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Social vulnerability of patients co-infected with hepatitis B and hepatitis delta viruses: data from the ANRS CO22 HEPATHER cohort

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Dear Editors,

We read with great interest the study by Beudeker B.J.B et al. [1] which reported a 2.0% prevalence of hepatitis delta virus (HDV) infection among 925 chronic hepatitis B virus (HBV) carriers in a large tertiary center in the Netherlands. In their study, many patients infected with HDV (the most severe form of chronic hepatitis) were migrants from Sub-Saharan African and Middle Eastern countries. Among these patients, language barriers were frequent and may impact access to care. The authors also highlighted a lack of data on HDV prevalence in the scientific literature.

We aimed to document the prevalence of HDV infection and the socio-economic characteristics of patients with HDV among chronic HBV carriers enrolled in the French, nationwide, prospective, multicenter cohort ANRS CO22 HEPATHER [2]. Patients with hepatitis B or C followed in 37 hepatology expert centers were eligible to participate in the cohort. HDV antibodies (EIA) were searched for in patients chronically infected with hepatitis B, and HDV RNA (quantitative RT-PCR) was assessed if HDV antibodies were present.

For the present analyses, we used data collected at cohort enrolment. Of the 5,213 chronic HBV carriers with no loss of hepatitis B surface antigen, 5,134 (98.5%) had data on their HDV status and therefore comprised the final study population. These patients were enrolled in the cohort between February 2013 and April 2018. Sixty-three percent of them were men, 69.8% were migrants, mostly from Africa, and 46.7% lived in poverty (defined as a standard of living below the 2015 French poverty threshold i.e., 1,015€ per month per household consumption unit) (Table 1). Median age [interquartile range, IQR] was 43 [34 – 55] years and median time since HBV diagnosis was 9 [4 – 17] years. HDV infection was identified in 199 patients (3.9%; 95% confidence interval [3.3-4.4] %), and HDV viremia confirmed in 90 patients (1.7% [1.4-2.1] %). The proportion of patients with advanced liver fibrosis (FIB-4>3.25 [3]) was higher in viremic HBV-HDV co-infected patients than in the other patients (24.4% *versus* 4.3%, $p<10^{-3}$). The socio-economic characteristics of viremic HBV-HDV co-infected patients also differed significantly from those of the other patients. A higher proportion were migrants (90.0% *versus* 69.5%, $p<10^{-3}$) and lived in poverty (62.2% *versus* 46.5%, p=0.001). Among viremic HBV-HDV co-

54 infected patients, 43.3% were from Africa, whilst the other patients born abroad were mainly from
55 Eastern Europe (in particular Georgia and Romania), Turkey, and Asia (in particular Mongolia, Russia,
56 and China). These findings support previous research showing that HDV patients living in Europe are
57 mostly migrants from endemic countries [4]. Importantly, these findings also show that most HDV
58 patients are socially vulnerable and this may delay their access to care.
59 As a conclusion, we agree with Beudeker B.J.B et al. [1] that data on HDV prevalence are urgently
60 needed. We also advocate for increased research on the linkage and retention in care of HDV patients
61 (and, more generally, of socially vulnerable HBV patients) in European countries.
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64 **Table 1 - Characteristics of HBV chronic carriers in the study population: comparison according to**

65 **HDV status (n = 5,134; ANRS CO22 HEPATHER cohort)**

		HBV-HDV co-infection[1]		
	Whole study population (n = 5,134)	**No** (n = 5,044)	**Yes** (n = 90)	
Characteristics (% of missing values)	No. of patients (%) or median [IQR]			*p-value*[2]
CLINICAL CHARACTERISTICS				
Time since HBV diagnosis - *in years*	9 [4 – 17]	9 [4 – 17]	10 [4 – 20]	*0.290*
Chronic HCV co-infection (0)	81 (1.6)	80 (1.6)	1 (1.1)	*1.00*
Advanced liver fibrosis[3] (11.5)	241 (4.7)	219 (4.3)	22 (24.4)	*< 10^{-3}*
SOCIODEMOGRAPHIC AND ECONOMIC CHARACTERISTICS				
Male sex (0)	3252 (63.3)	3196 (63.4)	56 (62.2)	*0.824*
Age (0) - *in years*	43 [34 – 55]	43 [34 – 55]	43 [35 – 49]	*0.415*
Educational level **≥ high school diploma** (2.5)	2533 (49.3)	2491 (49.4)	42 (46.7)	*0.584*
Being employed (1.6)	2870 (55.9)	2826 (56.0)	44 (48.9)	*0.192*
Living in poverty[4] (4.5)	2399 (46.7)	2343 (46.5)	56 (62.2)	*0.001*
Being a migrant (0.1)	3585 (69.8)	3504 (69.5)	81 (90.0)	*< 10^{-3}*
Place of birth (0.1)				
France	1451 (28.3)	1444 (28.6)	7 (7.8)	*< 10^{-3}*
Europe (excluding France)	554 (10.8)	523 (10.4)	31 (34.4)	
Africa	2296 (44.7)	2257 (44.7)	39 (43.3)	
Asia	763 (14.9)	750 (14.9)	13 (14.4)	
America	63 (1.2)	63 (1.2)	0	

66 HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D virus; IQR = interquartile range.

67 [1] Viremic patients.

68 [2] Comparison of characteristics between patients co-infected or not with HDV (Chi-square or Fisher exact test for
69 categorical variables, Kruskal-Wallis test for continuous ones). Analyses were performed using the Stata version
70 14.2 for Windows software (StataCorp, Texas, USA).
71 [3] Defined as FIB-4 >3.25 [3].
72 [4] Defined as a standard of living below the 2015 French poverty threshold i.e. 1,015€ per month per household
73 consumption unit.
74
75
76
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Conflict of interest

The authors have no conflict of interest to disclose.

Ethics approval statement

Study registered with ClinicalTrials.gov, number NCT01953458. Written informed consent was obtained from each cohort participant before enrolment. The protocol was designed in accordance with the Declaration of Helsinki and French law for biomedical research, and was approved by the 'Comité de Protection des Personnes (CPP) Ile de France 3' Ethics Committee (Paris, France) and the French Regulatory Authority (ANSM).

Patient consent statement

Written informed consent was obtained from each cohort participant before enrolment.

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