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

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26

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28 Dear Editors,

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

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

41 For the present analyses, we used data collected at cohort enrolment. Of the 5,213 chronic HBV  
42 carriers with no loss of hepatitis B surface antigen, 5,134 (98.5%) had data on their HDV status and  
43 therefore comprised the final study population. These patients were enrolled in the cohort between  
44 February 2013 and April 2018. Sixty-three percent of them were men, 69.8% were migrants, mostly  
45 from Africa, and 46.7% lived in poverty (defined as a standard of living below the 2015 French poverty  
46 threshold i.e., 1,015€ per month per household consumption unit) (Table 1). Median age [interquartile  
47 range, IQR] was 43 [34 – 55] years and median time since HBV diagnosis was 9 [4 – 17] years. HDV  
48 infection was identified in 199 patients (3.9%; 95% confidence interval [3.3-4.4] %), and HDV viremia  
49 confirmed in 90 patients (1.7% [1.4-2.1] %). The proportion of patients with advanced liver fibrosis  
50 (FIB-4>3.25 [3]) was higher in viremic HBV-HDV co-infected patients than in the other patients (24.4%  
51 *versus* 4.3%,  $p<10^{-3}$ ). The socio-economic characteristics of viremic HBV-HDV co-infected patients also  
52 differed significantly from those of the other patients. A higher proportion were migrants (90.0%  
53 *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.

62

63

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)**

	Whole study population (n = 5,134)	HBV-HDV co-infection <sup>1</sup>		<i>p</i> -value <sup>2</sup>
		No (n = 5,044)	Yes (n = 90)	
Characteristics (% of missing values)	No. of patients (%) or median [IQR]			
<b>CLINICAL CHARACTERISTICS</b>				
Time since HBV diagnosis - <i>in years</i>	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 <sup>3</sup> (11.5)	241 (4.7)	219 (4.3)	22 (24.4)	< 10 <sup>-3</sup>
<b>SOCIODEMOGRAPHIC AND ECONOMIC CHARACTERISTICS</b>				
Male sex (0)	3252 (63.3)	3196 (63.4)	56 (62.2)	0.824
Age (0) - <i>in years</i>	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 <sup>4</sup> (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 <sup>-3</sup>
Place of birth (0.1)				
France	1451 (28.3)	1444 (28.6)	7 (7.8)	< 10 <sup>-3</sup>
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 <sup>1</sup> Viremic patients.

68 <sup>2</sup> 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 <sup>3</sup> Defined as FIB-4 >3.25 [3].

72 <sup>4</sup> Defined as a standard of living below the 2015 French poverty threshold i.e. 1,015€ per month per household  
73 consumption unit.

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84 **Conflict of interest**

85 The authors have no conflict of interest to disclose.

86

87 **Ethics approval statement**

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

93

94 **Patient consent statement**

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

96

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