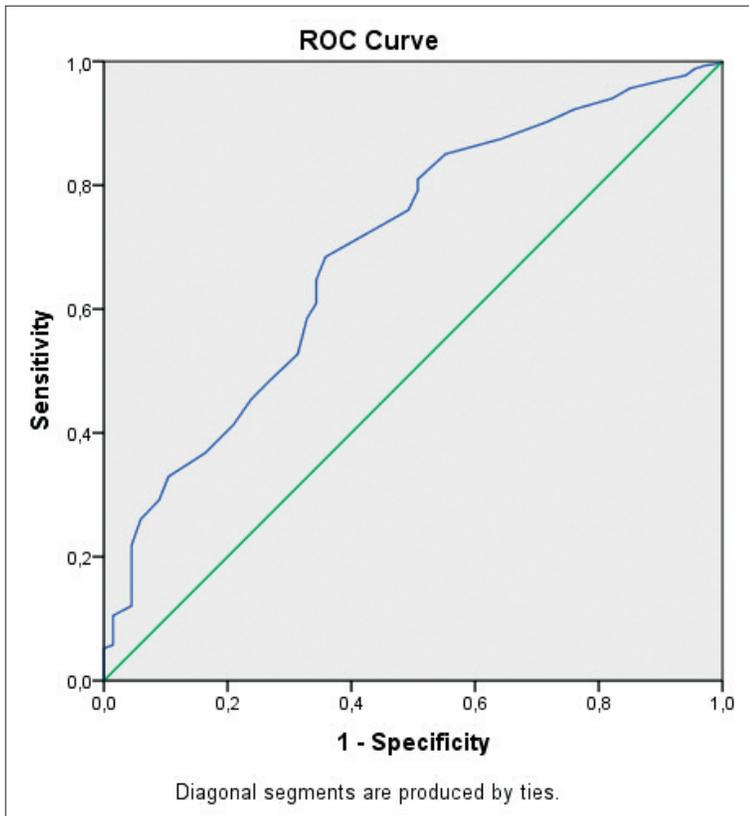


Figure 2 - The ROC Curve.

mains high among middle-aged and elderly individuals and there is a need for children vaccination [9]. Given that anti-HAV vaccination was included in the vaccination program in 1997, the presence of antibodies in adults is attributed to immunity due to previous childhood infections. Based on World Health Organization data, the prevalence of HAV immunity in Western Europe (where Greece is categorized) is approximately 35% in people aged 20-25 years and gradually increases with each decade that goes by [10]. In the USA, 29-35% of

the population have serologic evidence of previous HAV infection [11]. Therefore, the rate of patients with anti-HAV antibodies in this study (35%) is similar to the rates reported in the same age group population of countries with low HAV incidence. Likewise, an older study from Italy reported that there was no particular difference in anti-HAV antibodies rates between MSM and heterosexuals [12].

On the contrary, epidemiological data from other countries, including Poland and Spain, report a high antibody incidence among MSM, probably as a result of acute HAV outbreaks [13, 14].

Indeed, while the overall incidence of HAV decreased during the last decade, several epidemics were recorded among MSM in USA, Europe and Australia. In the United States, it is estimated that more than 10% of patients with acute HAV were MSM [15]. In Europe, increased incidence of acute hepatitis A virus (HAV) infection among homosexual males has been reported in some regions, like Northern Italy [16]. HAV epidemics among MSM are reported almost annually in large European cities since 1995 [17]. Epidemics observed in high risk

Table 3 - Logistic regression for factors associated with the detection of anti-HAV antibodies in HIV-infected men having sex with men in Greece.

	<i>p-value</i>	<i>OR (95% CI)</i>
Age (years)	<0.001	
Origin		
Greek		1.000
Foreigner†	<0.001	20.029 (10.274; 39.048)

†Patients of foreign descent come from countries with high HAV endemicity (Africa, Asia, Eastern Europe)

groups have also a significant impact on the general population. In 2008, 1616 cases of acute HAV were reported, in the Czech Republic, a 10-fold increase compared to the yearly incidence in the years 2003-2007 [18]. The infection was first observed in drug addicts and in the second half of the year it spread to the general population. Similarly, in the acute HAV infection outbreak in Latvia, more than 35% of the victims during the first 4 months were drug users [19].

In Greece, no epidemic has been reported among MSM and, perhaps, this is why the immunity levels recorded in the present study are not particularly high.

Nevertheless, the recent study by Weerakoon et al. suggests that although the recorded number of MSM with acute HAV infection was small, we must not underestimate the risk of infection [20]. The authors linked HAV infection with the general immunity rate. In areas with high immunity rates (40-50%) due to past epidemics, few cases of hepatitis were recorded. In areas with an incidence of antibodies of 20-30%, the risk of manifesting the disease is higher. Thus the necessity of vaccination is substantiated, both on grounds of self protection as well as in order to maintain the increased immune population rate. In HIV-infected patients in particular, hepatitis prevention is important, because acute hepatitis may lead to increased viral load (HIV-RNA) [21]. In addition, in HIV-patients, prolonged HAV viremia was observed, which may lead to higher infectiousness and increased risk of transmission [22].

Furthermore, a multivariate analysis showed that the only factors associated with the presence of anti-HAV antibodies were age and country of origin of the evaluated patients. Age older than 36.6 years is associated with increased likelihood for the detection of antibodies. Older patients have obviously developed HAV immunity due to childhood infection. In fact, only 8 of the immune patients had a history of acute HAV infection in adulthood, which may be associated with their sexual behaviour. Thus, despite the fact that a high rate of study

subjects (31%) report at least one case of syphilis or gonorrhoea, the logistic analysis did not reveal any correlation between immunity to HAV and history of STDs.

These results must not be considered to doubt the risk of sexual transmission of HAV in MSM. The report of outbreaks confirms that in this population group, the exposure and transmission of HAV are higher. Moreover, it may be worth to perform also tests for other STDs during a HAV infection outbreak in MSM [23].

Furthermore, patients with a history of infection had a higher antibody titre compared to the antibodies observed in vaccinated patients. Similarly, in healthy adults with immunity after infection, the antibody concentration is reported to be 10 to 100 times higher [24]. It is confirmed that the strong antibody response observed following the infection, even during childhood, is preserved even in HIV-infected patients. On the contrary, vaccinated patients have a much lower antibody titre and reduced response to vaccination [25-28]. In vaccinated HIV-patients, the anti-HAV titer monitoring may be necessary in order to evaluate response and duration of immunity [29]. Considering that the anti-HAV titer following vaccination may be lower than the detection level of some commercially available diagnostic assays, a sensitive method for the quantitative measurement of anti-HAV antibodies is required.

Limitations of this study are that it was performed on a single site and there was no control arm with healthy MSM.

Nevertheless, we believe that the recording of anti-HAV antibodies in HIV-infected MSM provides significant information on their immunity on hepatitis A. As vaccination is a key component of the HIV-patient care, results from this and other related studies may be useful to assess the risk of HAV infection and plan vaccination strategies.

Keywords: HIV, Hepatitis A, Men having Sex with Men, Greece.

Conflict of interest: none.

SUMMARY

Hepatitis A remains a serious vaccine-preventable disease for HIV patients. We tested 897 HIV-infected men having sex with men (MSM) for antibodies against hepatitis A virus (anti-HAV) and measured the geometric mean antibody titres (GMTs) in a group of patients who received a hepatitis A vaccine and in patients with immunity to HAV due to infection in childhood. In all, 320 patients (35%) had positive anti-HAV antibodies. Multivariate analysis showed that only age ($p<0.001$) and ethnic origin (OR 20.029, $p<0.001$) had a statistically significant effect on the presence of antibodies. In ad-

dition, age was a fairly sensitive (68.4%) and specific (64.2%) marker, patients being separated by the 36.5 years cut-off point. The response rate of patients who get vaccinated ($n=383$), one month following the administration of the second dose of the vaccine, was 76%. The GMT of the vaccinated patients was 305 mIU/ml versus 7105 mIU/ml of patients with past infection. The vast majority of HIV-infected MSM patients in Greece is susceptible to HAV. Immunity to HAV in newly vaccinated patients, unlike patients with natural immunity, is low and probably requires monitoring.

RIASSUNTO

Per i pazienti con infezione da HIV, l'epatite associata a HAV continua a rappresentare una malattia temibile, ancorché prevenibile mediante vaccinazione. Nel nostro studio abbiamo valutato il titolo anticorpale anti-epatite A (anti-HAV) in 897 maschi omosessuali con infezione da HIV e abbiamo misurato la media geometrica dei titoli anticorpali in un gruppo di pazienti vaccinati per l'epatite A e in pazienti con immunità per HAV acquisita in seguito all'infezione contratta in età pediatrica.

Complessivamente, 320 pazienti (35%) sono risultati positivi per la presenza di anticorpi anti-HAV. L'analisi multivariata ha evidenziato che solo l'età ($p<0,001$) e l'etnia (OR 20,029, $p<0,001$) presentano un effetto statisti-

camente significativo sulla presenza di anticorpi. Inoltre, l'età costituisce un marcatore abbastanza sensibile (68,4%) e specifico (64,2%), con un cut-off di 36,5 anni. Il tasso di risposta dei pazienti vaccinati ($n=383$), dopo un mese dalla somministrazione della seconda dose di vaccino, è stato pari al 76%. In tali pazienti, la media geometrica del titolo anticorpale è risultata pari a 305 mIU/ml versus 7105 mIU/ml rilevata nei pazienti che avevano già contratto l'infezione. In Grecia, la maggioranza dei pazienti omosessuali maschi con infezione da HIV è sensibile a HAV. Nei pazienti neo-vaccinati, diversamente da quanto accade per quelli con immunità naturale, l'immunità verso l'HAV è bassa e necessita di essere monitorata.

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