

BRIEF REPORT

Impact of hepatitis D reflex testing on the future disease burden: A modelling analysis

Maria Buti^{1,2} | Raquel Domínguez-Hernández³ | Adriana Palom^{1,2}  | Rafael Esteban^{1,2} | Miguel Ángel Casado³

¹Liver Unit, Hospital Universitari Vall d'Hebron, Barcelona, Spain

²CIBERHERD, Instituto de Salud Carlos III, Madrid, Spain

³Pharmacoeconomics & Outcomes Research Iberia (PORIB), Madrid, Spain

Correspondence

Maria Buti, Liver Unit, Hospital Universitari Vall d'Hebron, Passeig Vall d'Hebron 119-129, Barcelona 08035, Spain.

Email: mariaasuncion.butivallhebron.cat

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Abstract

Chronic hepatitis D (CHD) is a severe form of viral hepatitis that leads to liver cirrhosis and hepatocellular carcinoma. CHD is underdiagnosed, and this study aimed to assess the impact of hepatitis D reflex testing in HBsAg-positive individuals in Spain over the next 8 years. Two scenarios were compared: the current situation (7.6% of HBsAg-positive patients tested for anti-HDV) and reflex testing for all positive samples. A decision tree model was designed to simulate the CHD care cascade. Implementing reflex testing would increase anti-HDV detection to 5498 cases and HDV-RNA to 3225 cases. Additionally, 2128 more patients would receive treatment, with 213 achieving undetectable HDV-RNA levels. The cost per anti-HDV case detected would be €132. In the median time of the analysis, liver complications (decompensated cirrhosis, HCC and liver-related deaths) would be reduced by 35%–38%, implying an estimated cost savings of 36 million euros associated with the management of such complications. By 2030, implementing anti-HDV reflex testing would reduce the clinical and economic burden of CHD by 35%–38%.

KEYWORDS

burden, hepatitis D virus (HDV), reflex testing, screening

1 | INTRODUCTION

Chronic hepatitis D (CHD), the most severe form of chronic viral hepatitis, can rapidly progress to liver cirrhosis and hepatocellular carcinoma. The epidemiology of hepatitis D virus (HDV) infection is still controversial and incompletely understood. HDV is endemic in certain geographic areas, whereas in others, it is predominantly confined to high-risk groups such as people who inject drugs and migrants from HDV-endemic countries.¹

The peculiar distribution of HDV infection explains why international guidelines have different recommendations for hepatitis

D testing. The 2017 European Association for the Study of the Liver (EASL) recommends testing all hepatitis B surface antigen (HBsAg)-positive people for anti-HDV antibodies.¹ Adherence to this recommendation has not been widely evaluated. A study in the Northern area of Barcelona (Spain) showed that anti-HDV was tested in only 7.6% of 1392 HBsAg-positive individuals, indicating that the standard two-step testing approach is suboptimal for diagnosing HDV infection.² In the case of hepatitis C, reflex testing for HCV-RNA considerably increased the number of people diagnosed with chronic hepatitis C in our area.³ In a similar manner, the implementation of reflex testing for HDV infection quintupled the

Abbreviations: AASLD, American Association for the Study of Liver Diseases; CHD, chronic hepatitis delta; EASL, European Association for the Study of the Liver; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; INE, *Instituto Nacional de Estadística*, National Statistics Institute; IPC, *Índice de Precios de Consumo*, Consumer Price Index; Peg-IFN, pegylated interferon.

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absolute number of cases diagnosed.² These results contrast with the recommendations of the American Association for the Study of Liver Diseases, which advocate anti-HDV testing only in HBsAg-positive individuals who are at risk, such as people who inject drugs, men who have sex with men, individuals at risk of acquiring sexually transmitted disease and immigrants from areas where HDV is endemic. In our experience, 60% of people with HDV infection have no recognized risk factors.² The impact of HDV testing on the economic consequences of the burden of disease has not been previously assessed. The aim of this study was to estimate the impact of anti-HDV reflex testing in all HBsAg-positive individuals on the burden of CHD in Spain by the year 2030.

2 | METHODS

A decision tree was designed (Excel 2010) to simulate the CHD care cascade from screening to treatment, comparing two scenarios: the current one, in which 7.6% of HBsAg-positive patients are tested for anti-HDV and a reflex test screening scenario (100% of HBsAg-positive patients tested). The target population of 35 893 049 individuals was estimated from the Spanish population aged 18–80 years recorded by the *Instituto Nacional de Estadística* (INE, National Statistics Institute), and the estimated HBsAg prevalence of 0.22% was obtained from *Encuesta Seroprevalencia, Ministerio Sanidad* (Seroprevalence Survey, Spanish Health Ministry), representing 78 965 individuals. The anti-HDV prevalence was established at 7.7%⁴ to 9.6% of HBsAg-positive individuals,² and the presence of HDV-RNA was established at 60%⁵ to 73% of cases.⁶ Based on data from the literature, it was assumed that 66% of viremic patients would receive pegylated interferon alfa (Peg-IFN),⁷ the only treatment currently reimbursed in Spain at the time the study was designed. The estimated long-term response would be 10%, assuming similar efficacy between patients with and without liver cirrhosis.⁵

Disease progression and related costs were based on the results of a Spanish cohort of CHD patients followed for a median period of 8 years.⁶ The incidence of complications and hepatic mortality were calculated according to the presence or absence of HDV-RNA (Table S1).

'From a National Health System perspective, the direct health-care costs associated with screening, diagnosis, included linkage to care by a specialist, management of HDV-related disease and treatment cost were obtained from official sources and published literature⁸ and were updated to 2022 according to the Índice de Precios de Consumo (IPC, Consumer Price Index).'

The following outcome measures were used in the comparison of the two scenarios: (1) number of cases detected with anti-HDV antibodies and HDV-RNA; (2) impact of the burden of liver disease, that is number of liver-related events, including cirrhosis, decompensated cirrhosis (ascites, hepatic encephalopathy and variceal bleeding), hepatocellular carcinoma and liver-related deaths; and (3) the total cost of managing liver complications was estimated from published data.⁶ These costs were extrapolated to the Spanish cohort of

CHD patients, considering the disease course over the time horizon evaluated in the analysis.

3 | RESULTS

3.1 | Population

Anti-HDV reflex testing will lead to a > 9-fold increase in the number of diagnoses of anti-HDV antibodies, yielding 5498 positive individuals compared to the current scenario (582–6080 individuals). The number of people with HDV viremia will increase from 423 to 3648 cases, resulting in an overall increase of 3225 new cases (Figure 1A). These results applied to the Spanish population show that screening 78 965 HBsAg-positive individuals will detect 1 case per every 22 HBsAg-positive individuals.

Not all individuals with detectable HDV-RNA will receive Peg-IFN. Excluding those with contraindications for IFN, the number of potential treatment candidates would be 2408 with reflex testing versus 279 with the current strategy. Therefore, through reflex testing, 2128 additional patients would receive treatment, and 213 would achieve undetectable HDV-RNA in the median time of the analysis.

3.2 | Impact on the clinical and economic burden of liver disease

As compared to the current rate of testing, HDV reflex testing will reduce the number of liver complications by 35% to 38%, with the greatest impact on the progression of cirrhosis. Reflex testing will also reduce liver-related mortality by 37% (Figure 1B).

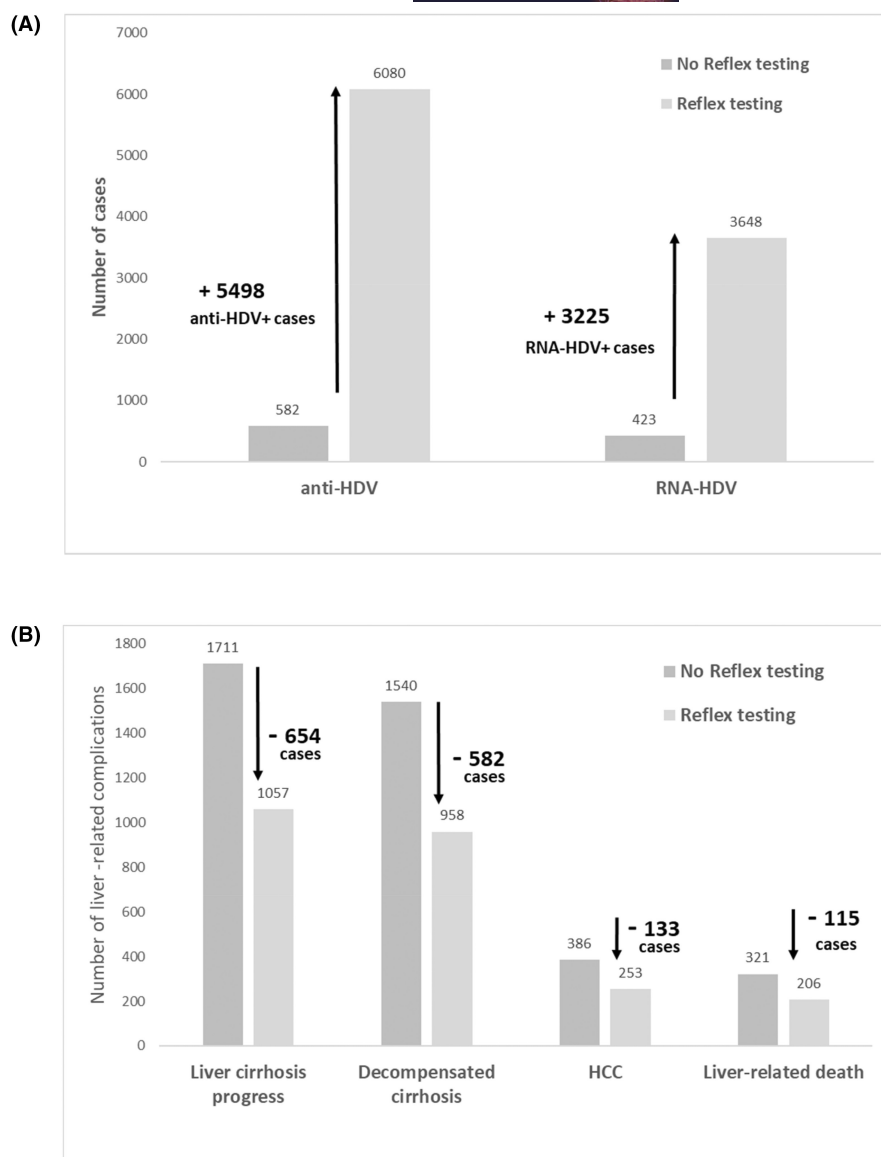
The cost of testing would be €132 for each anti-HDV positive case and €557 for each HDV-RNA positive case. Prevention of liver complications would yield a cost savings of approximately 36 million euros over a median follow-up of 8 years.

4 | DISCUSSION

This is the first study showing that the implementation of reflex testing reduces the clinical and economic burden of viral hepatitis. These data are important to inform decision-makers about the value of HDV reflex screening programmes, in which all HBsAg-positive individuals would be tested for HDV at least once. In a country with an HDV prevalence of 7.7% among HBsAg carriers, reflex testing will result in >5-fold greater detection of HDV, and avert 336 deaths related to liver complications and 134 hepatocellular carcinoma cases by 2030. Our findings could be applicable to other countries with a similar HDV prevalence.

From the decision-maker's perspective, a major concern regarding the uptake of reflex testing is the impact on the budget. Implementation of this testing programme through the existing

FIGURE 1 Analysis results for 78 965 HBsAg-positive individuals. (A) Anti-HDV and HDV-RNA detection. (B) Number of liver complications and liver-related death. HBsAg, hepatitis B surface antigen; HDV, hepatitis D virus.



laboratory would require an upfront investment that would translate into a future reduction in the number of liver events and mortality. The logistical issues associated with reflex testing (i.e. if a sample tests anti-HDV positive, the same sample is then used to verify chronic HDV infection) should be taken into consideration. To enable reflex testing, venous blood samples must undergo centrifugation, freezing and cold-chain storage within 6–24 h after collection to prevent sample degradation. In addition, the laboratory has to exclude previous anti-HDV determinations to avoid repetitions that would increase cost. Only people with ongoing risk factors should be retested for HDV.

Our analysis has several limitations. First, the horizon of our simulation was limited to the 8 years with available data; hence, the clinical and economic benefits of reflex testing could be underestimated. Second, the therapy administered was Peg-IFN. Currently, bulevirtide, a drug with fewer contraindications and limitations than IFN, has been approved and reimbursed in some European countries. It would be important to assess the impact of bulevirtide on treating CHD. Third, it was assumed that all individuals diagnosed

with HDV were linked to care and benefited from therapy. Fourth, we did not account for the potential benefits that could occur from a reduction in HDV transmission.

In summary, the use of anti-HDV reflex testing would lead to a >9-fold increase in CHD diagnoses, reduce the clinical and economic burden of the disease and contribute to the elimination of hepatitis by 2030.

CONFLICT OF INTEREST STATEMENT

MB and RE: Speaker and Advisor for Abbvie and Gilead. RDH and MAC: Employees of Pharmacoeconomics & Outcomes Research Iberia, a consultancy firm specializing in the economic evaluation of healthcare interventions that has received unconditional funding from Fundació per la Recerca Biomèdica de Vall d'Hebron. AP: None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.



ORCID

Adriana Palom  <https://orcid.org/0000-0002-0130-1302>

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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