

Diagnosis and treatment of hepatitis B. What contributions can prisons make?

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ABSTRACT

Hepatitis B is a parenterally and sexually transmitted infection. Vaccination for the disease is highly effective, and its inclusion in Spain as part of a systematic and universal schedule for newborns has led to a significant decrease of incidence in the national population. However, the number of inmates born in other countries - some from endemic areas of HBV infection -, the mechanisms of transmission and lack of vaccination in third world countries mean that its prevalence in the prison population is higher than in the general population. These institutions therefore play an essential role in detecting and managing hepatitis B. In this paper, the situation of hepatitis B in prisons is reviewed and recommendations are proposed to optimize its control.

Keywords: prisons; hepatitis B; vaccination; prevention and control.

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INTRODUCTION

Chronic hepatitis B virus infection (CHBVI) is a major international issue. Every year, 1.4 million people die from viral hepatitis (47% after contracting hepatitis B). It is estimated that there are currently 240 million people with CHBVI worldwide¹. Such figures are deeply worrying; not least in view of the fact that there is a highly effective vaccine. However, it is not widely available, given it is only included in the vaccination programmes of developed countries.

In Spain, acute hepatitis B virus infection has been a reportable disease since 2014. The number of notifications has dropped noticeably in recent years. This is believed to be due to vaccination and the corresponding drop in incidence, which has been observed in some regions in Spain². However, a recently published Spanish study showed that the most common cause of acute viral hepatitis continues to be hepatitis B (20% of all cases³).

Recent figures place Spain at a low level of endemicity, with a rate of acute HBV infection of 0.84 per 100,000 inhabitants⁴, thanks to the introduction of vaccination amongst vulnerable groups in the late 1980s and universal administration of the vaccine in the 90s. Other measures that have also contributed to a progressive reduction of the prevalence of this infection include blood transfusions checks and systematic detection of serological results in pregnant patients. However, when the diagnosis is made, treatment is not always uniform and immigrant populations have less access to antiviral medication, probably due to factors such as the language barrier or difficulties in adhering to treatment because of their work or social situation⁵.

HBV AND PRISON

The epidemiology of hepatitis B in prisons is not always uniform, given the variations in the socio-

economic level and public health programmes of the country where the prison is located.

In the USA, a report on the infectious disease load amongst inmates and recently released persons showed a prevalence of hepatitis B that was five times higher than in the community⁶. Despite these figures, some federal prisons in the USA do not offer routine anti-HBV vaccination, as is the case in other countries⁷.

The prison population in Spain presents a higher risk of infection, due to factors such as: background (for example: in December 2020 there were 3,780 foreign inmates in Catalonian prisons, many of whom were from countries with highly endemic levels of hepatitis B⁸), or a background of drug abuse (13.7% of prison inmates in Spain report having consumed drugs intravenously “at some time in their lives”⁹) However, the risk of infection is progressively decreasing in both populations thanks to vaccination programmes.

As mentioned in a number of reviews^{7,10}, the prevalence of CHBVI in prisons varies greatly, ranging from percentages below 1% to as much as 23-25% amongst inmates of prisons in countries such as Ghana or Nigeria. The prevalence of this group in Spain has dropped considerably (Table 1), due more than anything to systematic vaccination of this group, which commenced more than 30 years ago¹¹. A study in 1990 of young inmates in Catalonia (under 21 years of age), showed a prevalence of CHBVI of 7.5%¹². Two subsequent studies, in 2007¹³ and 2014¹⁴, agree when they show that prevalence went down considerably. The figures at that time were approximately 2.6%, although one of the studies¹⁴ found significant differences in the prevalence of infection between Spanish and foreign inmates (1.5% and 3.8%, respectively).

In a recent study, Chahal et al., used a Markov model to analyse the cost and efficacy of a vaccination and treatment strategy in populations with a high risk of presenting CHBVI, which included incarcerated patients. The results showed more profitability if management included both vaccination and treatment¹⁵. It is therefore necessary to ensure that this population has access to preventive measures and treatment during incarceration, and to guarantee

continuity when inmates are released¹⁶, given that this process provides both individual benefits by reducing morbidity and mortality, along with collective benefits thanks to reduced transmission of the disease.

NATURAL HISTORY OF CHBVI

HBV is a DNA virus that infects only mammals. It is a common cause of acute and chronic liver disease and can develop into a hepatocellular carcinoma through integration into the hepatocyte genome. HBV is not cytopathic in and of itself. Its capacity to do harm depends on the inflammatory process caused by the immune system¹⁷, to the extent that chronic conditions depend on an attenuated response to the viral antigens expressed on the cell surface.

The basic factor associated with chronicity is age. Patients infected at birth show chronicity in 90% of cases, 30% show chronicity if they acquire the disease between 1 and 5 years of age, while <5% of adult immunocompetent patients show chronicity after infection. CHBVI turns into liver cirrhosis in 20-30% of cases and 0.3-2.2% develop liver cancer^{18,19} with a lifetime probability of 10-25%.

When the infection is diagnosed, it is important to determine the surface antigen of hepatitis B (HBsAg), the e antigen (HBeAg), the antibody and to quantify the viral load via the HBV-DNA. This data can be used to establish the phase of the CHBVI, although such data is dynamic and can change over time. Determining the phases of the CHBVI can be complex and often requires specialised personnel.

The phases of CHBVI can be seen in Table 2.

Phase 1 of positive VHB_eAg chronic infection

This phase is distinguished by normal levels of alanine aminotransferase (ALT), very high HBV-DNA and the absence of histological changes, since the immune system does not create an inflammatory process. It is usually common amongst young people who have generally acquired the infection from

Table 1. Studies of prevalence of chronic hepatitis B virus infection in the Spanish prison population.

Population (n)	Year	Region	Prevalence	Reference
Inmates of 16-21 years (686)	1989	Catalonia	7.6%	Bayas JM et al. ¹¹
Inmates of 18 prisons (342)	2011	Spain	2.6%	Saiz de la Hoya P et al. ¹²
Inmates of 9 prisons (7,704)	2014	Catalonia	2.6%*	Marco A et al. ¹³

Note. *1.5% amongst Spaniards compared to 3.8% amongst foreign inmates.

vertical transmission, and the sero-rate to negative HBeAg is very low. The high viral load makes hepatocellular carcinoma screening a recommendable measure.

Phase 2 of positive VHBsAg chronic hepatitis

Characterised by high levels of ALT and HBV-DNA, and a progression of fibrosis that can evolve into liver cirrhosis (LC). If it affects adults, the fibrosis progresses more rapidly.

Phase 3 of negative VHBsAg chronic hepatitis

Inflammatory activity persists in some patients even in the absence of HBeAg positivity. This phenomenon is mostly due to the presence of certain mutations of the genome that stop infected hepatocytes from producing HBeAg.

This phase is characterised by fluctuating levels of ALT and HBV-DNA that in some cases may be normal. Therefore it is important for the tests to be carried out sequentially to ensure correct categorisation. This phase is more common in the Mediterranean area and Asia, and is common in our region.

Phase 4 of negative HBeAg chronic infection (previously inactive carrier)

This phase is defined by persistently normal ALT values and low levels of HBV-DNA (generally below 2,000 UI/mL, although some patients present values of between 2,000 and 20,000 UI/mL). Quantifying the level of HBsAg can help in differentiating this phase from patients situated in the “grey zone” (ALT normal or <1.5 above the upper limit of normality with oscillating HBV-DNA at >20,000 UI/mL). A quantified level of HBsAg below 1.000 UI/mL is highly suggestive of negative HBeAg chronic infection^{20,21}. The long-term prognosis of patients in this phase is good, although the infection sometimes reactivates with increases in levels of HBV-DNA and ALT, which makes it advisable to monitor these parameters at least once a year.

There is an additional phase of functional improvement that takes place with the loss of HBsAg, with or without anti-HBs and positive anti-HBc. It is characterised by normal ALT values, generally, undetectable levels of serum HBV-DNA. However, covalent, circular and closed (cccDNA) DNA can be detected in the liver.

The loss of HBsAg in patients with advanced fibrosis is associated with a minimal risk of HC, decompensation and HCC and improved survival. However, if the LC has developed before the loss of HBsAg, patients still run a risk of developing HCC. It is important to remember that HBV replication may reactivate in this phase and in contexts of immunosuppression (caused by administering chemotherapy or biopharmaceuticals), which makes it important to assess the use of antiviral medication according to the risks involved in such cases^{22,23}.

DIAGNOSTIC EVALUATION OF HEPATITIS B

Diagnosis is based on: clinical history, physical examination, biochemical parameters, HBV serological markers, determination of HBV-DNA, ultrasound studies and overall evaluation of fibrosis, using non-invasive methods, although a liver biopsy may be necessary in some cases.

Tools for diagnosing hepatitis B:

- Biochemical parameters: these should include serological tests that enable the presence of concomitant infections (chronic hepatitis from HCV or HDV or HIV infection) to be discounted. Other liver diseases also need to be ruled out, such as haemochromatosis (levels of iron, ferritin and transferrin saturation levels) or autoimmune hepatitis (antinuclear antibody tests).
- Serological markers: basic for establishing the phase of the CHBVI.
- Abdominal ultrasound: to confirm/rule out LC and HCC.
- Evaluation of liver fibrosis:

Table 2. Phases of chronic hepatitis B.

Nomenclature	Positive HBeAg		Negative HBeAg	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
DNA-HBV	>10,000	20,000-10,000.000	<2,000 (or <20,000)	>2,000 (or >20,000)
ALT	Normal	High	Normal	High
Histología	Normal	Changed	Normal	Changed

Note. DNA: deoxyribonucleic acid; ALT: alanine aminotransferase; HBeAg: hepatitis B antigen; HBV: hepatitis B virus.

- Transient elastography (TE) or FibroScan®: used to establish the degree of liver fibrosis. It is now the most commonly used non-invasive procedure. It should be borne in mind that TE presents some particular features in chronic HBV infection and that the cut-off values are lower than in hepatitis C. A transient elastography groups patients with CHBVI into four classes of fibrosis (mean approximate values plus 1-2 more points for high transaminases): not significant (<6 kilopascals [kPa], grey zone (6-9 kPa), significant (>9 kPa) and cirrhosis (>12 kPa).
- Liver biopsy: TEs have brought about a considerable reduction in the use of liver biopsies. However, a meta-analysis has concluded that the diagnostic precision of the TE is greater in excluding the presence of LC²⁴ than in confirming it. Accuracy is directly related to the ALT levels, and so the higher the ALT, the greater the dispersal between the biopsy and the TE²⁵.

Other methods such as the use of non-invasive serological markers (e.g. aspartate aminotransferase-to-platelet ratio index [APRI] and/or fibrosis-4 [FIB-4]) have shown a very moderate correlation with the level of liver fibrosis. This means that their use in hepatitis B is not very advisable²⁶.

- Liver biopsy: the gold standard in evaluating the level of fibrosis, which makes it a recommendable option for patients in the grey zone to assess the risk of progression and any possible need for antiviral treatment.

TREATMENT OF CHBVI

As I mentioned above, the phase of infection in patients with CHBVI needs to be determined, while an evaluation of the level of fibrosis and an initial ultrasound to rule out other pathologies and the presence of HCC is also required.

The general aim of the treatment is to improve the patient's quality of life and survival, preventing the disease from progressing to cirrhosis, terminal liver disease, HCC and death²⁷. However, technically speaking and in more concrete terms, the aim of the treatment is the transition from immunoactive to immunoinactive, as this leads to a lower rate of clinical progression. The ideal outcome is the clearance of the HBsAg (functional cure), which only takes place in a small proportions of patients undergoing treatment²⁸. It should be borne in mind that

total eradication of the infection is impossible, given the persistence in the cells of cccDNA in the nucleus of the hepatocytes²⁹.

The need (or not) to prescribe treatment, and determining the phase of infection, are often complex issues and, as I mentioned above, require specialised personnel.

There are two clinical practice guides published by the European Association for the Study of the Liver (EASL)³⁰ and the American Association for the Study of Liver Diseases (AASLD)³¹ that contain, with some differences, the main recommendations for managing and treating patients with CHBVI. The therapeutic criteria are based on three parameters: ALT levels, HBV-DNA levels and the level of cellular damage based on liver biopsies and non-invasive methods. At least two of the three criteria need to be met to prescribe treatment, such as higher than normal ALT levels, HBV-DNA levels of >20.000U/L and/or a grade of fibrosis that is 2 or higher²⁹.

Generally speaking, patients with chronic hepatitis, both positive HBeAg and negative HBeAg, have treatment indications, while others who present chronic infection require regular monitoring. Treatment for the latter case is recommended only in special situations: if there is detectable cirrhosis and HBV-DNA, if they are cases with a family background of HCC and if immunosuppressant or immunomodulating treatment is prescribed.

HBV/HIV co-infected patients should also maintain an anti-retroviral therapy that includes tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF). Figure 1 shows systematised cases with or without indications for antiviral treatment according to EASL recommendations.

There are two types of approved drugs for treating CHBVI:

- Conventional 2a and 2b interferons and the 2a pegylated form. The second treatment is the one most commonly used, due to greater ease of administration (one weekly dose instead of three), greater efficacy and better tolerance.
- Nucleoside analogues (lamivudine [LAM], entecavir [ETV], telbivudine [TBV]) and nucleos(t)ides (adefovir dipivoxil [ADV], and two tenofovir prodrugs: TDF and TAF). The use of LAM, ADV y TBV, is currently not recommended because of the low genetic barrier and the risk of resistant mutations appearing. As regards TAF, which has been approved by the European Medicines Agency since 2017, there is no reimbursement price in Spain for CHBVI treatment in patients not infected by HIV.

Pegylated interferon

Treatment with pegylated interferon alfa-2a is based on a twofold antiviral and immunostimulant action, which enables higher rates of functional cures than nucleos(t)ide analogues. One advantage of this approach is its the fixed treatment period: 48 weeks³⁰. However, it does have some disadvantages that can limit use: adverse effects, parenteral administration (subcutaneous), low antiviral activity and a wide range of contraindications. However, it is the only treatment to show a certain degree of efficacy in patients co-infected with HBV and HIV.

Nucleos(t)ide analogues

Nucleos(t)ide analogues are now the pillars of CHBVI treatment. Current recommendations are: ETV at doses of 0.5 mg/day (1 mg/day if there is resistance to lamivudine); and TDF at doses of 245 mg/day. Both are administered orally and require dosage adjustments in the event of kidney failure if glomerular filtration is <50 mL/day, as indicated in the data sheet. The efficacy of both drugs in bringing about a response that is biochemical (normalisation

of ALT) and virological (clearance of HBV-DNA) is over 95%^{32,33}.

Treatment is prolonged, with an initially indefinite duration, and adherence is essential to prevent another resurgence of infection if the patient abandons treatment. Some rather controversial decisions were recently made to withdraw treatment under the following conditions, as long no previously existing LC had been established:

- In patients with positive HBeAg, if there is seroconversion with undetectable DNA for at least 12 months.
- In patients with negative HBeAg, if viral suppression has been maintained for ≥3 years of treatment³⁰.

Evolution should be closely monitored if the decision is made to discontinue treatment. Some patients who stop taking nucleotide analogues present functional cures with clearance of the HBsAg, but there are cases where the biochemical and/or virological reactivation makes it necessary to recommence treatment, although it appears that on occasions such as these that the patients present a response to treatment, without liver failure^{34,35}.

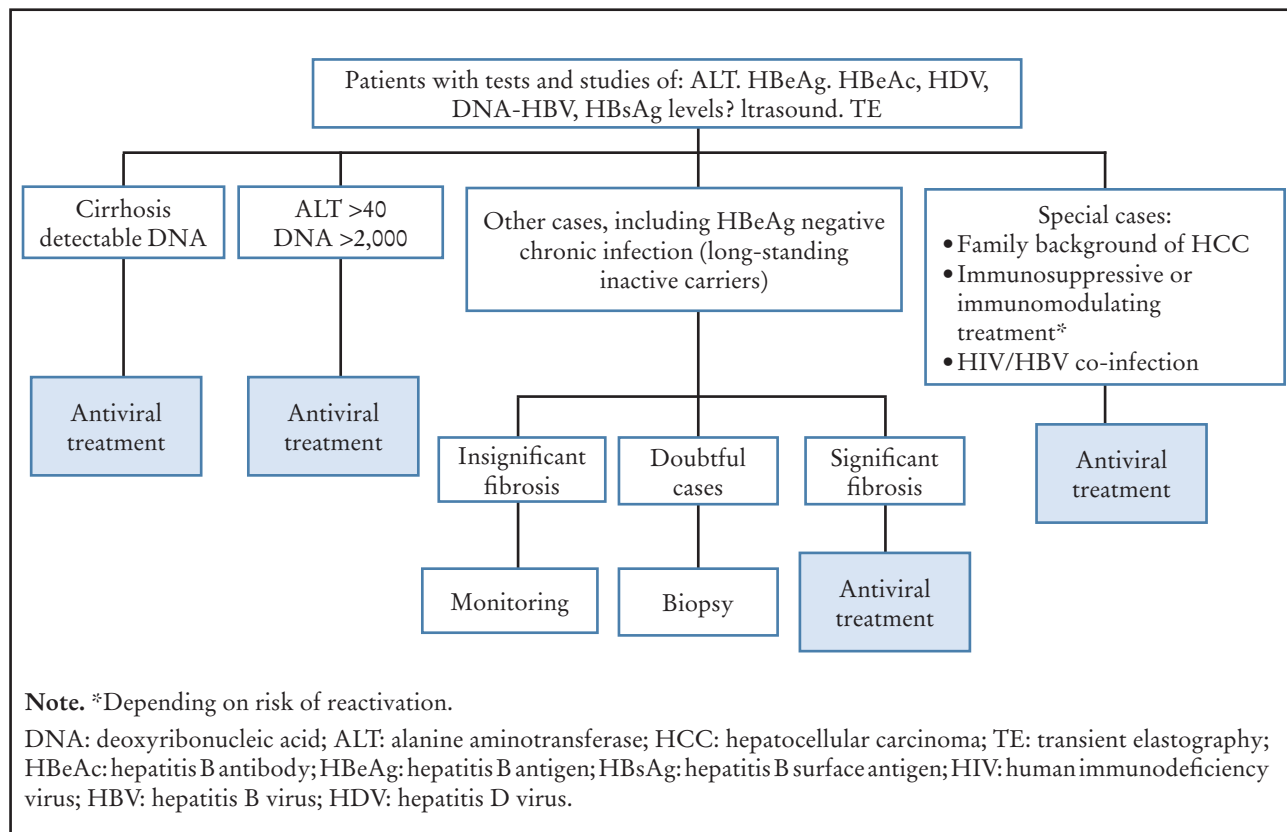


Figure 1. Antiviral treatment indications for hepatitis B.

However, the data should be confirmed with studies that include more patients and more monitoring.

Patients who have been treated for many years with nucleos(t)ide inhibitors have been found to reverse LC, prevent HCC and not require liver transplants³⁶.

PREVENTION AND SCREENING INDICATIONS FOR HCC

The primary prevention of HCC in patients with CHBVI is based on anti-hepatitis B vaccination²⁹, while the secondary approach consists of prescribing antiviral treatment in line with current recommendations^{29,30}. Clinicians are generally aware that people born in Spain before 1980 are not vaccinated, while those born between 1980 and 1998 may not be. From 1998 onwards universal vaccination has been the norm for newborns in Spain.

LC is the main risk factor in the development of HCC³⁷. However, hepatitis B infection is a risk factor for HCC even in the absence of LC. The degree of risk has yet to be defined and depends on a number of factors such as origin (more common amongst persons from Africa and Asia than Europe), levels of HBV-DNA and gender (more common amongst men than women). There are other factors associated with CHBVI that can also act as predictors: positive HBeAg, high viral load and the C genotype³⁸⁻⁴⁰.

HCC screening should be carried out on the population when the risk is at least 0.2% a year. On the other hand, when antiviral treatment is started in patients at risk, the regression of fibrosis and the undetectable nature of the HBV-DNA make for a certain degree of uncertainty in terms of when to start treatment and when it is no longer necessary to screen such patients for HCC. The most recommendable measure would be to more closely monitor patients with a background of first degree family members with HCC or with an earlier acquisition of the infection. On the other hand, the risk should be evaluated individually in populations who come from highly endemic areas, given that the impact in such cases has not been well established.

A number of indices have been developed and validated that evaluate the risk of developing HCC in patients with CHBVI and antiviral treatment. One of the most commonly used ones is the PAGE-B, validated in Caucasian patients receiving treatment with nucleos(t)ide analogues, with a good predictive capacity for the development of HCC in the first five years of treatment with ETV or TDF. This index

(Table 3) can be easily applied in clinical practice because it is based on easily available parameters (platelets, age, sex). The accumulated probability of developing HCC at five years in patients with low, moderate and high risk was 0%, 3% and 17%, respectively⁴¹, but the incidence does not appear to depend on the type of nucleos(t)ide analogue used⁴².

A new index has been recently developed and validated that evaluates age, sex, the presence of CH and albumen levels to determine the risk of developing HCC in patients receiving treatment with ETV or TDF. The results have been compared to other indices such as PAGE-B and RESCUE-B and obtain better predictive data⁴³, although external validation studies are needed to confirm them.

Screening should be carried with a six-monthly ultrasound scan. The justification for carrying out the scan on a six-monthly basis is based on the estimate that the time taken by the HCC to double in size is 4-6 months. Other commonly used parameters, such as determining plasma alpha-fetoprotein (AFP), are more controversial nowadays and are not recommended by the EASL or the AASLD, since it is calculated that 20-40% of patients with HCC do not present increases of AFP, and between 20 and 30% of patients with no HCC do have abnormal AFP. However, when there is a high AFP, the presence of HCC needs to be ruled out, since AFP levels are a prognostic factor of mortality in confirmed cases of HCC.

WHAT CONTRIBUTIONS CAN PRISONS MAKE TOWARDS DETECTING AND MANAGING HEPATITIS B?

Prisons are important locations for the control of hepatitis B and other infectious diseases, thanks to a number of factors listed below:

- They are ideal epidemiological observatories of the evolution of HBV infection and other infectious diseases in sentinel populations, such as drug users or illegal immigrants, many of whom come from countries with high endemic levels of HBV.
- Systematic and universal screening programmes can be carried out for infections that are highly prevalent in this group, thus guaranteeing the detection of hidden infections.
- Access can be facilitated to groups who sometimes do not make use of conventional healthcare resources and others who are key players in transmitting the infection.
- Awareness-raising and educational activities and programmes can be developed, alongside specific

Table 3. PAGE-B model for predicting development of hepatocellular cancer in Caucasian patients treated with nucleotide/nucleoside analogues.

Variable	Score	Assessment of risk of HCC
Age		
16-29	0	≤9: low
30-39	2	
40-49	4	10-17: moderate
50-59	6	
60-69	8	
>70	10	≥18: high
Sex		
Male	6	
Female	0	
Platelets		
≥200,000	0	
100,000-199,000	6	
≤100,000	9	

HCC: hepatocellular carcinoma.

preventive measures, such vaccination of groups who often engage in high-risk practices.

- Harm reduction strategies for drug users can be implemented or continued if they have already been set in motion.
- They can help in the general treatment of infected patients, especially in diagnosing and treating high priority groups such as HIV/HBV co-infected inmates and “difficult” patients, such as IDUs, illegal immigrants and the mentally ill.
- They can link patients who have been recently detected or who already have a clinical record of HBV with medical services outside prison via healthcare continuum programmes after they are released.

Prisons can play a major role in eliminating B. This was highlighted in the *Guidelines for better management of hepatitis B in Spain*⁴⁴, which includes recommendations taken from a European document adapted to the Spanish situation by the Hepatitis B Study Group (*Grupo de Estudio de la Hepatitis B*)⁴⁴. If such recommendations are applied by social agents, policy makers and healthcare professionals, then hepatitis B would receive the necessary balanced attention in Spain and throughout the EU.

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