Hepatitis Delta virus in migrants: The challenge of elimination (ANRS CO22 HEPATHER cohort)

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Research letter addressed to the recently published paper : Loureiro D, *et al*. New therapies for hepatitis delta virus infection. Liver Int. 2021;41 Suppl.1:30-37.

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Word count: 1487

Abbreviations: hepatitis B virus (HBV), hepatitis Delta virus (HDV), hepatocellular carcinoma (HCC), National Reference Centres (CNR), European centre for disease prevention and control (ECDC), Virus de l'immunodéficience humaine (VIH), Interquartile range (IQR), Bulevirtide (BLV), Chronic Hepatitis Delta (CHD).

Conflict of interest: The authors have no conflict of interest to disclose

Financial support: The cohort HEPATHER received financial support from the INSERM_ANRS MIE (France Recherche Nord & Sud Sida-VIH Hépatites | Maladies Infectieuses Emergentes), the French ANR (Agence Nationale de la recherché), Equipex and Cohort, the French DGS (Direction générale de la Santé), Merck Sharp and Dohme, Janssen, Gilead, Abbvie, Bristol-Myers Squibb and Roche. Those financial supports had no role in the writing of the manuscript or the decision to submit it for publication.

Acknowledgements: We thank the study participants and the participating clinicians at each site. We also thank the INSERM-ANRS MIE for sponsoring, funding and conducting the ANRS CO22 HEPATHER cohort in collaboration with the French Association for the Study of the liver (Association Française pour l'Etude du Foie: AFEF). Finally, our thanks to Jude Sweeney for the English revision of our manuscript and to Clémence Ramier for statistical analyses.

Data availability: The data that support the findings of this study are available from the cohort's scientific board upon request.

Key words: Hepatitis B virus, Hepatitis Delta virus, migrants, vulnerabilities, precarity, treatment adherence.

The review by Loureiro *et al.* [1] explores the promising opportunities that new therapies provide against hepatitis B virus (HBV) and hepatitis Delta virus (HDV) co-infection, which affects 5% of people with chronic HBV infection worldwide. HBV-HDV co-infection is associated with a more rapid progression to cirrhosis and hepatocellular carcinoma (HCC), and a higher risk of mortality than HBV mono-infection. HDV was endemic among injecting drug users in Europe until the 1980s. The introduction of the HBV vaccine and harm reduction interventions subsequently reduced its prevalence in this population [2]. Although HDV elimination in the continent seemed feasible at the end of the 1990s, it is still present due to increasing migration from geographical areas where prevalence is high [2].

The HDV-infected population in Europe mostly comprises young migrants from HDV-endemic areas [2]. The Deltavir study in France, which used data collected between 2001 and 2011 in the National Reference Centres (CNR) biobank, found that 86.2% of the 1112 recorded patients with HDV infection were from HDV-endemic regions including Africa (59.5%), Southern and Eastern Europe (21.3%), Asia (4.5%) and the Middle East (2.9%) [3]. Data collected between 2013 and 2018 in the ANRS CO22 HEPATHER cohort showed that 90.0% of HBV-HDV co-infected patients in France with chronic HDV were migrants [4].

Preliminary results from a more recent HEPATHER study[1] show that the risk of all-cause mortality is 3.55 times (95% confidence interval 1.74 – 7.23) higher in HBV-HDV co-infected migrants than in their HBV mono-infected counterparts[2]. Furthermore, the burden of liver disease is widespread in migrant populations [5]. The emergence of new promising therapies for HBV-HDV co-infection [1] is to be welcomed as an important step in combatting the risks HDV presents. However, for treatment to be effective, infected people need to know their serostatus, have access to healthcare facilities, be provided care, and adhere to treatment.

Despite the European centre for disease prevention and control (ECDC) guidelines which recommend that European countries offer hepatitis B screening and treatment to migrants from countries with intermediate (≥2%) or high (≥5%) HBV prevalence, screening programmes fail to reach those who are most vulnerable [6]. Few standardized strategies or outreach approaches exist

[1] Characteristics of the HBV-HDV co-infected migrant population in France (n = 159; ANRS CO22 HEPATHER cohort). ANRS CO22 HEPATHER is a French national, multicentre, prospective, observational cohort comprising 5216 patients with chronic active or inactive hepatitis B virus (HBV). Data were collected during a medical follow-up visit in one of the 32 expert hepatology centres throughout France.

[2] Risk factors for mortality in univariable analysis. Migrant population: n=159 HDV-HBV co-infected ; n=3375 HBV mono-infected.

for HBV screening [5]. More generally, HBV and HDV prevention campaigns in Europe are almost non-existent for migrants. In addition, this population also faces barriers to prevention, treatment and follow-up for HCC [7]. These facts highlight the importance of i) questioning the limitations of health systems in adequately providing care for all sociodemographic patient categories, ii) taking into account the specificities of populations most affected by HDV and their needs, as well as the obstacles they encounter, and iii) analysing missed appointments between the migrants and the health system at all levels of the care cascade.

Migration is often accompanied by the accumulation of forms of vulnerability and exclusion in the new host country. Preliminary results from HEPATHER (Table 1) show that the majority (61.6 %) of this population live in poverty (index defined as a standard of living below the 2015 French poverty threshold (1,015€), calculated as disposable income divided by the number of consumption units in the household), that half (49.7%) do not have a secondary school certificate, and that only 54.7 % are employed (despite 74.8% being <50 years old). Moreover, half were diagnosed and a quarter of those who initiated HBV treatment had been in France for no more than two years, a period when language skills are often still poor and when knowledge of the health and administrative system may be lacking. Socioeconomic vulnerability combined with situations of statutory insecurity translate into difficulties accessing stable, safe and adequate accommodation, as well as protected employment. Social precarity and the migratory condition also negatively impact the opportunity to stay permanently in a territory [7], and the possibility to project a long-term future, beyond daily emergencies. All these dimensions of vulnerabilities can affect people in this population and may also have repercussions on relational precarity, which can lead to social distress, relational isolation and lack of support [8]. All the above elements inform us about the obstacles many migrants encounter in their new country.

Table 1. Characteristics of the HBV-HDV co-infected migrant population in the study population: (n=159; ANRS CO22 HEPATHER cohort)

Characteristics[a]	No. of patients (%)[b] or median [IQR]
Male	99 (62.3%)

Age at inclusion (years)	
< 50	119 (74.8%)
50-59	29 (18.2%)
60-69	9 (5.7%)
>= 70	2 (1.3%)
Employed†	87 (54.7%)
Continent of birth	
Europe	33 (20.8%)
Africa	108 (67.9%)
Asia	18 (11.3%)
Living in poverty‡[c]	98 (61.6%)
Educational level < secondary school certificate‡	79 (49.7%)
Number of years between arrival in France and HBV diagnosis‡	1.9 [0.1 – 6.0]
Number of years between arrival in France and HBV treatment initiation[d]	4.7 [2 – 9.7]

Note

[a] Variables with less than 5% missing data are indicated by a †, and with less than 9% by ‡.

[b] Missing data are included in the denominator.

[c] Index defined as a standard of living below the 2015 French poverty threshold (1,015€), calculated as disposable income divided by the number of consumption units in the household.

[d] Data missing: 39%. To date, HBV treatment (generally with Pegylated interferon alpha) is not prescribed to everyone with HBV-HDV co-infection, mainly because of side effects and contraindications in patients with decompensated cirrhosis, active psychiatric disorders and autoimmune diseases.

Little public health research has been conducted in this population to investigate the effects that these elements may have in HDV screening opportunities, follow-up, and treatment pathways. In particular, few data are available on how multiple forms of social and economic vulnerability

affecting migrants with HDV may influence access to care [4], and on the effects these difficulties can have on patient care, their perceptions of viral hepatitis, its severity and its consequences, their experience of living with hepatitis, and on the forms of the "stratified" stigmatization they suffer [8]. While the effects of disease knowledge, health literacy, language issues and access to social rights regarding care have all been highlighted for other infections (tuberculosis, HIV), it is necessary to explore their influence on HDV infection.

These obstacles impact the quality of life of those affected, and can i) lead them to give secondary importance to certain care options [7], ii) cause late treatment initiation, and iii) affect their adherence and commitment to care. Clinical reports of doctors following patients treated with new HDV treatments suggest that therapeutic failure is probably due to patients' difficulties in adhering to treatment. The treatment protocols to be followed may clash with the constraints and the priorities that their life context imposes. Moreover, female migrants generally face greater difficulties [9] in treatment adherence, which is influenced by their relationship with the community and the social context.

For instance, although preliminary results highlight the virological efficacy and safety of Bulevirtide (BLV) in patients with chronic HDV and compensated liver disease [10], the logistical constraints associated with this treatment may impact adherence and treatment interruption in several ways: first, BLV uptake may require long-term commitment by the patient; the optimal treatment duration has not yet been determined and accordingly BLV may be considered a maintenance therapy [10]. As daily BLV is administered by subcutaneous injection, it may not be well tolerated by some patients over the long term. Second, BLV needs to be refrigerated, which is not always possible given people’s working conditions, travel commitments, and, in some cases, social precarity. Third, platelet counts and increased bile acid must be regular monitored in an expert centre for persons on BLV [11].

We believe that efficacy studies of new HDV therapies need to be combined with the exploration and qualitative assessment of barriers to care for migrant populations. In the Deltavir study, place of birth, HDV genotype and persistent viremia, were identified as significant determinants of liver damage and treatment response in patients with chronic HDV infection [3]. This suggests that the influence of environmental factors also needs to be studied, by analysing the material, relational and cognitive resources available to migrants to interact with the health system and to deal with HDV treatment constraints.

The experience of migration and correlated concerns, as well as barriers to care and the therapeutic process, all emphasize the need to adapt medical approaches to the specific needs of this population. The doctor-patient relationship needs to be evaluated, as it may also influence therapeutic success, as has been shown in a study on chronic diseases [7]. For instance, it is necessary to reflect on the need for patient counselling and social and administrative support programmes, including the use of professional interpreters, therapeutic education programmes, support for the administration of new HDV therapies that requires handling the drug, subcutaneous and daily injections, etc. These interventions could facilitate access to and retention of patients in medical care, by avoiding or reducing treatment interruptions because of structural barriers, unease, and misunderstanding between medical profession and patients. They could also serve to improve patients' knowledge of the issues involved in the proposed treatment (time of treatment, effects of chronic hepatitis, adherence constraints, etc.), and reduce the care-related barriers they face.

Treating HDV is a challenge, and despite little research to date, public health authorities are now committing resources. Indeed, clinical trials on new therapies [1] are already underway. Complementary social science research, and in particular qualitative studies, is therefore needed to adapt communication and care around viral hepatitis, and inform and orient medical services and public health actors about the difficulties that migrants encounter. Embedding social research concerns in the clinical evaluation of the effectiveness of novel therapies for HDV may not only improve delivery of care, but also foster migrants' engagement and adherence to treatment, which is an essential pillar of HDV elimination.

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