# HBV infection in Belgium : Results of the BASL observatory of 1,456 HBsAg carriers

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## Abstract

***Introduction :*** **Nationwide studies are mandatory to assess changes in the epidemiology of HBV infection in Europe.**

***Aim :*** **To describe epidemiological characteristics of HBsAg-positive patients, especially inactive carriers, and to evaluate how practitioners manage HBV patients in real life.**

***Methods :*** **Belgian physicians were asked to report all chronically infected HBV patients during a one-year period.**

***Results :*** **Among 1,456 patients included, 1,035 (71%) were classified into one of four phases of chronic infection : immune tolerance (n = 10), HBeAg-positive hepatitis (n = 248), HBeAg-negative hepatitis (n = 420) and inactive carrier state (n = 357 HBeAg-negative patients with ALT < upper limit of normal (ULN) and HBV DNA < 2,000 IU/mL). Using less restrictive criteria for ALT (1-2 ULN) or HBV DNA (2,000-20,000 IU/mL), 93 unclassified patients were added to the group of inactive carriers. These 93 additional inactive carriers were younger, more frequently males, with similar risk factors for HBV infection and histological features compared to inactive carriers according to recent guidelines. Recent guidelines on management of HBV patients were generally followed, but systematic HBV DNA measurements and HDV co-infection screening should be reinforced.**

***Conclusion :*** **In Belgium, an inactive carrier state was a common form of chronic HBV infection. Using less restrictive criteria for classification of inactive carriers did not modify their main characteristics and seemed better adapted to clinical practice. Recent guidelines on management of HBV patients should be reinforced.** (Acta gastroenterol. belg., **2012**, 75, **35-41**).

**Key words** : chronic hepatitis, cirrhosis, fibrosis, inactive carrier, phases of infection.

### List of abbreviations

ALT, alanine aminotransferase ; HBV, hepatitis B virus ; HCV, hepatitis C virus ; HDV, hepatitis delta virus ; HIV, human immunodeficiency virus ; ULN, upper limit of normal.

## Introduction

One of the main difficulties in dealing with HBV patients lies in accurate identification of patients in the inactive carriage phase who cannot easily be differentiated from patients suffering from HBeAg-negative chronic hepatitis (1). Recent reviews and guidelines on chronic HBV infection recommended considering patients as inactive carriers when HBeAg was negative and anti-HBeAb positive, and when HBV DNA levels were below 2,000 IU/mL with normal alanine aminotransferase (ALT) values (2,3). However, this cut-off in the HBV DNA level is not clear-cut, as some HBeAg-negative patients with HBV DNA higher than 2,000 IU/mL may have inactive disease (4-8). On the other hand, patients with HBV DNA levels below 2,000 IU/mL may show a slight rise in ALT values for other reasons (9-11). According to recent guidelines, these patients with borderline criteria for the definition of inactive carriage state are too often considered "active" carriers despite the fact that they do not require antiviral treatment.

Large cohort studies that include representative samples of the population and incorporate useful clinical information on epidemiology, presentation and biological characteristics are mandatory for assessing the burden of HBV infection. However, such epidemiological studies are usually reported from tertiary medical centers, where patients are likely to have a more severe form of the disease. In order to avoid bias related to selection of patients at more advanced stages of the disease, cohort studies must include patients from both academic and non-academic centers.

In Belgium, a low endemic area with an estimated prevalence of chronic HBsAg carriers of around 0.7% (12,13), entecavir and tenofovir were not reimbursed for naive patients until November 2009. One reason why Belgian medical agencies refused this reimbursement was that national epidemiological data on

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chronic HBV infection were lacking. Accordingly, under the aegis of the Belgian Association for the Study of the Liver (BASL), we launched a nationwide prospective observatory that ultimately included 1,456 HBsAg-positive patients prospectively collected during a 1-year period in Belgium. Our aims were to describe epidemiological characteristics of chronically infected HBV patients, particularly inactive carriers, and evaluate how Belgian physicians manage HBV patients.

## Materials and methods

*Patients*

Members of the BASL were asked to collect selective data on all chronic HBsAg-positive carriers (recognized for at least 6 months) consecutively seen at outpatient clinics from March 01, 2008 to February 28, 2009. Both newly diagnosed (incidental) and already recognized (prevalent) cases were to be included. It was strongly recommended to physicians not to change their usual clinical practice as a result of their participation to the registry. Patients signed an informed consent. This prospective registry was approved by the central ethical committee of the UZ Antwerpen (local reference : B30020072691 – 7/39/212) and by the local ethical committee of each participating center.

*Data collection*

Data were anonymously collected in a pre-established file and results were sent to the Jolimont Hospital. The file included : 1/ demographic data (age, gender, racial origin, prevalent or incidental case, risk factors for HBV infection, and age at infection) ; 2/ biochemical data (ALT and aspartate aminotransferase values expressed as multiples of the upper limit of normal range (ULN), presence or absence of persistently normal ALT for more than 1 or 2 years, bilirubin level ≤ or > 1.5 mg/dL, albumin level > or < 3.5 g/L, and INR value > or < 1.5) ; 3/ virological data (HBsAg, HBeAg, HBeAb, HBV DNA levels, hepatitis C virus (HCV), human immunodeficiency virus (HIV) and hepatitis delta virus (HDV) antibodies) ; 4/ histological data (proportion of patients with histological assessment, activity score and fibrosis stage) ; 5/ information on past, ongoing or planned treatment (to assess the proportion of patients requiring treatment) ; and 6/ surveillance for hepatocellular carcinoma (tools and rhythm of surveillance).

*Serological methods*

Testing for HBs and HBe antigens and for anti-HBe, HCV, HIV and HDV antibodies was carried out using commercial enzyme immunoassays. HBV DNA was searched for using sensitive quantitative methods according to the specific habits of each center, including a signal amplification assay based on branched DNA (bDNA) technology and real-time PCR.

*Histological examination*

When performed, liver biopsy, either percutaneous or transjugular, was assessed by light microscopy. Specimens were evaluated according to the METAVIR score (14,15). The METAVIR score was assessed by local pathologists. A central review of biopsies was not performed.

*Patient classification into one of the four phases of chronic HBV infection*

Two steps were used for classification. In a first step, participating physicians were asked to classify their patients into one of the four acknowledged phases of chronic HBV infection : the immune tolerance phase, HBeAg-positive chronic hepatitis, HBeAg-negative chronic hepatitis and an inactive carrier state. In a second step, the status of inactive carriers was reviewed according to 2 different definitions :

– *Inactive carrier stage according to criteria recommended in recent guidelines (2, 3) :* HBsAg-positive and HBeAg-negative patients with HBV DNA levels < 2,000 IU/mL (3.3 $\log^{10}$ IU/mL) and normal ALT values (*restrictive definition of inactive carriers*).
– *Inactive carrier stage according to enlarged criteria :* HBsAg-positive and HBeAg-negative patients with HBV DNA < 20,000 IU/mL (4.3 $\log^{10}$ IU/mL) and normal ALT values *or* HBsAg-positive and HBeAg-negative patients with HBV DNA levels < 2,000 IU/ml and ALT < 2 ULN (*enlarged definition of inactive carriers*)

Patient classifications were reviewed independently by 2 investigators (PD and JH). Discrepancies in data interpretation were resolved by consensus. Classification remained undetermined if the physician in charge did not classify his patient, if HBeAg status was unknown, in cases of obvious erroneous classification by the physician or in transplanted patients. In addition, patients classified as inactive carriers could not be co-infected by HCV, HIV or HDV, could not have been considered for a treatment, and results of HBV DNA levels and ALT values had to be known.

*Statistical analysis*

Data were expressed as percentage or median (95% CI). HBV DNA levels were expressed in $\log^{10}$ IU/mL. Analyses were conducted using variance analysis, the chi-square test, two-sided Fisher exact test, Mann–Whitney test, Wilcoxon test and two-sample Student's t-test when appropriate. All statistical testing was two-tailed at the 5% level. Independent discriminative values of variables reaching a univariate p value ≤ 0.1 were then assessed by logistic regression analysis. All statistical analyses were performed using NCSS 2007 software (NCSS, Kaysville, UT, USA).

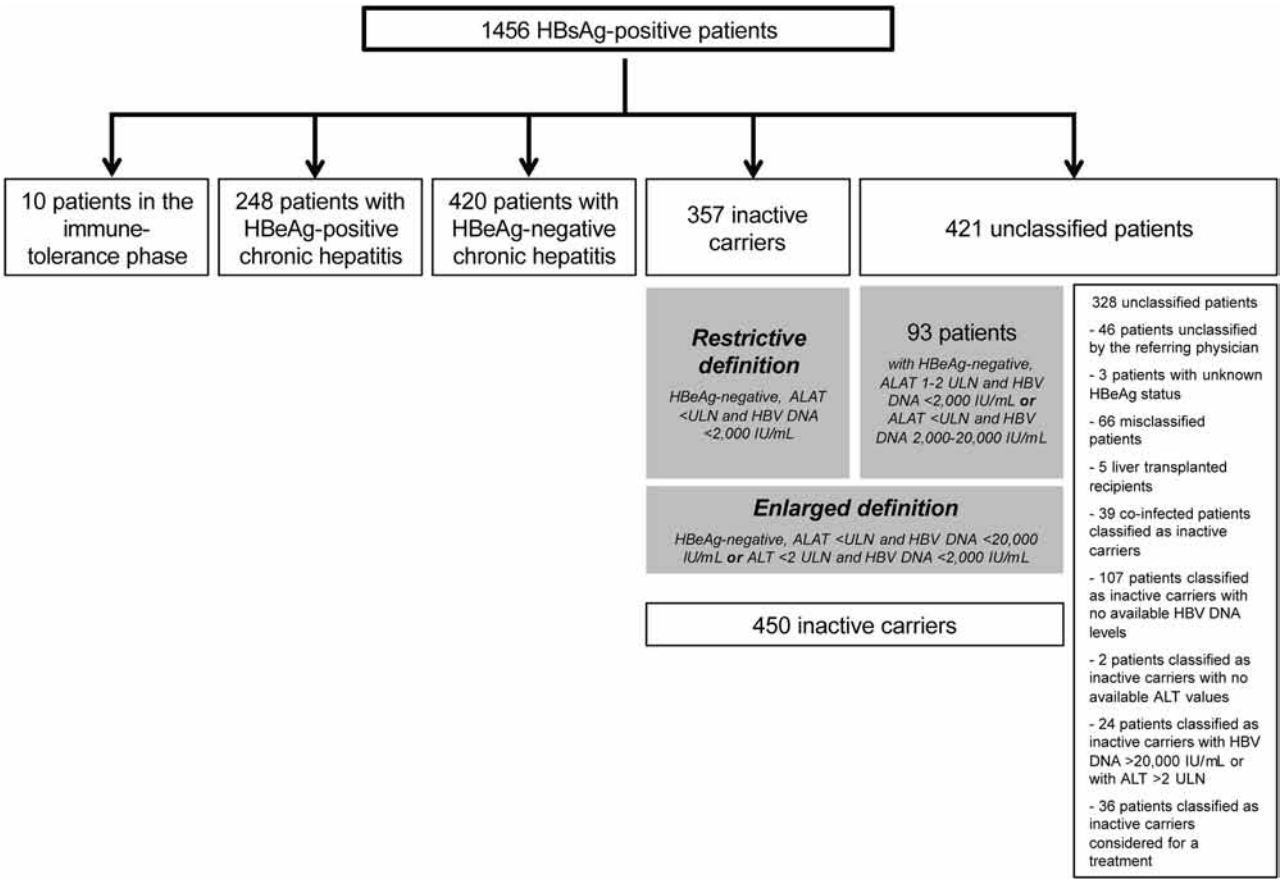


Fig. 1. — Classification of HBsAg-positive patients into one of the four phases of chronic HBV infection

## Results

Fifty-two physicians from 27 centers participated to this registry, comprising 6 academic hospitals and 21 general hospitals, and 1,456 patients were included.

### *Epidemiological characteristics of patients with chronic HBV infection*

Baseline demographic characteristics of the study population are presented in Table 1. Most (70%) patients were previously known to be HBsAg chronic carriers (prevalent cases) and 52% were of Caucasian origin.

A total of 1,035 patients (71% of the entire population) were easily classified into one of four phases of infection : 10 patients (1%) were classified as being in the immunotolerance phase, 248 (17%) in the HBeAg-positive chronic hepatitis phase and 420 (29%) were in the HBeAg-negative chronic hepatitis phase (Fig. 1). According to the definition of inactive carriers recommended in recent guidelines (restrictive definition) (2,3), 357 (25%) patients were classified as inactive carriers. A group of 421 patients (29%) remained unclassified (see Figure 1 for reasons for not classifying these patients). Among these unclassified patients, 93 could be added to the group of inactive carriers when the more clinical definition (so-called "enlarged" definition) was used (see Figure 1 and Materials and methods for more details).

Characteristics of patients classified into one of the four phases of chronic infection are given in Table 2. This Table does not include "unclassified patients", with the exception of the 93 cases considered as unclassified according to the restrictive definition of inactive carriers but who could be added to this group according to the enlarged definition. Ethnic origin, percentage of prevalent cases and risk factors for HBV infection were not different between the 357 inactive carriers according to the restrictive definition and the 93 additional inactive carriers according to the enlarged definition. Inactive carriers according to the restrictive definition were older (40 vs. 36 years, $p = 0.04$) and less frequently male (56 vs. 71% of males, $p = 0.01$) than those added to this group according to the enlarged definition. As expected with the pre-established criteria, inactive carriers defined using the restrictive definition had lower HBV DNA levels (1.778 vs. 3.215 $\log^{10}$ IU/mL, $p < 0.0001$) and lower rates of ALT > ULN (0 vs. 50%, $p < 0.0001$) than the added inactive carriers defined according to the enlarged definition.

When inactive carriers under the enlarged definition ($n = 450$) were compared with patients with HBeAg-negative chronic hepatitis ($n = 420$), inactive carriers

were younger (39 vs. 44 years, $p < 0.0001$), less frequently male (59 vs. 74%, $p < 0.0001$), had lower median HBV DNA levels (2 vs. 3.176 $\log^{10}$ IU/mL, $p < 0.0001$), were less frequently co-infected with HCV, HDV or HIV (0 vs. 14%, $p < 0.0001$), had less frequent ALT > ULN (10 vs. 50%, $p < 0.0001$), less frequent ALT > 2 ULN (0 vs. 21%, $p < 0.0001$), more frequent bilirubin ≤ 1.5 mg/dL (98 vs. 92%, $p = 0.0001$), a similar frequency of albumin > 3.5 g/dL (95 vs. 92%, $p = 0.07$), and a similar frequency of INR < 1.5 (93 vs. 93%, NS). Considering inactive carriers according to the restrictive definition did not change these results (data not shown).

When HBe-positive (n = 248) and HBe-negative (n = 420) patients with chronic hepatitis were compared, HBeAg-positive patients were younger (38 vs. 44 years, $p < 0.0001$), less frequently previously diagnosed (70 vs. 80%, $p = 0.01$), had a higher median HBV DNA level (4.580 vs. 3.176 $\log^{10}$ IU/ml, $p < 0.0001$), and more frequently ALT > 2 ULN (31 vs. 21%, $p = 0.005$). Sex ratio, ethnic origin, risk factors for HBV infection, presence of co-infection, bilirubin ≤ 1.5 mg/dL, albumin ≥ 3.5 g/dL, and INR < 1.5 did not differ in HBeAg-positive and HBeAg-negative patients with chronic hepatitis.

*Standard management of patients with chronic HBV infection by Belgian hepatologists*

HBV DNA levels and screening for viral co-infections

HBV DNA levels were assessed in 1,214 patients (83% of the cases). Co-infection with HDV, HCV and HIV was assessed in 785 (54%), 1,386 (95%) and 1,309 (90%) patients, respectively. Twenty-nine patients were co-infected with HDV (3.7% of the tested patients), 35 with HCV (2.5%) and 36 with HIV (2.8%). As 6 patients were co-infected with more than one virus, a total of 94 HBsAg-positive patients were co-infected with at least one other chronic viral infection (Table 1).

Histological examination

Liver biopsy was performed in 647 patients (44% of the patients) (Table 2). The median age at the time of liver biopsy was 39 years (95% CI : 38-41 years). Liver biopsy was more often performed in males (50 vs. 36% in females, $p < 0.0001$) and in patients with ALT > 2 ULN (75 vs. 41% in patients with ALT < 2 ULN, $p < 0.0001$). Patients who underwent a liver biopsy were also older (43 vs. 39 years, $p < 0.0001$) and had higher median HBV DNA levels (3.24 vs. 2.29 $\log^{10}$ IU/mL, $p < 0.0001$) than patients who did not have a liver biopsy. Thirty-five percents of patients had extensive fibrosis or cirrhosis (Table 1).

Among the few inactive carriers who underwent liver biopsy, those defined with the restrictive definition had median activity scores (1 vs. 0, NS) and fibrosis stages (1 vs. 1, NS) similar to those added to this group according to the enlarged definition. Seven inactive carriers defined with the restrictive definition and 1 patient added to this group according to the enlarged definition had extensive fibrosis (F3 according to METAVIR classification) or cirrhosis (Table 2). When considering patients with chronic hepatitis, median activity score and median fibrosis stage were not different between HBeAg-positive and HBeAg-negative patients. The rate of extensive fibrosis was similar. However, the rate of cirrhosis was higher in HBeAg-negative patients with chronic hepatitis (13 vs. 21% for HBeAg-positive and HBeAg-negative patients with chronic hepatitis, respectively, $p = 0.03$) (Table 2).

Table 1. — **Baseline epidemiological characteristics of the study population**

| | **n = 1,456** |
|---|---|
| Sex ratio (male, %) | 67 |
| Age (years) * | 41 (40-42) |
| Prevalent / incidental cases (%) | 70/30 |
| Origin | |
| Caucasian (%) | 52 |
| Black Africa (%) | 25 |
| Maghreb (%) | 11 |
| Asia (%) | 11 |
| Viral load ($\log^{10}$ IU/mL) * | 2.699 (2.554-2.762) |
| Co-infection (n positive/n tested) | 94/765 |
| HCV co-infection (n positive/n tested) | 35/1386 |
| HDV co-infection (n positive/n tested) | 29/785 |
| HIV co-infection (n positive/n tested) | 36/1309 |
| Combination of HCV, HDV and/or HIV (n) | 6 |
| Liver biopsy performed (n) | 647 |
| Activity score ° * | 1 (1-1) |
| Activity score ° A0-A1-A2-A3 (%) | 15-46-29-10 |
| Fibrosis stage ° * | 2 (2-2) |
| Fibrosis stage ° F0-F1-F2-F3-F4 (%) | 17-25-23-17-18 |

* Data expressed as median (95% CI)
° According to the METAVIR scoring system.

Significant predictors of extensive fibrosis or cirrhosis after adjustment for factors identified by univariate analyses were : age > 40 years ($p = 0.0001$), male sex ($p = 0.01$), HDV co-infection ($p = 0.02$), ALT > 2 ULN ($p = 0.006$) and an activity score ≥ 2 ($p = 0.006$).

Antiviral treatment

As reported in Materials and methods, questions concerning antiviral therapy sought to assess the proportion of chronic HBsAg carriers who potentially necessitated treatment. A treatment was either past, ongoing or planned in 591 patients (41%). Antiviral therapy was considered for 199 patients with chronic HBeAg-positive hepatitis (80%) and for 298 patients with chronic HBeAg-negative hepatitis (71%).

Table 2. — **Characteristics of HBsAg-positive patients classified into the four phases of chronic HBV infection**

| | Immune tolerance phase *(n = 10)* | HBeAg-positive chronic hepatitis *(n = 248)* | HBeAg-negative chronic hepatitis *(n = 420)* | Inactive carriage state (enlarged definition) *(n = 450)* | |
|---|---|---|---|---|---|
| | | | | Restrictive definition *(n = 357)* | Patients added under enlarged definition *(n = 93)* |
| Sex ratio (male, %) | 70 | 73 | 74 [d] | 56 | 71 [e] |
| Age (years) * | 29 (25-39) | 38 (35-40) [b] | 44 (42-46) [d] | 40 (38-42) | 36 (33-40) [e] |
| Ethnic origin (% Caucasians) | 10 | 58 | 54 | 49 | 47 |
| Familial / sexual transmission (%) | NA / NA | 25 / 50 | 33 / 33 [c] | 37 / 43 | 35 / 53 |
| Prevalent cases (%) | 44 | 70 [a] | 80 [d] | 64 | 56 |
| HBeAg-positive (%) | 100 | 100 [b] | 0 | 0 | 0 |
| HBeAb-positive (%) | 10 | 8 [b] | 97 | 98 | 100 |
| HBV DNA level ($log^{10}$ IU/mL) * | 8.068 (5.894-8.956) | 4.580 (4.273-5.420) [b] | 3.176 (2.965-3.372) [d] | 1.778 (1.699-2.000) | 3.215 (2.699-3.350) [f] |
| Co-infection with HCV, HDV or HIV (%) | 0 | 13 | 14 [d] | 0 | 0 |
| ALT values | | | | | |
| ALT < ULN (%) | 90 | 39 | 50 | 100 | 50 |
| ALT 1-2 ULN (%) | 10 | 30 | 29 | 0 | 50 |
| ALT 2-5 ULN (%) | 0 | 22 | 14 | 0 | 0 |
| ALT > 5 ULN (%) | 0 | 9 | 7 | 0 | 0 |
| Bilirubin < 1.5 mg/dL (%) | 100 | 93 | 92 [d] | 98 | 98 |
| Albumin > 3.5 g/dL (%) | 90 | 92 | 92 | 95 | 95 |
| INR < 1.5 (%) | 90 | 95 | 93 | 93 | 93 |
| Liver biopsy performed (n, %) | 6 (60) | 186 (78) | 298 (73) [d] | 29 (8) | 16 (17) [e] |
| Activity score ° * | 0 (0-0) | 1 (1-1) | 1 (1-2) [d] | 1 (0-1) | 0 (0-1) |
| Fibrosis stage ° * | 0 (0-0) | 2 (2-2) | 2 (2-2) [c] | 1 (0-2) | 1 (0-1) |
| Extensive fibrosis ° (n, %) | 0 (0) | 34 (19) | 53 (18) [c] | 2 (7) | 0 (0) |
| Cirrhosis ° (n, %) | 0 (0) | 23 (13) [a] | 60 (21) | 5 (17) | 1 (6) |

* Data expressed as median (95% CI).
° According to the METAVIR scoring system.
NA, not available.
[a] $p < 0.05$ and [b] $p \leq 0.0001$ for comparison between HBeAg-positive and HBeAg-negative patients with chronic hepatitis.
[c] $p < 0.05$ and [d] $p \leq 0.0001$ for comparison between HBeAg-negative patients with chronic hepatitis and inactive carriers defined according to the enlarged definition.
[e] $p < 0.05$ and [f] $p \leq 0.0001$ for comparison between inactive carriers defined with restrictive definition and inactive carriers added according to the enlarged definition.

Surveillance for hepatocellular carcinoma

Ultrasonographic surveillance of HBsAg-positive patients was scheduled for 94% of patients whatever the stage of chronic HBV infection. In almost all cases, it was planned in combination with alfa-fetoprotein measurements. Surveillance was scheduled every 6 months for 60% of patients with chronic hepatitis, for 26 and 28% of inactive carriers according to the restrictive definition and those added to this group according to the enlarged definition, respectively ($p < 0.001$), and yearly for all other cases. In patients with biopsy-proven cirrhosis, ultrasonographic surveillance was planned every 6 months in 95% of cases.

## Discussion

This large nation-wide cross-sectional registry of HBsAg-positive patients conducted over a one-year period prospectively included 1,456 patients. This was a real-life registry, with no stringent inclusion criteria. It did not suffer from major referral biases ; thus, results provide a valid indication of chronic HBV infection in Belgium. As in other European studies, many patients were inactive carriers (1,16), and HBeAg-negative hepatitis was the most common form of chronic hepatitis B (1,17-22). One remarkable finding of this study is the low proportion of patients within the immune

tolerance phase. One explanation could be that we applied strict criteria to classify patients into one of the four stages of HBV infection (see Methods).

One advantage of the registry was to be able to identify inactive carriers in clinical practice. We compared the restrictive definition of inactive carriers currently recommended in most guidelines (HBeAg-negative, HBV DNA < 2,000 IU/mL and normal ALT levels) (2,3) with a less restrictive but probably more useful definition (HBeAg-negative, HBVDNA < 20,000 IU/mL and normal ALT values *or* HBVDNA levels < 2,000 IU/ml and ALT < 2 ULN). Using enlarged criteria, 93 initially unclassified patients (6.4% of all HBsAg-positive patients) could be included in the inactive carrier state (Fig. 1). These 93 patients added to the inactive carrier group showed characteristics (including histological characteristics) similar to those of the 357 inactive carriers according to restrictive criteria. Because these 93 patients had all been considered inactive carriers by their personal physician and as most of the collected data did not differ between inactive carriers according to the two classifications, enlarged criteria seemed more appropriate for defining an inactive carrier state in clinical practice, although there is no definite proof of this concept. However, since long-term follow up was not available, we cannot be sure that patients with enlarged criteria remained inactive carriers several years later. At first glance, it may appear surprising that some patients defined as inactive carriers (7 with restrictive criteria and 1 with enlarged criteria) had extensive fibrosis or cirrhosis. This suggests that some of them had significant histological lesions despite a low HBV replication phase (10). In view of the dynamic natural history of chronic HBV infection, it is likely that such lesions had developed during a previous phase of HBeAg-positive chronic hepatitis. Considering inactive carriers according to restrictive criteria did not change this result. However, due to the cross-sectional design of this study, histological data cannot really help to classify patients into one of the four stages of HBV infection.

Although HBeAg-negative patients with HBV DNA > 2,000 IU/mL or ALT > ULN may have a higher risk of developing chronic hepatitis B and should undergo more regular follow-up (23), it is generally accepted that HBV DNA levels and ALT values cannot always differentiate inactive from active chronic carriers (6,10,24). In our opinion, there are two reasons why currently recommended criteria lack sensitivity for identification of inactive carriers. First, some HBeAg-negative patients with normal ALT and HBV DNA > 2,000 IU/mL do not have chronic hepatitis (7,8), and it is interesting to note that recent studies and reviews also used higher HBV DNA cut-offs for identification of inactive carriers (1,24,25). Secondly, since ALT is not a specific marker of chronic hepatitis B activity, a slight rise in ALT levels may be observed in some HBeAg-negative patients with HBV DNA < 2,000 IU/mL (10). In those cases, it is unlikely that a rise in ALT reflected active chronic hepatitis B, but rather, indicated other features such as those related to metabolic syndrome (9-11). However, regular follow-up over several years remains mandatory before a patient can be considered a long-term inactive carrier (26,27).

This registry also provided insight into how Belgian physicians manage HBV patients. European clinical practice guidelines on management of chronic hepatitis B recommend HBV DNA detection and measurement of HBV DNA levels in all chronically infected HBV patients (28). In that registry, 83% of patients underwent HBV DNA determination, indicating that this recommendation was not systematically followed. In addition, HDV co-infection was assessed in only 54% of patients, while HCV and HIV co-infection were assessed in more than 90%. One explanation could be that analysis of HDV antibodies is available in only a few laboratories in Belgium. That registry also revealed that treatment was considered in 41% of patients, mainly those with chronic hepatitis (70 to 80%). Regarding surveillance for hepatocellular carcinoma, most chronically infected HBV patients underwent ultrasonography at least once a year, and cirrhotic patients were screened every 6 months in almost all cases, as recommended in guidelines.

This work had several limitations. Due to its cross-sectional design, our registry provided a view of HBV infection in Belgium in 2008-2009, but data on long-term evolution were not available. In addition, due to the real-life design of this work and the number of participating physicians, the decision to perform liver biopsy was heterogeneous. Finally, other non-invasive means of fibrosis assessment, such as transient elastography, were not regularly performed and thus could not help in classifying patients into one of the four stages of chronic HBV infection.

In conclusion, in Belgium, an inactive carrier state was a frequent form of chronic HBV infection, while HBeAg-negative chronic hepatitis was the most frequent form of chronic hepatitis B. Defining inactive carriers with a less restrictive cut-off for either HBV DNA (< 20,000 IU/mL) or ALT values (< 2 ULN) did not modify their main characteristics and seemed better suited for clinical practice. However, enlarged criteria cannot be used in a new definition of the long-term inactive carrier state ; indeed, the latter necessitates both the absence of active disease and low HBV DNA levels over a period of several years. Thus, regular follow-up remains mandatory. Recent clinical guidelines seemed to be followed satisfactorily, but systematic HBV DNA measurements and screening for HDV co-infection should be reinforced.

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## Disclosures

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

## References


1. CADRANEL J.F., LAHMEK P., CAUSSE X., BELLAICHE G., BETTAN L., FONTANGES T. *et al*. Epidemiology of chronic hepatitis B infection in France : risk factors for significant fibrosis-results of a nation-wide survey. *Aliment. Pharmacol. Ther.*, 2007, **26** : 565-576.
2. FATTOVICH G., BORTOLOTTI F., DONATO F. Natural history of chronic hepatitis B : special emphasis on disease progression and prognostic factors. *J. Hepatol*., 2008, **48** : 335-352.
3. ROTMAN Y., BROWN T.A., HOOFNAGLE J.H. Evaluation of the patient with hepatitis B. *Hepatology*, 2009, **49** : S22-27.
4. CHU C.J., HUSSAIN M., LOK A.S. Quantitative serum HBV DNA levels during different stages of chronic hepatitis B infection. *Hepatology*, 2002, **36** : 1408-1415.
5. CHU C.J., LOK A.S. Clinical utility in quantifying serum HBV DNA levels using PCR assays. *J. Hepatol*., 2002, **36** : 549-551.
6. YUEN M.F., YUAN H.J., WONG D.K., YUEN J.C., WONG W.M., CHAN A.O., *et al*. Prognostic determinants for chronic hepatitis B in Asians : therapeutic implications. *Gut*, 2005, **54** : 1610-1614.
7. LIN C.L., LIAO L.Y., LIU C.J., YU M.W., CHEN P.J., LAI M.Y. *et al*. Hepatitis B viral factors in HBeAg-negative carriers with persistently normal serum alanine aminotransferase levels. *Hepatology*, 2007, **45** : 1193-1198.
8. CHU C.M., CHEN Y.C., TAI D.I., LIAW Y.F. Level of hepatitis B virus DNA in inactive carriers with persistently normal levels of alanine aminotransferase. *Clin. Gastroenterol. Hepatol*., 2010, **8** : 535-540.
9. KIM H.C., NAM C.M., JEE S.H., HAN K.H., OH D.K., SUH I. Normal serum aminotransferase concentration and risk of mortality from liver diseases : prospective cohort study. *BMJ*, 2004, **328** : 983.
10. KUMAR M., SARIN S.K., HISSAR S., PANDE C., SAKHUJA P., SHARMA B.C. *et al*. Virologic and histologic features of chronic hepatitis B virus-infected asymptomatic patients with persistently normal ALT. *Gastroenterology*, 2008, **134** : 1376-1384.
11. PITON A., POYNARD T., IMBERT-BISMUT F., KHALIL L., DELATTRE J., PELISSIER E. *et al*. Factors associated with serum alanine transaminase activity in healthy subjects : consequences for the definition of normal values, for selection of blood donors, and for patients with chronic hepatitis C. MULTIVIRC Group. *Hepatology*, 1998, **27** : 1213-1219.
12. BEUTELS M., VAN DAMME P., AELVOET W., DESMYTER J., DONDEYNE F., GOILAV C. *et al*. Prevalence of hepatitis A, B and C in the Flemish population. *Eur. J. Epidemiol*., 1997, **13** : 275-280.
13. QUOILIN S., HUTSE V., VANDENBERGHE H., CLAEYS F., VERHAEGEN E., DE COCK L. *et al*. A population-based prevalence study of hepatitis A, B and C virus using oral fluid in Flanders, Belgium. *Eur. J. Epidemiol*., 2007, **22** : 195-202.
14. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. *Hepatology*, 1994, **20** : 15-20.
15. BEDOSSA P., POYNARD T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *Hepatology*, 1996, **24** : 289-293.
16. STEFOS A., GATSELIS N., ZACHOU K., RIGOPOULOU E., HADJICHRISTODOULOU C., Dalekos G.N. Descriptive epidemiology of chronic hepatitis B by using data from a hepatitis registry in Central Greece. *Eur. J. Intern. Med*., 2009, **20** : 35-43.
17. HADZIYANNIS S.J., VASSILOPOULOS D. Hepatitis B e antigen-negative chronic hepatitis B. *Hepatology*, 2001, **34** : 617-624.
18. BRUNETTO M.R., OLIVERI F., COCO B., LEANDRO G., COLOMBATTO P., GORIN J.M. *et al*. Outcome of anti-HBe positive chronic hepatitis B in alpha-interferon treated and untreated patients : a long term cohort study. *J. Hepatol*., 2002, **36** : 263-270.
19. ZARSKI J.P., MARCELLIN P., LEROY V., TREPO C., SAMUEL D., GANNE-CARRIE N. *et al*. Characteristics of patients with chronic hepatitis B in France : predominant frequency of HBe antigen negative cases. *J. Hepatol*., 2006, **45** : 355-360.
20. HADZIYANNIS S.J., PAPATHEODORIDIS G.V. Hepatitis B e antigen-negative chronic hepatitis B : natural history and treatment. *Semin. Liver Dis*., 2006, **26** : 130-141.
21. MANESIS E.K. HBeAg-negative chronic hepatitis B : from obscurity to prominence. *J. Hepatol*., 2006, **45** : 343-346.
22. RAPTOPOULOU M., PAPATHEODORIDIS G., ANTONIOU A., KETIKOGLOU J., TZOURMAKLIOTIS D, VASILIADIS T. *et al*. Epidemiology, course and disease burden of chronic hepatitis B virus infection. HEPNET study for chronic hepatitis B : a multicentre Greek study. *J. Viral Hepat*., 2009, **16** : 195-202.
23. ZACHARAKIS G., KOSKINAS J., KOTSIOU S., TZARA F., VAFEIADIS N., PAPOUTSELIS M. *et al*. The role of serial measurement of serum HBV DNA levels in patients with chronic HBeAg(-) hepatitis B infection : association with liver disease progression. A prospective cohort study. *J. Hepatol*., 2008, **49** : 884-891.
24. PAPATHEODORIDIS G.V., MANESIS E.K., MANOLAKOPOULOS S., ELEFSINIOTIS I.S., GOULIS J., GIANNOUSIS J. *et al*. Is there a meaningful serum hepatitis B virus DNA cutoff level for therapeutic decisions in hepatitis B e antigen-negative chronic hepatitis B virus infection ? *Hepatology*, 2008, **48** : 1451-1459.
25. YIM H.J., LOK A.S. Natural history of chronic hepatitis B virus infection : what we knew in 1981 and what we know in 2005. *Hepatology*, 2006, **43** : S173-181.
26. MANNO M., CAMMA C., SCHEPIS F., BASSI F., GELMINI R., GIANNINI F. *et al*. Natural history of chronic HBV carriers in northern Italy : morbidity and mortality after 30 years. *Gastroenterology*, 2004, **127** : 756-763.
27. VILLA E., FATTOVICH G., MAURO A., PASINO M. Natural history of chronic HBV infection : special emphasis on the prognostic implications of the inactive carrier state versus chronic hepatitis. *Dig. Liver. Dis*., 2011, 43, Suppl 1 : S8-14.
28. Liver EAFTSOT. EASL Clinical Practice Guidelines : management of chronic hepatitis B. *J. Hepatol*., 2009, **50** : 227-242.