Hepatitis B virus and hepatitis C virus infections in Belgium: similarities and differences in epidemics and initial management

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Introduction **Nationwide studies comparing patients with hepatitis B and C virus (HBV and HCV) infections are mandatory for assessing changes in epidemiology.**

Aim **The aim of this study was to compare epidemiological data and initial management of newly diagnosed patients with persistent HBV (HBsAg positive) or HCV (detectable HCV RNA) infection in Belgium.**

Patients and methods **Data were extracted from two Belgian observational databases.**

Results **A total of 655 patients (387 HBV and 268 HCV) were included. Compared with HCV patients, HBV patients were younger, more frequently men, more often of Asian or African origin (43 vs. 10%, $P<0.0001$), and less frequently contaminated by transfusion or intravenous drug use (9 and 6% vs. 34 and 44%, $P<0.0001$). Viral replication was assessed in 89% of HBV patients. Compared with HCV patients, HBV patients more frequently had normal alanine aminotransferase (ALT) levels (65 vs. 29%, $P<0.0001$), less frequently underwent liver biopsy (29 vs. 67%, $P<0.0001$), and were less often considered for antiviral therapy (25 vs. 54%, $P<0.0001$). When taking only HBV patients with detectable viral replication into consideration, results remained unchanged. During the multivariate analysis, ALT was a major factor for performing liver biopsy or considering antiviral therapy in both groups.**

Conclusion **HBV and HCV screening policies should be targeted toward immigrants and intravenous drug users, respectively. Guidelines recommending systematic search for viral replication should be reinforced in HBV patients. HBV patients less frequently underwent liver biopsy and were less often considered for antiviral therapy compared with HCV patients. Despite the lack of sensitivity and specificity, ALT remains a pivotal decision-making tool for liver biopsy and antiviral therapy in both infections. *Eur J Gastroenterol Hepatol* 25:613–619 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Hepatitis B and C virus (HBV and HCV) infections are due to structurally different viruses, a DNA virus for HBV and an RNA virus for HCV, but they share many similarities. Both circulate in the bloodstream, cause injury to the liver, and are the main viral agents responsible for chronic hepatitis [1–3]. They are the leading causes of cirrhosis and associated liver failure, hepatocellular carcinoma, and death [4–6].

However, HBV and HCV infections show major differences from an epidemiological point of view. Numerous scientific reports on their epidemiology have been published, but direct comparison between the two epidemiologies is hampered by differences in study objectives, methods, and target populations. In addition, epidemics of HBV and HCV are continuously evolving, mainly related to increased blood transfusion safety, improvement in healthcare conditions, continuous

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expansion of intravenous drug use, and immigration to Europe from endemic areas [7,8]. Although these factors involve both viral infections, their impact on the epidemics of HBV and HCV infections differs. Overall, available data indicate that the incidence of HBV infection has dramatically decreased in Europe and the USA during the past two decades, mainly because of vaccination programs and blood donor testing [9–11]. However, this has not translated into a decreased HBV burden as the absolute number of HBs antigen (Ag)-positive individuals continues to increase [10,12]. For HCV infection, although the annual incidence has decreased since the beginning of the 1990s because of systematic testing of blood donors, it is believed that the overall prevalence has just reached its maximal level and that the prevalence of liver complications will continue to increase over the next decade [13,14].

Although numerous studies have already focused on HBV and HCV epidemiology, no direct comparisons of the two infections have been carried out recently. Because of the persistently high HBV and HCV burden, studies focusing on the epidemiology of HBV and HCV infections remain crucial for improving screening. In addition, data on initial management of newly diagnosed patients with persistent HBV or HCV infection are useful for determining whether current guideline recommendations are correctly applied.

Belgium is considered a low endemic area for both HBV and HCV infections [9], with an estimated prevalence of chronic HBsAg carriers of around 0.7% [15,16] and an estimated prevalence of HCV antibodies of around 0.9% [15]. Over the past few years, two observational studies have been conducted in Belgium under the aegis of the Belgian Association for the Study of the Liver, one on chronic HBsAg carriers [17] and the other focusing on newly diagnosed patients with HCV infection [18]. In the present study, we sought to compare the main epidemiological characteristics of newly diagnosed patients with persistent HBV (HBsAg positive) or HCV infection (HCV RNA positive) identified in these two registries and to further extend this comparison to initial management, including virological and alanine aminotransferase (ALT) assessment, histological evaluation, and assessment of eligibility for antiviral therapy.

Patients and methods

Data from patients with newly diagnosed HBV or HCV infection were extracted from two Belgian databases, the HBsAg Carriers Registry (2008–2009) [17] and the Observational Survey of Hepatitis C (2003–2004) [18] (Fig. 1). The HBsAg Carriers Registry was a prospective registry study conducted at 27 academic and nonacademic centers that collected epidemiological, biological, histological, and therapeutic data on HBsAg-positive carriers presenting at the outpatient clinics from 1 March 2008 to 28 February 2009, including both newly diagnosed (incidental) and already recognized (prevalent) patients. In the current study, only incidental cases were considered. The Observational Survey of Hepatitis C was a prospective registry study conducted in nine academic and nonacademic centers that collected epidemiological, biological, histological, and therapeutic data on newly diagnosed HCV patients referred for the first time to either outpatient or inpatient clinics from November 2003 to November 2004. In the current study, only patients with detectable HCV RNA were considered. Participating centers in both registries were spread throughout the country and were thus representative of the overall Belgian population.

Physicians were asked not to change their usual clinical practice as a result of their participation in these registries. All patients signed informed consent forms. The HBV registry study was approved by a central ethical committee (UZ Antwerpen, local reference: B30020072691-7/39/212) and by the local ethical committee of each participating center. The HCV registry was approved by the local ethical committee of each participating center.

Extracted data from each registry were collected in a file. Comparable data included demographic information (age at diagnosis, sex, racial origin, and risk factors for infection), liver biochemistry [ALT expressed as multiples of the upper limit of normal values (ULN)], and overall management data, including assessment of viral markers and viral replication (expressed as detectable vs. undetectable viral nucleic acids), histological data (proportion of patients with histological assessment, activity score, and fibrosis stage, see the Histological examination section), and treatment data (information on planned vs. unplanned treatment to assess the proportion of patients eligible for treatment; Fig. 1). Because of the lack of available data, HBV patients coinfected with HCV, hepatitis delta virus, or HIV and HCV patients coinfected with HBV, or HIV were not excluded. Data on alcohol consumption were not available in the HBsAg Carriers Registry, precluding any comparison between the two groups in terms of alcohol consumption. Data on metabolic syndrome were not available for either HBV or HCV patients.

Serological methods

Testing for HBsAg and anti-HCV antibodies was carried out using commercial enzyme immunoassays. HBV DNA and HCV RNA were quantified using sensitive quantitative methods according to the specific habits of each center, including a signal amplification assay based on branched DNA technology and real-time PCR.

Histological examination

When performed, percutaneous or transjugular liver biopsies were assessed by light microscopy. Specimens were graded according to the METAVIR score [19,20].

The METAVIR score was assessed by local pathologists. A central review of biopsies was not performed.

Statistical analysis

Continuous data were expressed as means and SDs or as medians and 95% confidence intervals. Qualitative data were expressed as frequencies and percentages. The χ^2-test, the two-sided Fisher's exact test, the Mann–Whitney *U*-test, the Wilcoxon test, and the two-sample Student's *t*-test were used in variance analysis for qualitative and semiquantitative comparisons, as appropriate. All tests were two-tailed at a 0.05 level. Discriminative values or variables reaching a *P*-value lower than 0.05 in previous analyses were selected for multivariate conditional logistic regression analysis. All statistical analyses were carried out using the NCSS 2007 software (NCSS, Kaysville, Utah, USA).

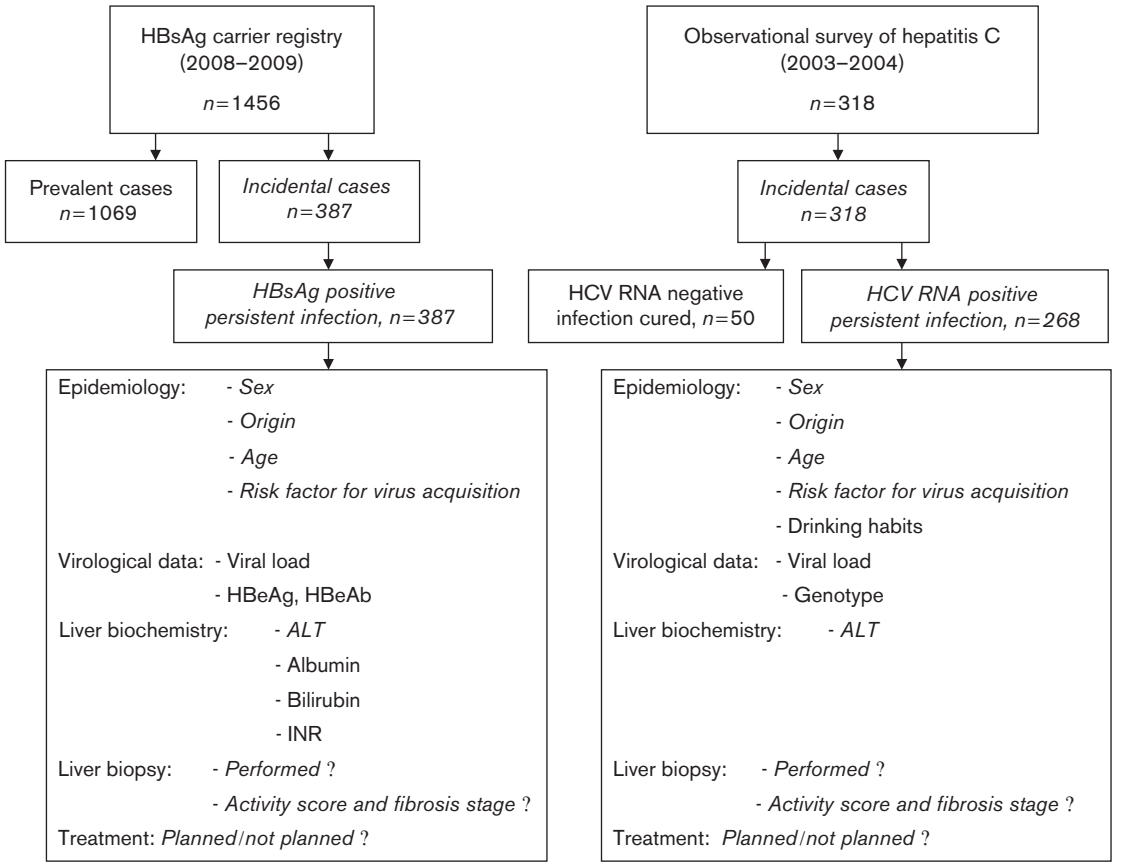
Results

A total of 655 patients were included: 387 HBsAg carriers and 268 HCV patients with detectable HCV RNA (Fig. 1). According to the definition of the four phases of chronic HBV infection recommended in recent international guidelines [21,22], five (1%) HBV patients were considered to be immunotolerant, 118 (30%) were inactive carriers, 66 (17%) were in the HBeAg-positive chronic hepatitis phase, and 76 (20%) were in the HBeAg-negative chronic hepatitis phase. A total of 122 HBV patients (32%), unclassified or misclassified by the physician in charge, remained unclassified (see Deltenre *et al.* [17] for more details).

Epidemiological characteristics of hepatitis B virus-infected and hepatitis C virus-infected patients

Demographic characteristics of the study population are presented in Table 1. Compared with HCV patients, HBV patients were younger, more frequently men, and more often from Asia or Africa (43 vs. 10%, $P < 0.0001$). A risk factor for infection was identified in 36% of HBV patients and in 73% of HCV patients ($P < 0.0001$). HBV patients were less frequently contaminated by transfusion (9 vs. 34%, $P < 0.0001$) and intravenous drug use (6 vs. 44%, $P < 0.0001$) and more frequently contaminated by sexual or familial transmission compared with HCV patients.

Fig. 1



The study population. Comparable data in the two registries are indicated in italics. ALT, alanine aminotransferase; HBeAb, hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen.

Table 1 Epidemiological data

	HBsAg-positive patients ($n=387$)	HCV patients with detectable HCV RNA ($n=268$)	*P*-value
Age (years)[a]	36 (34–37)	45 (43–46)	<0.0001
Sex ratio (male/female) [*n* (%)]	266/121 (69/31)	150/118 (56/44)	0.0008
Origin [*n* (%)]			
Known	386 (100)	252 (94)	<0.0001
White	165 (43)	214 (85)	
Black African	123 (32)	25 (10)	
Asia	44 (11)	1 (0.4)	
Maghreb	52 (13)	8 (3)	
Other	2 (1)	4 (1.6)	
Unknown	1 (0)	16 (6)	
Risk factor for infection [*n* (%)]			
Known	139 (36)	196 (73)	<0.0001
Transfusion	12 (9)	66 (34)	
Intravenous drug use	8 (6)	86 (44)	
Surgery	4 (3)	14 (7)	
Sexual transmission	56 (40)	2 (1)	
Familial transmission	42 (30)	1 (0.5)	
Other	17 (12)	27 (14)	
Unknown	248 (64)	72 (27)	

HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.
[a]Data expressed as median (95% confidence interval).

Table 2 Initial management data

	HBsAg-positive patients ($n=387$)	HCV patients with detectable HCV RNA ($n=268$)	*P*-value
Viral load data [*n* (%)]			
Viral load assessment	346 (89)	268 (100)	<0.0001
Viral replication	242 (70)	268 (100)[a]	<0.0001
ALT data [*n* (%)]			
ALT values assessment	387 (100)	267 (100)	1.0
ALT values			
<ULN	252 (65)	78 (29)	<0.0001
>2 ULN	60 (15)	114 (43)	<0.0001
Histological assessment data [*n* (%)]			
Performance of liver biopsy	109 (28)	180 (67)	<0.0001
Histological lesions			
Necroinflammatory activity			
Stage 2 or 3[b]	36/98 (37)	58/158 (37)	0.9
Fibrosis			
Stage 3 or 4[b]	33/104 (32)	34/172 (20)	0.02
Cirrhosis[b]	17/104 (16)	10/172 (6)	0.004
Treatment data [*n* (%)]			
Planned treatment	95/375 (25)	138/255 (54)	<0.0001

ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; ULN, upper limit of normal values.
[a]According to the pre-established inclusion criteria.
[b]According to the METAVIR scoring system.

Initial management of hepatitis B virus-infected and hepatitis C virus-infected patients

Data on initial management are reported in Table 2.

Assessment of viral markers and alanine aminotransferase levels

HBeAg status was assessed in 100% of HBV patients. In total, 78% of patients were HBeAg negative. Viral replication was assessed in 89% of HBV patients. HBV DNA was detected in 70% of these HBV patients. In the Observational Survey on Hepatitis C, all HCV patients underwent viral replication assessment (Fig. 1). As required by our pre-established criteria, all included HCV patients had detectable HCV RNA levels, so as to compare only patients with persistent infection (see the Patients and methods section). The HCV genotype was assessed for 77% of patients. Among these patients, 58, 6, 19, 15, and 2% were infected with genotypes 1, 2, 3, 4, and 5, respectively.

ALT levels were assessed in all HBV and HCV patients. Compared with HCV patients, HBV patients less frequently showed abnormal ALT levels (35 vs. 71%, $P < 0.0001$) and ALT levels of more than 2 ULN (15 vs. 43%, $P < 0.0001$).

When taking only HBV patients with detectable viral replication into consideration, these patients less frequently showed abnormal ALT levels (44 vs. 71%, $P < 0.0001$) or ALT levels of more than 2 ULN (22% vs. 43%, $P < 0.0001$) compared with HCV patients.

Histological examination

Liver biopsy was performed in 109 HBV patients (29%) and 180 HCV patients (67%) ($P < 0.0001$). Among the

two groups, liver biopsy was more often performed in patients with abnormal ALT levels (60 vs. 12% in HBV patients with normal ALT levels, $P < 0.0001$ and 76 vs. 46% in HCV patients with normal ALT levels, $P < 0.0001$). In addition, liver biopsy was also more often performed on HBV patients with detectable viral replication (38 vs. 16% in patients with undetectable HBV DNA levels, $P < 0.0001$) and in men, whites, and patients with sexually-acquired or family-acquired infection ($P < 0.05$). In HBV patients, there was no relationship between HBeAg status and liver fibrosis, which was assessed in 63 HBeAg-negative patients (63/302 = 21% of all HBeAg-negative patients) and 41 HBeAg-positive patients (41/84 = 49% of all HBeAg-positive patients): 35% (22/63) of HBeAg-negative patients had severe fibrosis or cirrhosis compared with 27% (11/41) of HBeAg-positive patients ($P = 0.39$).

When considering only HBV patients with detectable viral replication, liver biopsy was less frequently performed in HBV patients than in HCV patients (38 vs. 67%, $P < 0.0001$).

During multivariate analysis, the only significant predictor of performance of liver biopsy after adjustment for factors identified by univariate analyses was abnormal ALT levels in both groups ($P < 0.0001$ for HBV and HCV patients).

On assessment, the activity scores were comparable in the two groups, with moderate to severe scores observed in 37% of patients ($P = 0.9$). HBV patients had at least extensive fibrosis (32 vs. 20%, $P = 0.02$), or confirmed cirrhosis (16 vs. 6%, $P = 0.004$), more often compared with HCV patients. These results did not change when only HBV patients with detectable viral replication were considered. Factors significantly associated with extensive fibrosis and cirrhosis were ALT levels greater than 2 ULN, older age, and moderate to severe activity scores in both groups, and male sex in HBV patients ($P < 0.05$).

Antiviral treatment

Antiviral therapy was less frequently considered for HBV patients than for HCV patients (25 vs. 54%, $P < 0.0001$). In both groups, treatment was more frequently considered for patients with abnormal ALT levels (53 vs. 10% in HBV patients with normal ALT levels, $P < 0.0001$ and 67 vs. 23% in HCV patients with normal ALT levels, $P < 0.0001$), older patients, men, and patients who underwent liver biopsy ($P < 0.05$). In addition, treatment was also considered more often for HBV patients with detectable levels of HBV DNA (33 vs. 13% for those with undetectable HBV DNA levels, $P = 0.0001$), whites, and patients with moderate to severe activity scores ($P < 0.05$). Fibrosis did not correlate with consideration for antiviral treatment in HBV or HCV patients. Among HBV patients who underwent liver biopsy, treatment was planned for 82 and 71% of the patients with and without cirrhosis, respectively ($P = 0.3$). Among HCV patients who underwent liver biopsy, treatment was planned for 70 and 71% of the patients with and without cirrhosis, respectively ($P = 0.9$).

When taking only HBV patients with detectable viral replication into consideration, treatment was less frequently considered for HBV patients than for HCV patients (33 vs. 54%, $P < 0.0001$).

During multivariate analysis, significant predictors for eligibility for antiviral treatment after adjustment for factors identified by univariate analyses were, in both groups, abnormal ALT levels ($P = 0.0003$ for HBV and $P < 0.0001$ for HCV patients), older age ($P = 0.007$ for HBV and $P = 0.004$ for HCV patients), and performance of liver biopsy ($P < 0.0001$ for HBV and HCV patients).

Discussion

The epidemiology of HBV and HCV is evolving in Europe, notably because of regular HBV vaccination and systematic blood donor testing for the two viruses. The transmission route has changed, with increased intravenous drug use [7,9,23]. Despite recent improvement in prevention of transmission, HBV and HCV remain leading causes for chronic liver disease [1–3]. Thus, updated epidemiological surveys may be useful for optimizing screening. In addition, data on initial management of patients with persistent HBV or HCV infection may be helpful in assessing whether current guideline recommendations are correctly applied. Over the past several years, two Belgian registry studies have been carried out in patients with HBV and HCV infections [17,18]. Both were real-life registry studies conducted at academic and nonacademic centers throughout the country, with no stringent inclusion criteria. They did not suffer from major referral biases; thus, results provide a valid indication of HBV and HCV infections in Belgium. As the two registry studies were carried out in a similar manner and within proximate time periods, they offered a unique opportunity to compare current epidemiological and management data on newly diagnosed patients with either persistent HBV or persistent HCV infection.

The first result of our study was that patients in whom HBV infection was recently diagnosed were more frequently immigrants from Asia and Africa, where HBV infection is still highly prevalent, whereas newly diagnosed HCV infections were mainly encountered in intravenous drug users among whom 50–90% show the presence of HCV antibodies [7,24]. These findings are useful for defining key target populations for HBV and HCV screening and to confirm results of other studies conducted in neighboring European countries [7,25–27]. Indeed, the precarious living conditions of immigrants and intravenous drug users may include possible difficulties in obtaining access to standard medical care. Thus, new strategies for improved screening are needed

in these populations and every effort should be made to provide them access to public health services. Even when performed in resource-constrained settings, such a strategy has proven to be cost-effective [28–31]. At first glance, it is surprising that, in 2003–2004, 34% of 'new' cases of HCV infection continued to be related to blood transfusions performed before 1990. This indicates that screening for HCV infection was not yet systematically performed even in well-defined, easy-to-target, at-risk populations and at least partly explains why the overall prevalence of HCV infection is believed to currently reach (around 2010) its maximal level despite the fact that the annual incidence is now less than 10% of that before 1990 [13,14]. Another surprising finding is that less than half of the HBV patients reported a risk factor for HBV infection. This result may be related to under-reported sexual transmission or to underestimated familial transmission.

We observed relevant differences in initial management of patients with HBV and HCV infections. Indeed, viral replication was not systematically assessed in HBV patients, whereas all HCV patients identified in the 'Observational Survey of Hepatitis C' underwent assessment of viral replication. Why HBV DNA was less frequently searched for in HBV patients than HCV RNA in HCV patients is unclear, especially because the level of viral replication provides prognostic information on the natural history of hepatitis B [32,33], whereas this is not the case in HCV patients [34–36]. This might be explained by specific reimbursement policies in Belgium as HBV PCR reimbursement is currently restricted to HBV patients with abnormal liver tests. Nevertheless, current guidelines recommending a search for viral replication should be reinforced in HBV patients [4]. Second, liver biopsy was also more frequently performed in HCV patients than in HBV patients. This may be explained by a less severe disturbance in ALT levels and lower frequency of viral replication in HBV patients. In addition, the presumed 'inactive carrier' status may have discouraged clinicians from performing liver biopsies in HBV patients with normal ALT and undetectable HBV DNA levels.

Our third finding concerns antiviral therapy, more frequently considered for HCV patients than for HBV patients. This is related to the fact that, at present, nearly half of the HBsAg-positive patients are viewed as inactive HBV carriers who do not require immediate treatment [4,17,25]. Indeed, HBV patients more often had normal ALT levels compared with HCV patients, whereas ALT levels had high odds ratios (OR) for considering eligibility for antiviral therapy, for both HBV (OR = 3.7) and HCV (OR = 5.3) patients. Thus, despite the lack of sensitivity of ALT testing, which does not consistently differentiate between patients with active and inactive virus-induced disease [37,38], and despite its lack of specificity, because values may increase in other circumstances such as those related to metabolic syndrome [39], the ALT value remains a key criterion to consider eligibility for antiviral therapy in both HBV and HCV patients.

This work had several limitations. Because of their cross-sectional design, these two registries provided a view of newly diagnosed patients with HBV and HCV infection in Belgium, but data on long-term evolution were not available. In addition, liver biopsy was performed in a limited number of patients, whereas other noninvasive means of fibrosis assessment, such as transient elastography, were not regularly performed. This may explain, at least in part, why fibrosis was not predictive of treatment consideration. Another limitation is that the time periods during which the two registry studies were carried out were not exactly the same. However, considering the short time interval between the periods of inclusion and the similar 1-year duration of inclusion in the two registries, it is unlikely that this difference significantly affected the results of our study. Finally, virological tests used for assessing viral replication differed between centers for both HBV and HCV patients. In addition, the lower limit of detection was not homogenous between the tests used. However, during the time at which each registry study was conducted, Belgian centers already used sensitive tests for assessing both HBV and HCV replication.

Conclusion

Considering the epidemiological observations made in our study, HBV screening in Belgium should be more specifically targeted toward immigrants and HCV screening toward intravenous drug users. Despite widely available guidelines, viral replication was not systematically assessed in HBV patients; these patients less frequently underwent liver biopsy and were less frequently considered eligible for treatment compared with HCV patients. Despite its lack of sensitivity and specificity, ALT testing remains a pivotal tool that helps clinicians decide on performance of liver biopsy and/or eligibility for antiviral therapy when confronted with these two viral infections.

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Conflicts of interest

There are no conflicts of interest.

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