HEPATITIS E RABBIT GENOTYPE INFECTION in HIV-INFECTED PATIENTS

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Background and Aims

- Hepatitis E virus (HEV) is an emerging infectious disease worldwide. In Europe, the majority of cases are related to local infections, represented by HEV genotype 3.
- Although HEV infection by this autochthonous genotype usually presents as subclinical or self-limiting acute hepatitis, there are several related complications that substantially worsen the prognosis of the infection.
- Among the population in which HEV infections may have a worse prognosis, persons living with HIV (PLWH) represent a high-sensitivity population because of the high rate of advanced liver fibrosis due to common hepatotropic virus coinfection and the underlying immunosuppression.
- Our **aims** were to assess the prevalence and incidence of HEV, as well as the prevalence of chronic HEV infection, in a large national cohort of PLWH, describing the HEV viral strains.

Methods

- **Design:** retrospective longitudinal study.
- **Patients:** PLWH included in the cohort of adult HIV-infected patients of the AIDS Research Network (CoRIS). For the proposed study, we included patients recruited in the cohort at follow-up in 28 hospitals belonging to 15 Spanish provinces with available serum samples in the centralized BioBank in 2014 (prevalence) and 2015 (incidence).
- **Outcomes:** Three outcome variables were established: i) positivity for IgG antibodies against HEV, ii) positivity for IgM antibodies against HEV, and iii) detection of HEV RNA.
- **Procedures:** all samples were tested for HEV antibodies (IgG and IgM) and HEV RNA. Positive samples for HEV RNA were sequenced.
- Statistical analysis: prevalence and incidence rate were calculated.

Results

Study population

- A total of 845 individuals were included in the study.
- Seven hundred and fifty-one (88.9%) were male and had a median age of 36.9 years (30.7-45.2 years).

Prevalence of HEV infection

- One hundred and one patients showed positivity of IgG against HEV (11.9%; 95% CI: 9.9%-14.3%). There were no variables associated with IgG positivity in the univariate and multivariate analyses (Table 1).
- Any of the patients included in the study were positive for IgM anti-HEV

Incidence of HEV infection

- Of the 744 patients negative for IgG antibodies at baseline, 733 (98.5%) had available serum samples in the follow-up.
- Forty-two patients showed seroconversion for IgG antibodies after 1 year of follow-up, supposing a cumulative incidence of 5.7% (95% CI: 4.3%-7.7%).
- In Table 2 we show univariate and multivariate analysis for HEV seroincidence.

Table 1. Univariate and multivariate analysis for HEV anti IgG antibodies seroprevalence

Variable	IgG anti-HEV positive (N = 101)	IgG anti-HEV negative (N = 744)	Univariate p value	Adjusted OR (95% CI)	Multivariate p value
Age (year), mean (SD)	36.2 (19.8)	36.3 (14.3)	0.926	0.997 (0.98-1.01)	0.652
Gender, n (%)					
Male	86 (11.5)	665 (88.5)	0.236	1	
Female	15 (16)	79 (84)		0.905 (0.37-2.21)	0.828
HIV acquisition route, n (%)					
Heterosexual	24 (14.6)	140 (85.4)	0.643		
MSM	67 (10.9)	549 (89.1)			
PWID	5 (15.2)	28 (84.8)			
Other	1 (20)	4 (80)			
Unknown	4 (14.8)	23 (85.2)			
HIV acquisition route, n (%)					
MSM	67 (10.9)	549 (89.1)	0.134	1	
No MSM	34 (14.9)	172 (85.1)		0.738 (0.38-1.42)	0.363
AIDS defining criteria, n (%)					
No	88 (11.5)	677 (88.5)	0.207	1	
Yes	13 (16.2)	67 (83.8)		2.02 (0.99-4.13)	0.052
Time since HIV diagnosis, mean (SD)	3.67 (4.5)	3.58 (3.8)	0.823		
CD4+ cell count, mean (SD)	586 (307)	611 (292)	0.474		
CD4+ cell count, n (%)					
< 200	5 (9.6)	47 (90.4)	0.622		
200-349	11 (16.7)	55 (83.3)			
350-500	19 (12.8)	130 (87.2)			
>500	50 (11.4)	389 (88.6)			
CD4+ cell count, n (%)					
< 200	5 (9.6)	47 (90.4)	0.824	1	
≥200	80 (12.2)	574 (87.8)		0.61 (0.22-1.67)	0.343

Table 2. Univariate and multivariate analysis for HEV anti IgG antibodies seroincidence

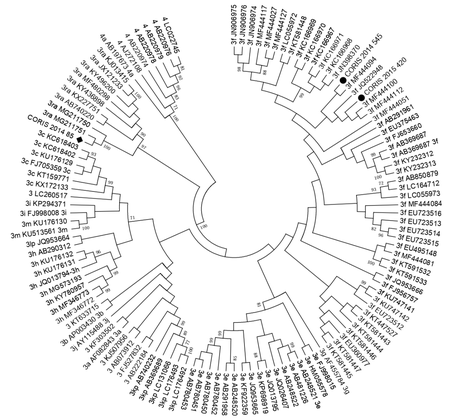
Variable	IgG anti-HEV positive (N = 42)	IgG anti-HEV negative (N = 691)	Univariate p value	Adjusted OR (95% CI)	Multivariate p value
Age (year), mean (SD)	36 (21)	36 (14)	0.279	0.99 (0.96-1.02)	0.735
Gender, n (%)					
Male	37 (5.6)	619 (94.4)	0.794	1	
Female	5 (6.5)	72 (93.5)		0.99 (0.21-4.67)	0.998
HIV acquisition route, n (%)					
Heterosexual	9 (6.5)	129 (93.5)	0.518		
MSM	30 (5.5)	511 (94.5)			
PWID	1 (3.6)	27 (96.4)			
Other	1 (25)	3 (75)			
Unknown	1 (4.5)	21 (95.5)			
HIV acquisition route, n (%)					
MSM	30 (5.5)	511 (94.5)	0.652	1	0.205
No MSM	11 (6.5)	159 (93.5)		0.44 (0.12-1.56)	
AIDS defining criteria, n (%)					
No	38 (5.7)	628 (94.3)	0.788	1	
Yes	4 (6)	63 (94)		2.11 (0.56-7.92)	0.267
Time since HIV diagnosis, mean (SD)	5.4 (6.9)	3.5 (3.8)	0.081	1.05 (0.96-1.16)	0.245
CD4+ cell count, mean (SD)	630 (238)	672 (280)	0.662		
CD4+ cell count, n (%)					
< 200	1 (7.1)	13 (92.9)	0.909		
200-349	1 (3.4)	28 (96.6)			
350-500	6 (6.5)	86 (93.5)			
>500	19 (5.2)	344 (94.8)			
CD4+ cell count, n (%)					
< 200	1 (7.1)	13 (92.9)	0.547		
≥200	26 (5.4)	458 (94.6)			

- Four patients presented detectable viral load by qPCR; two in the prevalence analysis and other two in the incidence analysis (Table 3).
- All these patients were negative for both IgG and IgM antibodies.
- All patients presented undetectable viral load 3 months after diagnosis.
- Genotyped of a 420bp region of the viral ORF2 region could be successfully performed in three cases (Figure 1)

Table 3. Characteristics of patients with detectable HEV RNA

ID	City	Country of origin	Year of sampling	Gender	Age	HEV viral load (IU/mL)	HEV genotype
545	Madrid	Germany	2014	Male	43	10,376	3f
85	Tarragona	Spain	2014	Male	52	217,024	3ra
420	Madrid	Spain	2015	Male	43	24,387	3f
466	Murcia	Nigeria	2015	Female	36	3,197	Ungenotyped

Figure 1. Phylogenetic analysis of HEV RNA samples



Conclusions

- Our study found that HEV infection in PLWH from Spain is frequent, showing a relatively high annual incidence.
- Despite the number of acute infections identified in our study, none of the cases involved chronic infection.
- We identified one case of infection by the HEV genotype 3ra, the main host of which is the rabbit, confirming the zoonotic role of this emerging genotype.