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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/mm^3) 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 T_{CD4+} 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.

Rita Filipe and Beatriz Prista-Leão contributed equally to this manuscript.

Conclusions: Seroprevalence of HEV was 25.4% in HIV-positive patients. Older age and higher GGT correlated to HEV reactive IgG test. No cases of current hepatitis E were found.

KEYWORDS
hepatitis E, HIV, seroprevalence

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 χ^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.

TABLE 1 Demographic data of enrolled patients.

	Total	Positive HEV serology	Negative HEV serology	*p* value
Demographic data				
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 Príncipe	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_{CD4+} 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_{CD4+} count (/mm^3), mean (SD)	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)

TABLE 1 (Continued)

	Total	Positive HEV serology	Negative HEV serology	*p* value
Albumin (mg/dl), mean (SD)	43 (4)	43 (5)	43 (4)	0.680
Prothrombin time (s), mean (SD)	73 (5)	74 (6)	73 (5)	0.269
Other hepatic diseases/risk factors				
Cirrhosis, *n* (%)	20 (6.7%)	9 (11.8)	11 (4.9)	0.115
Alcoholism, *n* (%)	27 (9.0%)	11 (14.5)	16 (7.17)	0.147
HAV positive IgG, *n* (%)	228 (81.4%)	66 (86.8)	162 (72.6)	0.116
HBV, *n* (%)				0.233
Positive anti-HBs and anti-HBc	102 (35%)	33 (43.4)	68 (30.5)	
Positive anti-HBs, negative anti-HBc	90 (30%)	21 (27.6)	69 (30.9)	
Positive HBs antigen	12 (4%)	0	12 (5.4)	
HCV, *n* (%)				0.893
Positive anti-HCV, negative RNA HCV	69 (23.2%)	19 (25.0)	50 (22.4)	
Positive anti-HCV and RNA HCV	12 (4.0%)	4 (5.3)	8 (3.6)	

Note: Bold value indicate statistical significance.

Abbreviations: AIDS, acquired immunodeficiency syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HAV, hepatitis A virus; HBc, HBV core-antigen; HBs, HBV surface-antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HIV, human immunodeficiency virus; IgG, immunoglobulin G; IQR, interquartile range; RNA, ribonucleic acid; SD, standard deviation.

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 T_{CD4+} lymphocyte count of 592 cells/mm^3 (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.

T_{CD4+} lymphocyte nadir was lower in patients with positive HEV serology (144/mm^3 vs. 195/mm^3; $p = 0.044$), 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 T_{CD4+} cell count <200/mm^3. 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%).[14]

We found a lower prevalence than previously reported in the Central African Republic (68%),[18] China (44%),[19] Nepal (43%),[20] Spain (26%),[21] but higher than the one described in Iran (10.4%)[22] and Brazil (6.7%).[23] In Denmark, a large series of 2506 patients with HIV was investigated over three decades: The overall HEV seroprevalence rates were stable during the 1980s, 1990s, and 2000–2013 (23.1%, 22.9%, and 23.7%, respectively).[24] The higher prevalence in African countries could be explained because HEV is endemic and epidemic in a significant number of those countries and may also be linked to a high prevalence of HIV. This contrasts with the current situation in Portugal where the HIV prevalence is below 0.5%.[25]

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[26] 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.[1,27] This finding is in line with previous studies, both nationally and internationally.[1,2,14]

Unlike previous studies,[18,20] 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.[28–30]

As reported in previous studies, we found no differences in transaminase levels.[18] 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.[21] 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 T_{CD4+} 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.[20] 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.[28]

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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REFERENCES

1. Goel AAR, Hepatitis E. Epidemiology, clinical course, prevention and treatment. *Gastroenterol Clin North Am*. 2020;49:315-330. doi:10.1016/j.gtc.2020.01.011
2. Hartl J, Otto B, Madden R, et al. Hepatitis E seroprevalence in Europe: a meta-analysis. *Viruses*. 2016;8(8):211. doi:10.3390/v8080211
3. Niederhauser C, Widmer N, Hotz M, et al. Current hepatitis E virus seroprevalence in Swiss blood donors and apparent decline from 1997 to 2016. *Euro Surveill*. 2018;23(35):1-7.
4. Capai L, Hozé N, Chiaroni J, et al. Seroprevalence of hepatitis E virus among blood donors on Corsica, France, 2017. *Euro Surveill*. 2020;25(5):1-9.
5. Mansuy JM, Sauné K, Rech H, et al. Seroprevalence in blood donors reveals widespread, multi-source exposure to hepatitis E virus, southern France, October 2011. *Euro Surveill*. 2015;2015:1-8.
6. Petrović T, Lupulović D, Jiménez de Oya N, et al. Prevalence of hepatitis E virus (HEV) antibodies in Serbian blood donors. *J Infect Dev Ctries*. 2014;8(10):1322-1327. doi:10.3855/jidc.4369
7. Huzly D, Umhau M, Bettinger D, et al. Transfusion-transmitted hepatitis E in Germany, 2013. *Euro Surveill*. 2014;19(21):3-6.
8. Slot E, Hogema BM, Kok TM, Molier M, Zaaijer HL. Silent hepatitis E virus infection in Dutch blood donors, 2011 to 2012. *Euro Surveill*. 2013;18(31):1-7.
9. Thom K, Gilhooly P, Mcgowan K, et al. Hepatitis E virus (HEV) in Scotland: evidence of recent increase in viral circulation in humans. *Euro Surveill*. 2018;23(12):1-10.
10. Rivero-juarez A, Frias MJM, Andújar-troncoso EMPLG, Machuca I, Camacho A, Antonio PM. Hepatitis E virus in Spanish donors and the necessity for screening. *J Viral Hepat*. 2019;26:603-608. doi:10.1111/jvh.13064
11. O'Riordan J, Boland F, Williams P, et al. Hepatitis E virus infection in the Irish blood donor population. *Transfusion*. 2016;00:1-9. doi:10.1111/trf.13757
12. Fischer C, Hofmann M, Danzer M, Hofer K, Kaar J, Gabriel C. Seroprevalence and Incidence of hepatitis E in blood donors in upper Austria. *PLoS One*. 2015;10(3):1-12. doi:10.1371/journal.pone.0119576
13. Cleland A, Smith L, Crossan C, et al. Hepatitis E virus in Scottish blood donors. *Vox Sang*. 2013;105:11-16. doi:10.1111/vox.12056
14. Nascimento MSJ, Pereira SS, Teixeira J, et al. A nationwide serosurvey of hepatitis E virus antibodies in the general population of Portugal. *Eur J Public Health*. 2018;28(4):720-724. doi:10.1093/eurpub/ckx213
15. Narayanan S, Abutaleb A, Sherman KE, Kottilil S. Clinical features and determinants of chronicity in hepatitis E virus infection. *J Viral Hepat*. 2019;26(4):414-421. doi:10.1111/jvh.13059.Clinical
16. Jothikumar N, Cromeans TL, Robertson BH, Meng XJ, Hill VR. A broadly reactive one-step real-time RT-PCR assay for rapid and sensitive detection of hepatitis E virus. *J Virol Methods*. 2006;131:65-71. doi:10.1016/j.jviromet.2005.07.004
17. Programa de Desenvolvimento Rural. *PRODER-Classificação.Das Freguesias Do Continente Em Rurais e Não Rurais*.
18. Demi Sibiro OA, Manirakiza AKN. Seroprevalence of hepatitis E virus infection among people living with HIV in the Central African Republic. *Open Forum Infect Dis*. 2015;5:1-5. doi:10.1093/ofid/ofy307
19. Zhou S, Ren L, Xia X, et al. Hepatitis E virus infection in HIV-infected patients: a large cohort study in Yunnan province, China. *J Med Virol*. 2018;90(6):1121-1127. doi:10.1002/jmv.25060
20. Shah SM, Baniya JB, Prasad B, Shrestha A, Rodin H, Boonstra A. Association between liver fi brosis and hepatitis E seroprevalence among HIV-positive individuals in Nepal. *Eur J Gastroenterol Hepatol*. 2018;31:503-505. doi:10.1097/MEG.0000000000001308
21. Pineda JA, Cifuentes C, Parra M, et al. Incidence and natural history of hepatitis E virus coinfection among HIV-infected patients. *AIDS*. 2014;28:1931-1937. doi:10.1097/QAD.0000000000000378
22. Shahriarirad R, Erfani A, Rastegarian M, et al. Seroprevalence of anti-hepatitis E antibodies and antigens among HIV- infected patients in Fars Province, southern Iran. *Virol J*. 2020;17:1-5. doi:10.1186/s12985-020-01384-0
23. Moss da Silva C, Oliveira JM, Mendoza-sassi RA, et al. Detection and characterization of hepatitis E virus genotype 3 in HIV-infected patients and blood donors from southern Brazil. *Int J Infect Dis*. 2019;86:114-121. doi:10.1016/j.ijid.2019.06.027
24. Harritshøj LH, Kirkegaard-klitbo DM, Mejer N, et al. Prevalence of anti-hepatitis E virus immunoglobulin G in HIV-infected individuals over three decades. *Int J Infect Dis*. 2019;84:67-72. doi:10.1016/j.ijid.2019.04.029
25. Portugal. Ministério da Saúde. Direção-Geral da Saúde/Instituto Nacional de Saúde DoutorRicardo Jorge. Infeção VIH e SIDA em Portugal - 2019. Lisboa: DGS/INSA; 2019.
26. Salvador D, Neto C, Jo M, Caeiro MF. Assessment of the presence of hepatitis E virus in surface water and drinking water in Portugal. *Microorganisms*. 2020;8:1-16.
27. Rocha S, Tejo S, Ferreira E, Trindade L, Rabadão E, Marques N. Prevalence of hepatitis A virus antibody in Portuguese travelers: a new paradigm. *Acta Med Port*. 2017;30(7-8):534-540.
28. Rivero-juarez A, Lopez-lopez P, Frias M, Rivero A. Hepatitis E infection in HIV-infected patients. *Front Microbiol*. 2019;10:1-11. doi:10.3389/fmicb.2019.01425
29. Capai L, Charrel R, Falchi A. Hepatitis E in high-income countries: what do we know? and what are the knowledge gaps? *Viruses*. 2018;10:1-23. doi:10.3390/v10060285
30. Payne BA, Medhi M, Ijaz S, et al. Hepatitis E virus seroprevalence among men who have sex with men, United Kingdom. *Emerg Infect Dis*. 2013;19(2):333-335. doi:10.3201/eid1902.121174

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