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A regular screening for hepatitis delta virus among chronic hepatitis B carriers improves the diagnostic of this infection and of subsequent cirrhosis development

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Abstract

Background and Objective: The prevalence of Hepatitis Delta Virus (HDV) is underestimated and the assessment of fibrosis is recommended for this infection. We tested the diagnostic impact of an annual screening for HDV serology in Hepatitis B Surface Antigen (HBs Ag) chronic carriers and followed the progression of fibrosis in these patients.

Methods: Between January 2014 and October 2021, we annually tested all chronic HBs Ag-positive patients for HDV antibody (HDV Ab). Each HDV Ab positive patient underwent annually repeated elastometry. Patients with detectable HDV RNA levels (group 1) were compared to those with undetectable HDV RNA (group 2).

Results: We identified 610 chronic HBs Ag-positive patients, and repeated screening for HDV Ab was performed in 534 patients. Sixty (11%) patients were HDV Ab positive at baseline and were considered as "coinfected". Seven cases of HDV superinfection were diagnosed through repeated screening. In co-infected patients, cirrhosis was initially diagnosed in 12/60 patients and developed in six patients during follow-up. HDV RNA PCR was performed in 57/67 patients and 27 had detectable levels (group 1). Cumulative incidence of cirrhosis at 7 years was 13.8% (95% CI 0–30) in group 1 and 0 (95% CI 0–0) in group 2 ($p = 0.026$).

Conclusion: A systematic screening for HDV in chronic HB Ag carriers revealed a high prevalence of HDV Ab. Repeated serological screening enables the diagnosis of superinfections in asymptomatic patients. Regular assessment of fibrosis using elastometry leads to the identification of incidental cirrhosis in patients with detectable HDV RNA.

KEYWORDS
antibodies, diagnosis, elastography, epidemiology, fibroscan, HBV, hepatitis D, viremia, virus

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INTRODUCTION

Hepatitis delta virus (HDV) infection is considered the most severe form of viral hepatitis. HDV infection only occurs in HBs Ag-positive individuals as the viral life cycle of this RNA virus requires the envelope proteins of the hepatitis B virus (HBV) to propagate into hepatocytes.[1] Transmission occurs either simultaneously for both viruses or as superinfection of HDV in patients with pre-existing HBV infection. Despite its significant medical burden, the global prevalence of HDV infection remains poorly defined. According to the World Health Organization (WHO), just under 300 million people worldwide are infected with hepatitis B, and about 5% of those are also infected with HDV.[2] Several recent meta-analyses aimed to determine more precisely the worldwide prevalence of HDV infection, but the results of these epidemiological studies are widely variable, ranging from 12 to 72 million.[3–5] This highlights the fact that the number of people affected by hepatitis delta worldwide is much larger than previous estimates. Indeed, screening strategies for HDV in patients at risk are currently suboptimal, contributing to these disparate numbers.[6] This lack of screening is observed despite the recommendations to test all HBs Ag positive patients for HDV infection in the European Association for the Study of the Liver and the Asian Pacific Association for the Study of the Liver guidelines.[7–9] On the other hand, the American guidelines recommend screening only HBs Ag-positive patients who also have additional risk factors such as intravenous drug use (IVDU), being a man having sex with men (MSM) or a migrant from endemic areas.[10] However, it was recently shown that the implementation of a reflex testing for HDV among *all* HBs Ag-positive patients led to a five-fold increase in the detection of hepatitis delta infection.[6]

HDV prevalence mirrors regions of HBV endemicity. More precisely, a recent meta-analysis estimated that the prevalence of HDV was highest in Mongolia, the Republic of Moldova and countries in Western and Middle Africa, with only limited data available for North America, Latin America and South Africa.[5]

Chronic HDV infection is deemed the most severe form of viral hepatitis since it is associated with rapid progression to cirrhosis[11] and higher risk of hepatocellular carcinoma (HCC).[12,13] Regular assessment for fibrosis and screening for cirrhosis and HCC is therefore particularly important in these patients.

Systematically screening for hepatitis delta among HBs Ag positive patients also allows an early diagnosis of the disease. This provides patients with the opportunity of receiving appropriate management. On the one hand, appropriate counseling can be given to prevent the transmission of the disease. On the other hand, it makes it possible to consider early antiviral treatments. Indeed, Bulevirtide is the first and only drug currently approved as a treatment for hepatitis delta in the European Union. This medication was shown to reduce HDV RNA levels as well as ALT levels in patients with chronic hepatitis D in an ongoing randomized trial.[14]

In this study, we aimed to implement a systematic annual screening strategy for HDV in a population of HBs Ag chronic carriers, in order to assess HDV prevalence and incidence over time. We also used non-invasive methods to systematically evaluate fibrosis progression during follow-up in these patients.

Key summary

Summarise the established knowledge on this subject

- Hepatitis delta virus (HDV) infection only occurs in patients infected with hepatitis B and is the most severe form of viral hepatitis.
- The prevalence of HDV infection is currently underestimated due to a lack of systematic screening.

What are the significant and/or new findings of this study?

- A systematic annual screening for HDV in Hepatitis B Surface Antigen chronic carriers is useful and leads to the identification of a high prevalence of HDV antibodies among patients with chronic hepatitis B.
- Repeated screening also allows the diagnosis of cases of hepatitis delta superinfections that are sometimes clinically occult.
- Regular assessment of cirrhosis with non-invasive methods is effective in patients with HDV antibodies, especially in those with detectable HDV RNA levels.

MATERIAL AND METHODS

Study population and follow-up

This is a monocentric retrospective analysis of a prospective database conducted at CHU Saint-Pierre, a Public University Center in Brussels. As part of standard regular care, patients with chronic HBs Ag have systematic follow-up visits with blood tests and liver ultrasound every 6–12 months in our Liver Clinic. All patients followed at our Liver Clinic and presenting positive HBs Ag were included in our prospective database between January 2014 and October 2021. During this period, we implemented a new strategy akin to the anti-HDV reflex testing that was described recently.[6] Each of these patients was meant to have a serological screening test for hepatitis delta on an annual basis. There were no other inclusion or exclusion criteria in this work based on real-life clinical experience.

For the purpose of this study, patient follow-up refers to the natural history of hepatitis delta and starts when each patient is diagnosed with their first positive delta serology.

"Coinfected patients" refer to patients who had a positive Ag HBs and positive delta Ab serology at their first visit in our Liver Clinic. Conversely, "superinfected patients" refer to patients who were previously known as HBs Ag positive and HDV antibody (Ab)

negative in our Liver Clinic who underwent a seroconversion for HDV Ab during their follow-up.

All patient samples and data used in this study were collected in the context of routine clinical patient care and the ethics committee of our institution approved the use of these data and samples.

Serological testing and HDV RNA PCR

The anti-HDV serology testing was performed on commercially available kits: from January 2014 to September 2019, using a competitive enzyme immunoassays method (ETI-AB-DELTAK-2 assay Ref. P 2808. DiaSorin, Saluggia) was semi-automatically analyzed on the ETI-MAX-3000 analyzer (DiaSorin, Saluggia). Since September 2019, HDV Ab has been routinely investigated using an automated chemiluminescence indirect immunoassay (CLIA) technology (LIAISON® XL MUREX Anti-HDV Ref. 311260. DiaSorin, Saluggia), assayed on a LIAISON® XL immunoanalysis analyzer (Diasorin, Saluggia). The sensitivity and specificity of these commercial tests are the following: specificity of 98.99% (95% IC: 97.81%–99.63%) and sensitivity of 99.42% (95% IC: 96.81%–99.99%) for the ETI-AB-DELTAK-2 assay; specificity of 99.35% (95% IC: 98.89%–99.66%) and sensitivity of 100% (95% IC: 97.90%–100%) for the Liaison® XL CLIA test. EDTA plasma samples were obtained for all the patients with positive HDV and RT-PCR for HDV RNA was run in order to quantify viremia. HDV RNA levels were measured using commercially available real-time PCR: RoboGene Hepatitis D Virus Quantification Kit 2.0 (AJ Roboscreen GmbH) from January 2014 until May 2018, followed by the RealStar HDV RT-PCR Kit 1.0 (Altona Diagnostics) since June 2018. HDV genotyping is not performed at our institution as part of routine clinical follow-up.

Fibrosis assessment

Each HDV Ab positive patient underwent an annual non-invasive evaluation of fibrosis progression by elastometry (Fibroscan®, Echosens). For the purpose of this study, the following cut-off values were chosen: >7.5 kPa for advanced fibrosis and >12.5 kPa for liver cirrhosis.[15]

Statistical analyses

Continuous variables are expressed as median (IQR) and categorical variables are reported as counts and percentages. Group comparisons were made using Student's *t* test, the Mann–Whitney test, the Chi-squared test, or Fisher's exact test, as appropriate. Cumulative incidence of cirrhosis (CI) with 95% confidence intervals (95% CI) was estimated at 7 years of follow-up. The Kaplan–Meier estimator was used to compute the survival over time. All tests were two-tailed and a *p* value of less than 0.05 was considered statistically significant. Analyses were performed with the SAS 9.3 (SAS Institute) and R software, version 4.0.3 (CRAN project).

RESULTS

Epidemiology of HDV coinfection in a population of chronic HBs Ag positive patients

Between January 2014 and October 2021, 610 chronic HBs Ag-positive patients were identified. Five hundred and forty-four patients were screened at least once for HDV Ab. Among these, 534 patients also underwent repeated HDV Ab testing during follow-up. Sixty (11%) patients with positive HDV Ab were identified at their first visit at our Liver Center and were thus considered as "coinfected" (Figure 1). The characteristics of the 60 chronic HBs Ag-positive patients co-infected with HDV are shown in Table 1. Mean age was 36.9 years; mean follow-up time was 5.2 years (95% CI 3.96–6.45). The majority (56.7%) of patients were men. Twenty-seven (45%) were of European origin and 30 (50%) were from Africa. Among Europeans, the majority (88.9%) were migrants from Eastern Europe, and among Africans, 83.3% were from Sub-Saharan Africa. Among patients with positive HDV Ab, four were co-infected with Human Immunodeficiency Virus and one with hepatitis C virus. Transmission was sexual in eight cases—among which two patients were sex workers and one was a MSM. Known risk factors could be identified in two more cases, namely IVDU and blood transfusions. Transmission was of unknown cause in the remaining 50 cases.

The prevalence of cirrhosis at baseline in these co-infected patients was 20%. Indeed, when HDV infection was first diagnosed, a liver biopsy was performed in 29 patients (48.3%), eight of whom had histologically proven cirrhosis. Four more patients were diagnosed with cirrhosis using non-invasive methods at the time of the diagnosis of HDV infection. When available, baseline elastometry levels in patients who underwent a liver biopsy are specified in Supporting Information S1.

Systematic annual screening allows for diagnosis of incidental HDV superinfection (Tables 1 and 2)

The annual screening initially scheduled for HDV Ab was achieved on average in 71% (extremes 28–100) of cases. This led to the diagnosis of seven cases of HDV superinfection in initially HDV Ab negative patients, which equates to an incidence of 1.48% over the seven-year-follow-up window, with a median follow-up time of 4 years (IQR 3.8–4.4) between the beginning of the systematic and repeated screening process and the diagnosis of HDV superinfection. HDV seroconversion was confirmed with at least two distinct positive HDV Ab tests in five out of the seven cases of superinfection. Among these initially seronegative patients, the median time to onset of

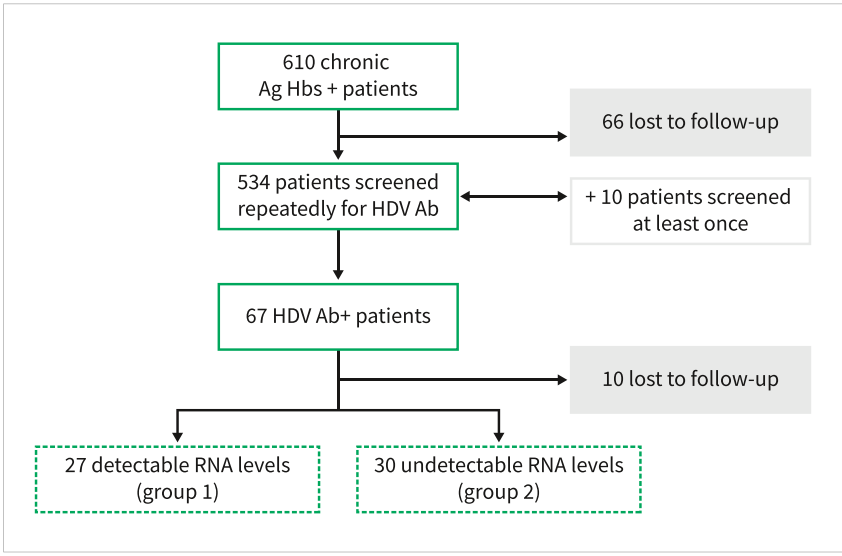


FIGURE 1 Flow chart of patients included in the study.

TABLE 1 Baseline characteristics of 67 HDV Ab-positive patients.

	All HDV Ab positive patients ($n = 67$)	Coinfected HDV patients ($n = 60$)	Superinfected patients ($n = 7$)	p-value
Age (years)	36.0 +/− 11.0	36.9 +/− 10.1	44.9 +/− 14.4	0.062
Sex, male (%)	37 (55.2)	34 (56.7)	3 (42.9)	0.692
Ethnicity (%)				0.315
European	29 (43.3)	27 (45.0)	2 (28.6)	
Eastern Europe	26 (38.8)	24 (40.0)	2 (28.6)	
Western Europe	3 (4.5)	3 (5.0)	0 (0)	
African	35 (52.2)	30 (50.0)	5 (71.4)	
Sub-Saharan Africa	30 (44.8)	25 (41.7)	5 (71.4)	
Northern Africa	5 (7.5)	5 (8.3)	0 (0)	
Asia	2 (3.0)	2 (3.3)	0 (0)	
Latin America	1 (1.5)	1 (1.7)	0 (0)	
HIV positive (%)	5 (7.5)	4 (6.7)	1 (14.3)	0.434
HCV positive (%)	1 (1.5)	1 (1.7)	0 (0)	0.999
Contamination (%)				0.004
Sexual transmission	13 (19.4)	8 (13.3)	5 (71.4)	
Sex workers	2 (3.0)	2 (3.3)	0 (0)	
MSM	2 (3.0)	1 (1.7)	1 (14.3)	
IVDU	1 (1.5)	1 (1.7)	0 (0)	
Blood transfusions	1 (1.5)	1 (1.7)	0 (0)	
ALT > ULN (%)	44 (65.7)	41 (68.3)	3 (42.9)	0.221
Cirrhosis (%)	13 (19.4)	12 (20.0)	1 (14.3)	0.999
Histologically proven	9 (13.4)	8 (13.3)	1 (14.3)	
Non-invasive method	4 (6.0)	4 (6.7)	0 (0)	

Note: Data are presented as mean +/− SD or number of patients (%).

Abbreviations: HDV, hepatitis delta virus; IVDU, intravenous drug use; MSM, men having sex with men.

TABLE 2 Characteristics of 7 cases of HDV superinfection.

Patient #	Origin	Age at HBV diagnosis (years)	Time between HBV diagnosis and HDV superinfection (years)	PCR HBV (UI/mL)	PCR HDV	ALT before super-infection	ALT after super-infection	HBe Ag	Fibrosis index before super-infection	HDV transmis-sion	Other STDs	Fibrosis at end of follow-up	Under analog treatment	Acute hepatitis in follow-up
1	African	27	6	<60[a]	ND	1 × ULN	4 × ULN	Neg.	F4	Sexual	No	F4	Yes	Yes
2	African	63	10	680	ND	1 × ULN	1 × ULN	Neg.	NA	Unk.	No	NA	No	No
3	African	44	7	140,304	ND	1 × ULN	3.5 × ULN	Neg.	F0	Sexual	No	F0	No	No
4	African	24	8	11,360	ND	1 × ULN	1 × ULN	Neg.	F0	Sexual	No	F0	No	No
5	African	46	4	1176	ND	1 × ULN	1 × ULN	Neg.	F0	Sexual	No	F0	No	No
6	European	30	12	<60[a]	NA	1 × ULN	1.3 × ULN	Neg.	NA	Sexual — MSM	HPV — HIV	NA	Yes	No
7	European	30	4	22,931	ND	1 × ULN	1 × ULN	Neg.	F0	Unk.	No	F0	No	No

Abbreviations: HDV, hepatitis delta virus; NA, not available; ND, not detectable; Neg., Negative; STDs, sexually transmitted diseases; ULN, upper limit of normal; Unk., Unknown.

[a]identifies patients under treatment with Tenofovir during superinfection.

hepatitis delta after diagnosis of hepatitis B was 5.2 years (IQR 4.1–8.3). Mean age was 44.9 years; mean follow-up time was 1.56 years (95% CI 0.48–2.65). Five patients were of Sub-Saharan African origin, and the remaining two came from Eastern Europe. Transmission was sexual in five cases and of unknown cause in two. Of note, only three patients had elevated ALT levels at the time of superinfection diagnosis, including one who developed acute-on-chronic liver failure (ACLF) and required a liver transplant (patient #1, Table 2). Cirrhosis was present at the time of HDV diagnosis in this patient and was histologically proven. All other precipitating factors for ACLF were excluded, and HDV superinfection was retained as the cause of the hepatic decompensation in this patient. ALT levels were normal in the four other patients. PCR could be performed in all cases but one, and there were no detectable RNA levels in all cases. Blood samples for PCR analysis were collected between two and 17 months after the seroconversion was diagnosed.

Patients with HDV antibodies originate more frequently from Eastern Europe and have a more severe course of liver disease (Table 3)

Among the 544 patients with chronic HBs Ag who were screened for HDV serology at our clinic, we identified a total of 67 patients with positive HDV Ab. The comparison of baseline characteristics of patients with positive HDV Ab and chronic HB Ag carriers who remained negative for HDV is displayed in Table 3. Further details about the HDV serological tests, repeated testing and comparison between the two techniques used are specified in Supporting Information S2. Of note, patients with positive HDV Ab were more frequently of Eastern European origin (38.8% vs. 10.5%), had more often elevated ALT levels (64.2% vs. 8.2%; p-value < 0.001) and cirrhosis (19.4% vs. 2.7%; p-value $= 0.01$) at the time of HDV diagnosis compared with patients who did not contract the disease.

Clinical outcome during follow-up of the 67 HDV Ab positive patients

After the implementation of a regular screening for fibrosis progression using elastometry as part of our study, six more cases of cirrhosis were diagnosed over time among the 54 HDV Ab positive patients who did not have a cirrhosis at the beginning of the follow-up. We had 24 patients lost to follow-up over time. Furthermore, 21 patients were still alive at the end of the study but were censored since they were not followed for the whole 7-year window period.

The cumulative incidence of cirrhosis in HDV Ab-positive patients at 7 years of follow-up was 10.2% (95% CI 0–20.5). There was no statistically significant difference in cumulative incidence of cirrhosis between co-infected and superinfected patients, although a potential bias due to the shorter follow-up time of patients with a

TABLE 3 Characteristics of 544 patients with chronic HBs Ag according to their HDV Ab status.

	All HBs Ag positive patients tested (n = 544)	HDV Ab positive patients (n = 67)	HDV Ab negative patients (n = 477)	p-value
Age (years)	38 +/− 11	37 +/− 17	42 +/− 10	NS
Sex, male (%)	292 (53.7)	37 (55.2)	255 (53.4)	NS
Ethnicity (%)				0.026
Eastern Europe	76 (13.8)	26 (38.8)	50 (10.5)	
Western Europe	15 (2.7)	3 (4.5)	12 (2.5)	
Sub-Saharan Africa	305 (56.0)	30 (44.8)	275 (57.6)	
North Africa	55 (10.1)	5 (7.5)	50 (10.5)	
Asia	31 (5.7)	2 (3.0)	29 (6.7)	
Latin America	1 (0.1)	1 (1.5)	0 (0)	
Not precised	62 (11.4)	0 (0)	62 (13.0)	
HIV positive (%)	14 (2.6)	5 (7.5)	9 (1.9)	0.03
HCV positive (%)	9 (1.6)	1 (1.5)	8 (1.7)	NS
ALT > ULN (%)	82 (15.1)	43 (64.2)	39 (8.2)	<0.001
Cirrhosis (%)	26 (4.7)	13 (19.4)	13 (2.7)	0.01
Analogs (%)	41 (7.5)	9 (13.4)	32 (6.7)	0.021

Note: Data are presented as mean +/− SD or number of patients (%).
Abbreviation: HDV, hepatitis delta virus.

superinfection cannot be excluded. One patient developed HCC during follow-up and died, while two more patients died of non-liver related causes. For the 67 HDV Ab positive patients and considering patients who were censored due to a loss of follow-up or because they were not followed for the whole 7-year period, survival was 96.0% (95% CI: 90.7–100) at 5 years, and 92.4% (95% CI: 84.2–100) at 7 years (Figure 2).

Patients with detectable HDV RNA levels are more frequently of European origin and have a more severe course of liver disease

HDV RNA PCR was performed in 57 out of the 67 HDV Ab-positive patients, 27 (47.4%) of which had detectable levels. Patients with detectable HDV RNA (group 1) had significantly higher ALT levels (93 vs. 58 IU/mL, p = 0.023) and were more frequently of European origin than undetectable patients (66.7% vs. 20%, $p < 0.001$, group 2) (Figures 3a,b). Treatment with PEG-IFN was administered to nine patients in group 1. Baseline characteristics of patients in group 1 are presented in Table S1 and are compared to those of patients with confirmed positive HDV Ab (patients who underwent at least two positive serological tests) with a negative HDV RNA PCR, and to chronic HBs Ag carriers who remained negative for HDV Ab. The cumulative incidence of cirrhosis was 13.8% (95% CI 0–30) in group 1 and 0 (95% CI 0–0) in group 2 (p = 0.026) (Figure 3c) at 7 years of follow-up. Eight patients from group 1 and 11 patients from group 2 were lost to follow-up. Cirrhosis was present at the beginning of follow-up in 12 patients (nine from group 1 and three from group 2) who were excluded from these analyses. Of note, the cumulative incidence of cirrhosis among co-infected patients only (without the seven superinfected cases) was 13.8% (95% CI 0–30) at the end of follow-up in group 1 versus 0 (95% CI 0-0) in group 2 (p = 0.027).

DISCUSSION

It is estimated that about 300 million people live with HBV infection worldwide. Current WHO numbers estimate that about 5% of those are also infected with HDV.[2] However, the exact prevalence of HDV infection is most likely underestimated due to a lack of systematic screening and access to diagnostic tools in many countries. It is precisely the relevance of a systematic and annual screening that we aimed to study in this work. Systematically screening *all* chronic Ag HB carriers at our Liver Clinic enabled us to diagnose a prevalence of HDV infection of 11% in our patients. Most recent epidemiological studies led in Western Europe found a prevalence of 4%–12% of HDV among chronic Ag HB carriers.[6,16–20] The prevalence of HDV in neighboring countries such as France and the Netherlands was lower in recent studies,[19–21] which could be due to a number of factors, among which an increase in migrant influx in the past decade, as well as differences in the types of hospitals and access to care. Indeed, our Liver Clinic has a significant number of patients from disadvantaged social backgrounds and provides care to all patients, even if they are

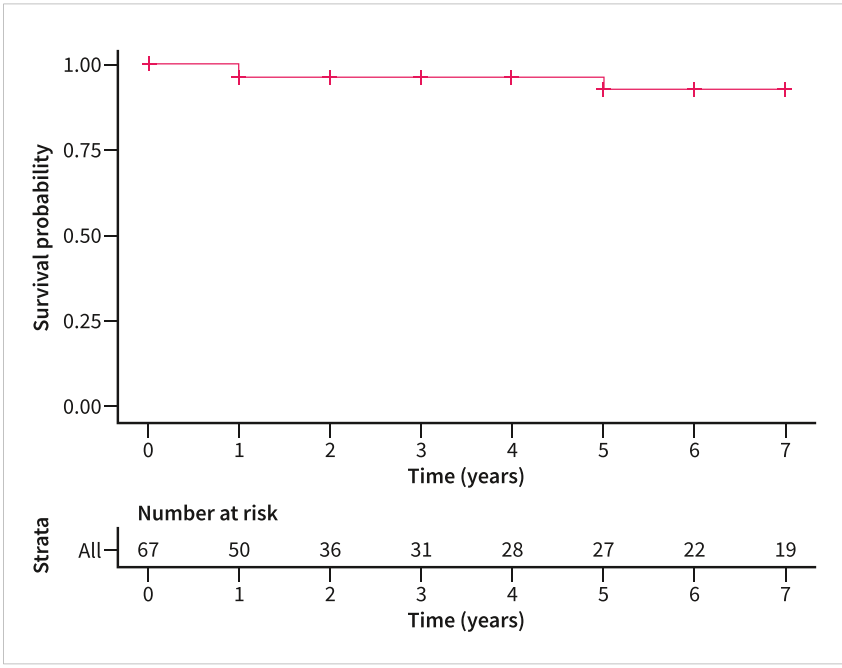


FIGURE 2 Kaplan Meier survival curve for 67 patients after diagnosis of HDV infection. Figure 2 shows the survival (in years) of chronic HBs Ag carriers after the diagnosis of HDV infection. The numbers of patients at risk are shown in the table below. "+" indicates censored patients (due to loss of follow-up or lack of completion of the 7-year follow-up). HDV, hepatitis delta virus.

not covered by health insurance. Recently, a study in Spain found that the implementation of anti-HDV "reflex testing" among patients positive for hepatitis B has dramatically increased the effective screening rate for this dual infection.[6] Our study confirms that the prevalence of HDV in chronic Ag HBs carriers is much higher than previous estimates, thus emphasizing the importance of "reflex" anti-HDV testing in all chronic Ag HBs carriers. Diagnosing patients with delta hepatitis has become all the more important since there are now new therapeutic options that can be offered to these patients, namely Bulevirtide.[14] Noteworthy, other antiviral drugs are currently also in development.[22]

The majority of patients with HDV infection in our cohort were migrants from Eastern Europe or Sub-Saharan Africa, with only three out of 67 patients who were originally from Western Europe. Interestingly, only six cases had known transmission risk factors (namely IVDU, sex work, MSM and blood transfusions). The low prevalence of known risk factors in our cohort of patients highlights the necessity to systematically screen all carriers of HBs antigen for HDV infection, regardless of whether they are deemed to be at risk.

Our study also confirms that patients with positive PCR for HDV infection are at a much higher risk of developing cirrhosis than those with negative PCR. Systematic annual screening with non-invasive tools such as liver elastometry allowed us to follow the progression of fibrosis and led to the diagnosis of incidental cirrhosis in some patients with delta hepatitis, which is particularly important in those patients at high risk of developing liver fibrosis during follow-up. Noteworthy, non-invasive methods of follow-up such as liver elastometry have not been formally validated for patients with delta hepatitis in large multicentre studies. However, it was recently demonstrated that elastometry had good diagnostic accuracy for the diagnosis of cirrhosis in these patients[23,24] although this should be confirmed in further studies and specific cut-off values should be established.[9]

Interestingly, while patients with positive HDV antibodies were almost evenly divided between people of European or Sub-Saharan African origins, 66.7% of patients with detectable RNA levels were of European origin. An association between European origin, persistent viremia and an increased risk of cirrhosis was also described in the French Deltavir study.[25]

Finally, our study underlines the fact that the repetition of screening for HDV in patients with positive HBs Ag can lead to the identification of cases of HDV superinfection in otherwise asymptomatic patients with normal ALT levels. Contrary to what has been previously described, HDV superinfection did not lead to chronic HDV infection in our patients since none of them had detectable blood RNA levels. However, understanding whether HDV superinfection leads to chronicity less frequently than previously estimated would require a large-scale prospective study and goes beyond the scope of our work.

Of course, our work has limitations. This study was a retrospective study based on a clinical experience in real life. Our hospital is a first-line public hospital located in Brussels with a large migrant's

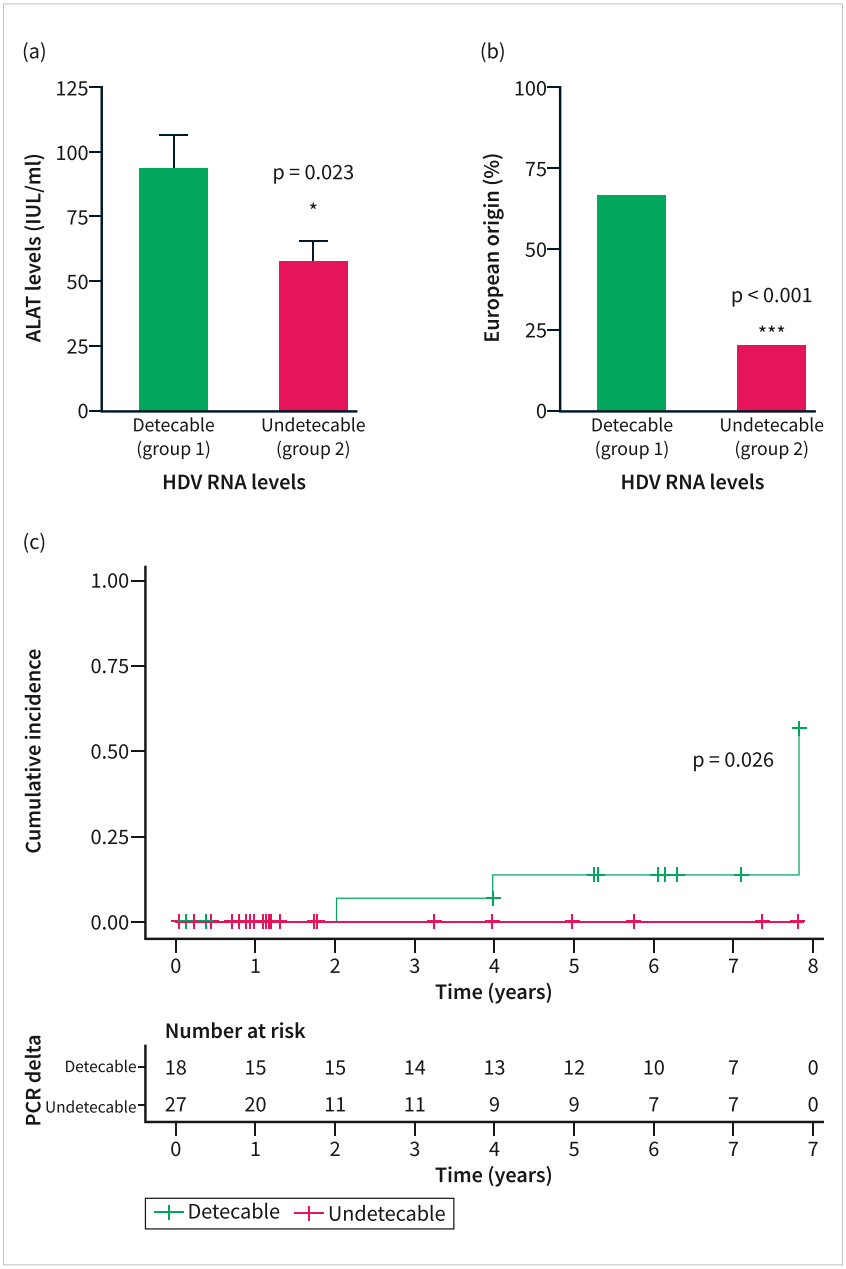


FIGURE 3 Patients with detectable HDV RNA levels are more frequently of European origin and have a more severe course of liver disease. (a) ALT levels in patients with detectable HDV RNA levels (group 1, $n = 27$) and undetectable HDV RNA levels (group 2, $n = 30$). Student's t-test was performed to examine the statistical difference between the two groups. (b) Proportion of subjects of European origin among patients with detectable HDV RNA levels (group 1, $n = 18/27$) and undetectable HDV RNA levels (group 2, $n = 6/30$). Fisher's exact test was performed to examine the statistical difference between the two groups. (c) Cumulative incidence of cirrhosis during follow-up in patients with detectable (continuous light gray line) and undetectable (dotted black line) HDV RNA levels. "Years" refers to the duration of follow-up of fibrosis progression. Log-rank test was performed to examine the statistical difference between the cumulative incidence of cirrhosis in the two groups. HDV, hepatitis delta virus. $^{*}p < 0.05$, $^{***}p < 0.001$.

population. Our cohort of patients is not representative of the whole Belgian population and the prevalence in our patients may not be generalizable to the country as a whole. Furthermore, our ability to implement a systematic follow-up and screening policy in our cohort of patients with positive HBs Ag was sometimes limited by the compliance of the patients or by the fact that they had to change hospital centres, which led to a significant number of patients lost to follow up. Despite this, or perhaps precisely because of the specific nature of our hospital, the prevalence figures we have found in our study remain significantly higher than previously estimated. This emphasizes the need to systematically screen all HBs Ag-positive patients for hepatitis delta.

CONCLUSION

A systematic screening strategy for hepatitis delta in patients with chronic HBs Ag patients enables the identification of a high prevalence of HDV Ab, much higher than previous estimates. Repetition of the screening also allows the diagnosis of cases of delta superinfection that were sometimes clinically occult. Finally, a regular assessment for fibrosis progression in HDV Ab positive patients using non-invasive methods allows the diagnosis of a significant amount of cirrhosis in patients with detectable HDV RNA levels.

CONFLICT OF INTEREST STATEMENT

No conflicts of interest exist for any of the authors in relation to this study.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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