Hepatitis E in a Portuguese cohort of human immunodeficiency virus positive patients: High seroprevalence but no chronic infections

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Abstract

Introduction: Hepatitis E virus (HEV) infection causes zoonotic hepatitis in Europe, with a higher risk of complications in immunocompromised hosts. HEV natural history in human immunodeficiency virus (HIV) positive patients is not fully understood, and its prevalence is unknown.

Objectives: To study the seroprevalence of HEV and prevalence of chronic HEV in HIV-positive patients from Porto, Portugal.

Methods: We randomly selected patients from the cohort of HIV-positive patients followed in our hospital. We performed an enzyme-linked immunosorbent assay to search for immunoglobulin G for HEV. When the absorbance/cut-off was inferior to 3.5, the test was repeated, and a confirmatory test executed in that sample. For reactive tests and for immunosuppressed patients (CD4 count < 200/mm3) with nonreactive test, a polymerase chain reaction (PCR) test was also performed.

Results: We included 299 patients. The mean age was 48 and 75.3% were men. Regarding HIV infection, the median follow-up time was 10 years, the acquisition was mainly heterosexual contact, and 94% were on antiretroviral therapy. Seventy-six patients (25.4%) had reactive immunoglobulin G (IgG) hepatitis E serology. Patients with a reactive test were older (statistically significant difference). Otherwise, there was no difference between groups concerning birthplace, rural residence, chronic viral hepatitis coinfection, or cirrhosis. Nadir and actual TCD4+ lymphocyte counts did not differ significantly from patients with HEV reactive and nonreactive serology. Gamma-glutamyl-transferase (GGT) was higher in patients with reactive IgG HEV. All serum HEV PCR tests were negative.
1 | INTRODUCTION

Hepatitis E infection in humans is mainly caused by genotypes 1–4, with distinct patterns of transmission and clinical manifestations.\(^1\) Genotype (GT) 1 and GT2 HEV infect only humans, are transmitted by the fecal–oral route, namely through contamination of water supplies, and are typically associated with outbreaks in developing countries in Asia and Africa.\(^1\) Conversely, GTs 3 and 4 can infect several mammalian animals, that act as reservoirs for transmission to humans and can be the cause of chronic infections.\(^1\) Other less common routes of transmission, such as transfusion of blood products or organ transplantation have also been described and its contribution to the global burden of disease is still unclear.\(^1\)

In Europe, hepatitis E virus (HEV) is mainly caused by GTs 3 and 4, acquired locally through consumption of undercooked and uncooked meat, and by close contact to animals.\(^1\) GT3 and GT4 are usually clinically silent or mildly symptomatic. However, in a small subset of patients, it can cause acute severe hepatitis and many extra-hepatic manifestations. In immunosuppressed patients, it can evolve to chronic hepatitis and lead to liver fibrosis and cirrhosis.\(^1\)

There is limited knowledge of the seroprevalence of HEV in the general population. In Europe, HEV seroprevalence seems to be highly variable between European countries, varying with age and risk of exposure, as described in a meta-analysis that included several epidemiological studies and found a wide range of seroprevalence, from 0.6% to 52.5%.\(^2\) Some published studies of HEV seroprevalence in blood donors from Europe in different countries show that this zoonotic virus is common: In a Swiss study in blood donors the average was 20.4%,\(^3\) 56.1% in another study in Corsica,\(^4\) 39.1% (varied from 20% to 71.3%) in southern France;\(^5\) 15% in a cohort of Serbian blood donors;\(^6\) 6.8% in Germany;\(^7\) 27% in a Dutch study \(^8\) and an increase in prevalence from 4.5% in 2004–2008 to 9.3% in 2014–2015 (\(p = 0.001\)) in Scotland.\(^9\) Occasionally, in some blood donors, a positive HEV polymerase chain reaction (PCR) was found.\(^10–13\) In Portugal, until recently, only a few small studies on HEV seroprevalence were done. In 2016, a survey included 1656 randomly selected Portuguese patient of all ages, from different areas of the country, and found a 16.3% prevalence.\(^14\)

Nevertheless, GT3 and GT4 prevalence is not well acknowledged and reported cases have been mostly recognized in certain high-risk patients, such as the immunocompromised, namely those with human immunodeficiency virus (HIV).\(^1,15\) However, studies on immunosuppressed patients are sporadic and, above all, are cases of reactivation in transplant recipients or other immunocompromised persons. The purpose of this study was to determine the seroprevalence of HEV and prevalence of chronic HEV in a population of HIV-positive patients from Porto, Portugal.

2 | METHODS

A sample size of 300 patients was calculated assuming an anti-HEV seroprevalence of 30% and a confidence interval of 95%, in a population of about 3000 HIV-positive patient followed regularly in our clinic (an HIV clinic in a large tertiary hospital). Demographic and clinical data were collected for every patient after the enrolment, which occurred in 2019.

In a random follow-up appointment, a venous blood sample was collected. An enzyme-linked immunosorbent assay (ELISA) assay (Wantai HEV-IgG ELISA; Beijing Wantai Biological Pharmacy Enterprise Co., Ltd.) was performed to search for immunoglobulin G (IgG) for HEV. Whenever the absorbance/cut-off was inferior to 3.5, the test was repeated, and a confirmatory test (recomLine HEV IgG/ IgM; Mikrogen Diagnostik) executed in the same sample. In all samples with reactive tests and also for immunosuppressed patients (defined as having a \(T_{CD4^+}\) lymphocyte count inferior to 200 cells/mm\(^3\)) an in-house PCR test for HEV was performed.\(^16\)

Data were analyzed using the statistical package IBM® SPSS® Statistics software, through the most suitable descriptive and inference statistics, using a significance level of 0.05. Categorical variables are presented as a percentage and were compared using a \(\chi^2\) test. In the continuous variables, the measure of central tendency and dispersion measure appropriate to the distribution of the variable was used and were compared using Mann–Whitney U test.

The study was conducted in accordance with the Declaration of Helsinki. Every patient received and signed an informed consent and the study protocol was approved by the institution’s ethics committee.

3 | RESULTS

We included 299 patients, 225 (75.3%) were men, with a mean age of 48.18 years (SD = 12.26). Almost all patients were Portuguese (279: 93.3%) and 46 (15.5%) of them lived in a rural area, according to the PRODER national score.\(^17\)

The complete data of the analyzed patients is presented in Table 1.
| Demographic data                                                                 | Total        | Positive HEV serology | Negative HEV serology | p value |
|----------------------------------------------------------------------------------|--------------|------------------------|-----------------------|---------|
| Patients enrolled, n (%)                                                          | 299 (100)    | 76 (25.4)              | 223 (74.6)            | -       |
| Age (years), mean (SD)                                                            | 48.18 (12.26)| 51.74 (11.10)          | 46.97 (12.42)         | 0.022   |
| Male sex, n (%)                                                                  | 225 (75.3)   | 59 (77.6)              | 166 (74.4)            | 0.578   |
| Place of birth, n (%)                                                             |              |                        |                      | 0.517   |
| Portugal                                                                         | 279 (93.3)   | 73 (96.1)              | 206 (92.4)            |         |
| Other                                                                            | 20 (6.7)     | 3 (3.9)                | 17 (7.6)              |         |
| Brazil                                                                           | 11 (3.7)     | 2 (2.6)                | 9 (4.0)               |         |
| Angola                                                                           | 3 (1.0)      | 0                      | 3 (1.3)               |         |
| Spain                                                                            | 2 (0.7)      | 0                      | 2 (0.9)               |         |
| France                                                                           | 1 (0.3)      | 0                      | 1 (0.4)               |         |
| Mozambique                                                                       | 1 (0.3)      | 0                      | 1 (0.4)               |         |
| Romania                                                                          | 1 (0.3)      | 0                      | 1 (0.4)               |         |
| São Tomé e Principe                                                              | 1 (0.3)      | 1 (1.3)                | 0                     |         |
| Residence in a rural area, n (%)                                                 | 46 (15.4)    | 9 (11.8)               | 37 (16.6)             | 0.586   |
| HIV infection                                                                     |              |                        |                      |         |
| HIV infection duration, median (IQR)                                             | 10 (4–17)    | 12 (5.50–18)           | 10 (3–17)             | 0.137   |
| HIV acquisition risk, n (%)                                                      |              |                        |                      | 0.547   |
| Heterosexual                                                                      | 151 (50.5)   | 45 (59.2)              | 106 (45.5)            |         |
| Men who have sex with men                                                         | 70 (23.4)    | 13 (17.1)              | 57 (25.6)             |         |
| Intravenous drug use                                                              | 66 (22.1)    | 14 (18.4)              | 52 (23.3)             |         |
| Other/unknown                                                                     | 12 (4.0)     | 4 (5.3)                | 8 (3.6)               |         |
| AIDS-defining disease                                                             | 99 (33.3%)   | 28 (36.8)              | 71 (31.8)             | 0.597   |
| **T**<sub>CD4+</sub> lymphocyte cell count nadir, median (IQR)                    | 186 (64–317) | 144 (29–269)           | 195 (74–332)          | 0.044   |
| Antiretroviral therapy, n (%)                                                    | 280 (94.0%)  | 71 (93.4)              | 208 (93.2)            | 0.950   |
| Number of years with antiretroviral therapy, median (IQR)                         | 9 (9)        | 10 (12)                | 9 (12)                | 0.099   |
| HIV viral load suppression, n (%)                                                 | 198 (70.0%)  | 48 (63.2)              | 150 (67.2)            | 0.509   |
| Most recent **T**<sub>CD4+</sub> count (/mm<sup>3</sup>), median (IQR)            | 640 (353)    | 592 (43)               | 656 (342)             | 0.176   |
| Most recent HIV viral load (cp/ml), median (IQR)                                  | 0 (0)        | 0 (0–12.75)            | 0 (0)                 | 0.296   |
| Liver function tests                                                              |              |                        |                      |         |
| AST (IU/L), median (IQR)                                                         | 23 (19–30)   | 23 (19–33)             | 23 (19–29)            | 0.346   |
| ALT (IU/L), median (IQR)                                                         | 20 (16–30)   | 23 (16–32)             | 20 (16–30)            | 0.499   |
| GGT (IU/L), median (IQR)                                                         | 28 (20–44)   | 33 (22–72)             | 27 (19–42)            | **0.004** |
| Alkaline phosphatase (IU/L), mean (SD)                                           | 79 (26)      | 80 (27)                | 80 (26)               | 0.163   |
| Direct bilirubin (mg/dl), median (IQR)                                            | 0.14 (0.1–0.36) | 0.17 (0.11–0.49)    | 0.14 (0.10–0.34) | 0.096   |
| Indirect bilirubin (mg/dl), median (IQR)                                         | 0.4 (0.22–0.57) | 0.39 (0.21–0.56)   | 0.42 (0.26–0.57) | 0.348   |

(Continues)
Regarding HIV infection, all patients had HIV-1 infection, and most patients had a sexually transmitted HIV infection (heterosexual: 51.9%; men who have sex with men [MSM]: 24.1%) or through injecting drug use (22.7%). The median follow-up period since diagnosis was 10 years (interquartile range: 4–17 years). Most patients (94%) were on antiretroviral treatment, 70% with suppressed viral load and with a mean TCD4+ lymphocyte count of 592 cells/mm³ (SD = 43).

A reactive IgG hepatitis E serology was detected in 76 patients (25.4%). Patients with positive HEV serology were older than those with negative serology (51.74 years old, SD = 11.10 vs. 46.97 years old, SD = 12.42; \( p = 0.002 \)). None of the other mentioned variables showed a significant difference between patients with positive and negative HEV serology.

TCD4+ lymphocyte nadir was lower in patients with positive HEV serology (144/mm³ vs. 195/mm³; \( p = 0.044 \)), but acquired immunodeficiency syndrome defining diseases was similar in both groups. As pointed out in Table 1, no differences were elicited between the two groups concerning the HIV acquisition route; time since HIV infection; detectable HIV viral load or CD4+ count.

Analysis of liver function tests by the time of HEV serology screening showed no differences between the two groups, except for a higher gamma-glutamyl transferase, which was higher in patients with positive IgG HEV serology.

The presence of contact or chronic hepatotropic virus infections (hepatitis A, B, and C), alcohol consumption or previous documentation of cirrhosis had no identifiable correlation between groups.

PCR HEV tests were performed in 99 patients: those 76 with reactive HEV IgG serology and 23 patients with negative HEV IgG who had a TCD4+ cell count <200/mm³. All patients tested negative.

**4 | DISCUSSION**

The present study is the first HEV seroprevalence study in the HIV population in Portugal. The overall seroprevalence of IgG anti-HEV in people living with HIV in our cohort of patients was 25.4%, higher than that found for the general population in the same region (18.1%). The absence of disparity between urban and rural areas may translate the likely route of transmission in these patients. Portugal is a country with a long and widespread tradition in consumption of pork meat, including undercooked meat. This might more likely
explain most infections in our patients, rather than close contact with animals. Besides, a worrisome study regarding samples analyzed in Portugal in 2019 revealed infectious HEV in 27.7% of tested concentrated samples of drinking water, showing a possible way of transmission and ultimately a threat to human health.

We found a positive association between older age and HEV seroprevalence, as with other fecal–oral transmitted diseases, which might be explained by increased exposure over time, and may also be related to the worse hygienic-sanitary conditions that existed in the past. This finding is in line with previous studies, both nationally and internationally.

Unlike previous studies, we did not find a greater prevalence among male patients. This may be, at least in part, related to a majority of heterosexual patients in our cohort, considering that MSM population has shown to have a higher seroprevalence than the general population in some studies, particularly among HIV-positive patients.

As reported in previous studies, we found no differences in transaminase levels. Regarding liver function tests performed in these patients, only GGT was higher in patients with HEV infection. The same association was found in a group of HIV patients in southern Spain. Sometimes, GGT isolated elevation, with normal AST and ALT, can be a proxy of excessive alcohol use. On the other hand, patients with excessive alcohol use may be more susceptible to infection, considering a potentially higher degree of previously established liver damage. In our cohort, in particular, HEV IgG-positive patients did not report a higher frequency of excessive alcohol use. However, considering alcohol consumption was self-reported, conclusions can hardly be drawn.

Both positive and negative HEV IgG patients had similar recent TCD4+ cell counts and HIV viral load. Of notice, most patients were on antiretroviral therapy (94%), and most of them had suppressed viral load (70%). Antiretroviral therapy not only decreases HIV viral load but also restores immunity, which may contribute to clearance of HEV. This might help explain why we did not find any cases of current hepatitis.

It is uncertain whether HEV clinical course differs in people living with HIV, namely in what concerns progression to liver fibrosis, as compared to HIV-negative patients. In our study, we did not find any case of infection. Also, the diagnosis of cirrhosis was not significantly higher among seropositive patients for HEV, unlike other colleagues have described. Unfortunately, we did not assess noninvasive scores like FIB-4 or nonalcoholic fatty liver disease scores to further investigate the extent of this association. Of note, the cited article that described a positive association between seropositivity and liver fibrosis was developed in a hyperendemic area for HEV, where GT 1 prevails. On the contrary, we expect that GT 3 would be responsible for most of infections in our patients. Eventually, different GTs could also influence differently the progression to fibrosis in the liver.

We also highlight the high prevalence of coinfection with other hepatotropic viruses, in particular HBV and HCV. In our cohort of HIV-positive patients, 39% and 27.2% had markers of past or current infection with HBV and HCV, respectively. It is known that in patients with underlying chronic liver diseases, acute HEV infection has a worse prognosis and higher mortality rate.

Our study has some limitations. Although enrolment and HEV study was prospective, some data were collected retrospectively, which may account for some inaccuracies or, sometimes, under-reporting of epidemiological and/or clinical data. At time of enrolment, we did not ask participants to fill out a questionnaire on HEV-related behaviors (like the consumption of raw pork meat). It would provide us more insight on transmission patterns in HEV-serology positive. We only performed HEV PCR in patients with HEV seroreactivity or if very immunosuppressed and we could have failed patients in the immunological window. Also, it involves only about 10% of the HIV patients of a single-center, in a city of the north of Portugal, and, thus, our findings may not accurately represent the country’s reality.

It would be interesting to extend this survey to a more representative population of HIV-positive Portuguese patients, including other parts of the country. It would also interest to replicate this evaluation over time, to better understand the evolution of HEV seroprevalence.

5 CONCLUSION

HEV seroprevalence in our study proved to be higher than in general population. Although we did not find any active case of disease, we believe that more data are needed to firmly establish the consequences of HEV infection in HIV-positive individuals.

AUTHOR CONTRIBUTIONS

Rita Filipe: data curation; formal analysis; writing – original draft; writing – review and editing. Beatriz Prista-Leão: data curation; formal analysis; writing – original draft; writing – review and editing. André Silva-Pinto: conceptualization; funding acquisition; writing – review and editing. Isabel Abreu: data curation. Rosário Serrão: project administration; supervision. Rosário Costa: investigation. Edite Guedes: investigation. Joana Sobrinho-Simões: investigation; validation. António Sarmento: supervision; writing – review and editing. Carmo Koch: investigation; validation. Lurdes Santos: supervision; writing – review and editing.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

TRANSPARENCY STATEMENT

This manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have
been omitted; any discrepancies from the study as planned have been explained.

**DATA AVAILABILITY STATEMENT**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**ETHICS STATEMENT**

The study was conducted in accordance with the Declaration of Helsinki. Every patient received and signed an informed consent and the study protocol was approved by the institution's ethics committee.

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