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High Frequency of HEV Seropositivity in HIV-Infected Patients in Southern Spain

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ABSTRACT (updated)

Background: HEV has been reported to be a cause chronic liver disease with rapid progression to cirrhosis in HIV-infected patients. Anti-HEV seropositivity has been observed in 9% HIV carriers in Northern Spain. Likewise, rates of seropositivity of 2.6% and 4% have been reported in HIV-infected patients with unexplained transaminase elevation in Switzerland and France, respectively. However, the prevalence of HEV infection may dramatically vary from one region to another. Moreover, the rate of evolution to chronic hepatitis C and the relevance of HEV coinfection as a cause of unexplained liver disease in HIV-infected patients remain unclear. The purpose of this study was to analyze the prevalence of HEV seropositivity and of active HEV infection, as well as the factors associated thereof in HIV-infected patients in Southern Spain.

Methodology: 613 HIV-infected patients who consecutively attended a Unit of Infectious Diseases in Seville, Southern Spain, were tested for HEV serum antibodies by EIA (Wantai, Beijing, China). Positive samples were confirmed by immunoblot (Mikrogen, Munich, Germany); those that tested positive by both procedures were considered as seropositive and were also submitted to a PCR test (Mikrogen) for serum HEV RNA. The associations between HEV seropositivity and demographics, as well as data of liver disease were analyzed.

Results: 593 (97%) subjects were born in Spain. Median age was 43 years. 416 (68%) were anti-HCV positive. 105 (17.2%) were seropositive for HEV antibodies. HEV-RNA was detected only in one subject. The older the age, the higher the rate of seropositivity: <40 years, 8.2%; 40-49 years, 17.6%; >49 years, 31.3% (p=0.00001). Among anti-HCV negative patients, the proportions of patients with AST >40 UI/L among HEV exposed and HEV unexposed were 5 (14.3%) and 9 (5.5%), respectively (p=0.078). The corresponding figures for ALT >40 UI/ were: 5 (14%) and 29 (18%), p=0.618, and, for GGT >40 UI/L: 12 (34%) and 36 (22%), p=0.077.

Conclusions: The rate of exposure to HEV is high among HIV-infected patients from Southern Spain, and it increases with age, but chronic infection is very uncommon. This suggests that most cases of acute HEV infection in this setting are self-limited. However, a trend to an association exists between prior HEV exposure and data of liver disease not related with HCV. Further studies are required to establish if there is actually a causative relationship.

BACKGROUND

- HEV has been reported to be a cause chronic liver disease with rapid progression to cirrhosis in HIV-infected patients.
- HEV seropositivity has been observed in 9% HIV carriers in Northern Spain. However, the prevalence of HEV infection may dramatically vary from one region to another.
- Likewise, rates of seropositivity from 1.5% to 45.3%% have been reported in HIV-infected patients around the world.
- It is critical to gain more information on the prevalence and factors associated with HEV infection in HIV carriers. A HEV vaccine has shown to be effective, although it is not commercially available everywhere. The proper use of vaccines will require knowing the precise prevalence of HEV infection in specific areas, as well as the subpopulations with the highest risk for infection. Likewise, if chronic hepatitis E were relatively common, surveillance could be warranted, since it is a potentially curable disease, which, if untreated, may evolve to end stage liver disease.

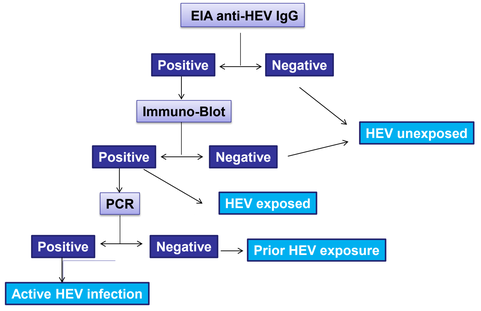
OBJECTIVE

This study aimed to analyze the prevalence of HEV seropositivity of active HEV infection, as well as the factors associated thereof in HIV-infected patients in Southern Spain.

PATIENTS AND METHODS

- **Study population:** 613 HIV-infected patients who consecutively attended a Unit of Infectious Diseases in Seville, Southern Spain, were included in this study.
- **Definition of HEV seropositivity:**
  - All patients were tested for HEV serum antibodies by EIA (Wantai, Beijing, China).
  - Positive samples were confirmed by an immunoblot test (Mikrogen, Munich, Germany).
  - Positive samples by both procedures were considered as seropositive, and were also submitted to a PCR test (Mikrogen, Munich, Germany) for serum HEV RNA. Seropositive patients were considered to be HEV exposed and those showing serum HEV-RNA as active HEV infection cases. For this analysis, patients without HEV antibodies were categorized as HEV unexposed.

***Figure 1*: Flow diagram of diagnostic procedures.**



- **Statistical analysis:** Categorical variables were compared applying the χ^2 test or the Fisher's test. HEV exposure was the primary outcome variable. A multivariate logistic regression analysis was conducted. Adjusted Odds Ratios (AOR) and confidence intervals (CI) were calculated.

RESULTS

***Table 1*: Characteristics of the study population (n=613)**

Characteristic	
Age (years)*	43 (18-79)
Male gender, no. (%)	487 (79.4)
Caucasians, no. (%)	600 (98)
Risk factor for HIV infection	
Injecting drug users, no. (%)	379 (62)
Homosexual/male, no. (%)	88 (14)
Heterosexual, no. (%)	130 (21)
Unknown, no. (%)	16 (3)
Alanine aminotransferase (IU/L)*	34 (21-58)
Aspartate aminotransferase (IU/L)*	33 (23-52)
Liver stiffness >7 kPa, no. (%)¶	80 (47.6)
CD4 cell count (cells/µL)*	479 (280-669)

*Median (Q1-Q3); ¶determined by transient elastometry, available in 110 patients.

One hundred and sixty one (26%) subjects tested positive for serum HEV antibodies by EIA at baseline. One (0.94%) exposed patient had detectable HEV-RNA in plasma.

***Figure 2*: Proportion of patients exposed to HEV (positive HEV antibodies by EIA and immunoblot) at baseline according to age; p for linear trend=0.0005.**

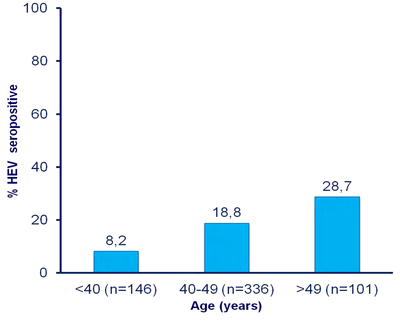


***Table 2*: Associations between HEV exposure and other factors at baseline**

Parameter	N (%)*	No (%)† HEV exposed	*p*	Adjusted OR (95% CI)	*P* multivariate
Age					
≤ 44 years	334 (55)	68 (20)	0.0003	1.06	0.000004
> 44 years	279 (45)	93 (33)		(1.03-1.09)¶	
Gender					
Male	126 (79)	138 (28)	0.022	1.71	0.040
Female	487 (21)	23 (18)		(1.02-2.86)	
Risk factor for HIV					
Homosexual sex	88 (14)	18 (20)	0.181	1.55	0.144
Other	525 (86)	143 (27)		(0.86-2.78)	
Area of residence					
Rural	43 (7)	14 (33)	0.331	-	-
Urban	570 (93)	147 (26)			
Professional exposure to swine					
Yes	64 (10)	19 (30)	0.511		
No	549 (90)	142 (26)			
Daily alcohol intake					
<50 g	515 (84)	134 (26)	0.711		
≥50 g	98 (16)	27 (28)			
Plasma anti-HCV					
Positive	417 (68)	109 (26)	0.918	-	-
Negative	196 (32)	52 (26)			
Cirrhosis‡					
Yes	39 (18)	13 (33)	0.201	-	-
No	179 (82)	42 (23)			
CDC clinical category					
C	166 (27)	50 (30)	0.186	1.08	0.714
A or B	447 (73)	111 (25)		(0.72-1.62)	
Plasma HIV-RNA load					
< 20 copies/mL	411 (67)	108 (26)	0.992	-	-
≥ 20 copies/mL	202 (33)	53 (26)			
CD4 cell count (cells/µL)					
<200	86 (14)	18 (21)	0.225	-	-
≥200	527 (86)	143 (27)			

*% of the overall population; †% in each category; ‡available in 218 subjects; ¶for each year older.

***Table 3*: Liver function test and liver stiffness, according to HEV exposure at baseline in HCV-seronegative patients (n=198).**

Parameter	HEV exposed (n=53) No (%)	HEV unexposed (n=145) No (%)	*p*
ALT >40 IU/mL	5 (14)	29 (18)	0.618
AST >40 IU/mL	5 (14.3)	9 (5.5)	0.078
GGT >40 IU/mL	12 (34)	36 (22)	0.126
Liver stiffness >7 kPa*	2 (33)	5 (20)	0.596

* Available in 31 patients.

In a multivariate analysis, factors associated with HEV exposure were: age [AOR (95%CI): 1.06 (1.03-1.09); p=0.000004] and male sex [AOR (95%CI): 1.71 (1.02-2.86); p=0.040].

CONCLUSIONS

1) The rate of exposure to HEV is high among HIV-infected patients from Southern Spain, and it increases with age, but chronic infection is very uncommon. This suggests that most cases of acute HEV infection in this setting are self-limited.
2) However, a trend to an association exists between prior HEV exposure and data of liver disease not related with HCV. Further studies are required to establish if there is actually a causative relationship.
3) HEV screening in HIV-infected patients is not warranted, unless unexplained liver disease is present.

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