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OPTI-HEP-D: a protocol for an intervention study comprising screening and linkage to care of people living with hepatitis D in Catalonia

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ABSTRACT

Introduction Hepatitis B virus (HBV) affects 296 million people globally, causing 780 000 annual deaths. It has been estimated that 12–43 million individuals are co-infected with hepatitis D virus (HDV). In Spain, the prevalence of HBsAg in adults is 0.22%, with an anti-HDV prevalence of 7.7%, although not extensively documented since many HBsAg-positive cases are not tested for anti-HDV. The primary objective of this project is to optimise hepatitis D care by implementing a screening programme for anti-HDV in all HBsAg-positive individuals over a 1 year period in Catalonia. Secondary objectives include evaluating hepatitis D prevalence, establishing a digital registry for all anti-HDV positive cases, testing them for HDV-RNA in a centralised laboratory and offering linkage to care.

Methods and analysis This prospective study will be performed in seven hospital centres in Catalonia, which attend to more than 95% of the adult population. Approximately, 9290 HBsAg-positive individuals are expected to be screened for anti-HDV in 1 year. All anti-HDV positive samples will be sent to a centralised laboratory for HDV-RNA quantification. All individuals testing positive for anti-HDV will be registered on an electronic platform and linked to care. The registry will collect data on demographics, infection stage, risk factors, disease awareness and previous diagnoses. No additional interventions will be conducted for those with adequate follow-up.

Ethics and dissemination The Vall d'Hebron Hospital Ethics Committee (PR(AG)628/2023) and the Spanish Agency of Medicines and Medical Devices approved this study. These findings will be disseminated through peer-reviewed publications and conference presentations.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Automatic anti-hepatitis D virus (HDV) testing for all HBsAg-positive samples will guarantee thorough screening without missing cases.
⇒ The centralised digital platform will enable consistent collaboration and data sharing between microbiologists and clinicians.
⇒ The protocol will ensure that all diagnosed patients are evaluated for linkage to care, increasing follow-up rates.
⇒ Differences between laboratories in circuit management and availability might be a potential limitation to implement the programme.
⇒ The 1 year study period may not capture long-term outcomes related to anti-HDV diagnosis and management.

INTRODUCTION

Hepatitis D virus (HDV) infection causes the most severe and progressive form of chronic viral hepatitis, presenting a twofold to threefold higher risk of developing liver cirrhosis and/or hepatocellular carcinoma compared with Hepatitis B virus (HBV) monoinfection.[1 2] The implementation of HBV vaccination programmes in the 1990s has decreased the prevalence of HDV in younger populations.[3] Despite this, the burden of HDV in high-income countries primarily affects aged patients with advanced liver fibrosis and young immigrants from endemic areas with lack or incomplete HBV vaccination programmes.[4]

In some countries, data on HDV prevalence is restricted to specific populations such as patients with liver disease or blood donors, making it difficult to achieve a complete overview of HDV infection. Although theEuropean Association for the Study of the Liver (EASL) guidelines recommend anti-HDV testing in all HBsAg-positive individuals,[5] the adherence to this recommendation is low and heterogeneous depending on the setting. These factors contribute to the underestimation of HDV infection.

A previous study performed in Barcelona (Spain) evaluated the rate of hepatitis D testing in 17 primary care centres and one academic hospital, showing that only 7.64% of HBsAg-positive patients were tested for anti-HDV.[6]

In a subsequent study, the implementation of anti-HDV reflex testing proved to be a successful tool to increase hepatitis D diagnoses, resulting in a fivefold increase in absolute hepatitis D cases across all HBsAg-positive samples coming from the same participant centres. In addition, 40% of the patients did not report risk factors associated with HDV infection.[7]

An additional measure to contemplate involves double reflex testing, where all individuals positive for HBsAg undergo testing for anti-HDV, followed by HDV-RNA testing for those anti-HDV-positive. This proved to be feasible given the low number of newly diagnosed HBV cases.[8]

The reflex testing strategy was initially introduced to facilitate screening and diagnosis of HCV infection and has been widely used in micro-elimination studies such as Hep C free Baleares study where anti-HCV and HCV-RNA were performed in one visit.[9]

Catalonia is a region located in the northeast of Spain that has 6.35 million adult inhabitants.[10] This region is supported by the Catalan Health Institute, which has a universal health coverage and beholds complete free diagnosis and therapy as well as a centralised health platform able to register laboratory analysis and medical records.

The Catalan Health Institute has a catchment population of >95% of all adults living in Catalonia including hospitals, primary care centres, addiction centres and prisons, being the main point of contact between population and healthcare.

The key points of this programme, including active screening and linkage to care, are in line with the WHO recommendations for viral hepatitis elimination by 2030.

The primary objective of this protocol is to optimise hepatitis D care and ensure linkage to care for those HDV-RNA positive. All HBsAg-positive samples that arrive at one of the participant centres will undergo a double reflex testing for anti-HDV and HDV-RNA. Linkage to care will then be assessed and offered to those who are not being monitored.

The secondary aims are to assess the anti-HDV prevalence in Catalonia, to set up a digital registry for patients with hepatitis D and to centralise HDV-RNA quantification for optimal diagnosis.

METHODS AND ANALYSIS

Protocol design

This will be a prospective study from March 2024 to March 2025, which expects to receive a total of 9290 HBsAg-positive individuals' samples over the duration of 1 year. This number has been calculated taking into account that from the 95% adult population coverage of our seven participant centres (figure 1), approximately 70% of the subjects will have a blood test during this year. With a 0.22% of HBsAg-positive prevalence and 7.7% of anti-HDV,[11] roughly 715 anti-HDV-positive subjects are expected to be diagnosed.

Development and implementation

Anti-HDV reflex testing will be newly performed in every non-duplicated HBsAg-positive sample that arrives to the laboratory. Anti-HDV positive results will be highlighted creating an alert system in medical records, and a sample

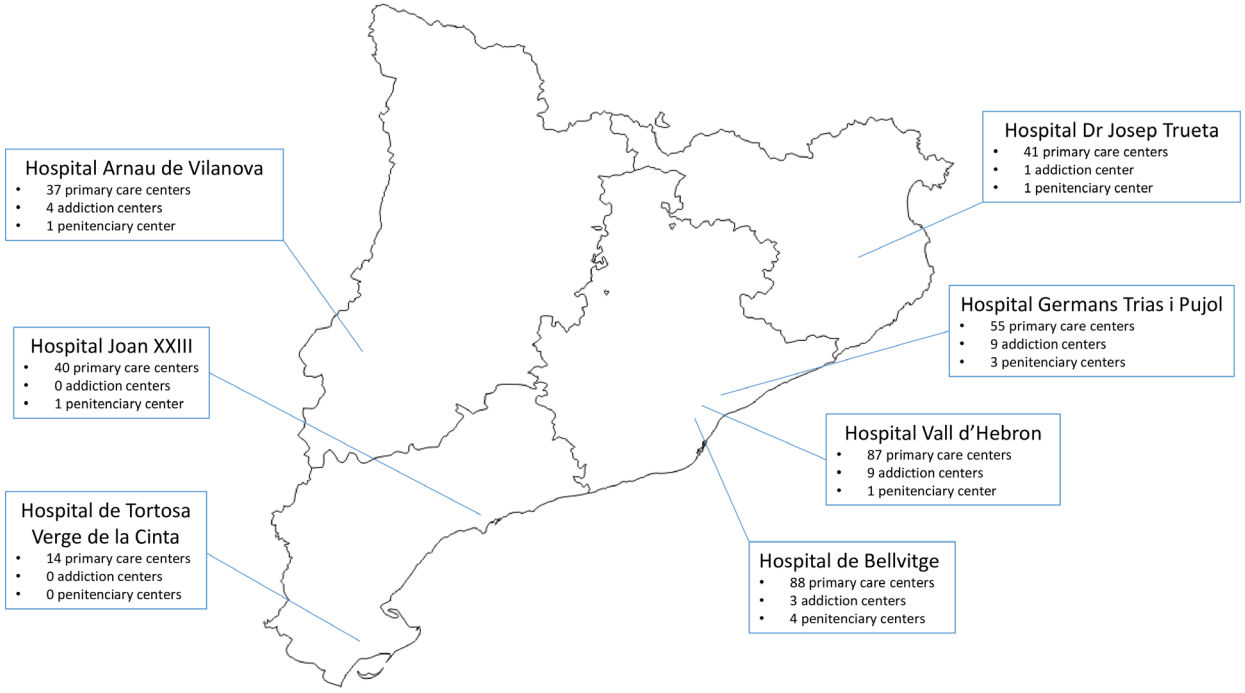

Figure 1 Participant centres of the OPTI-HEP-D screening programme in Catalonia.

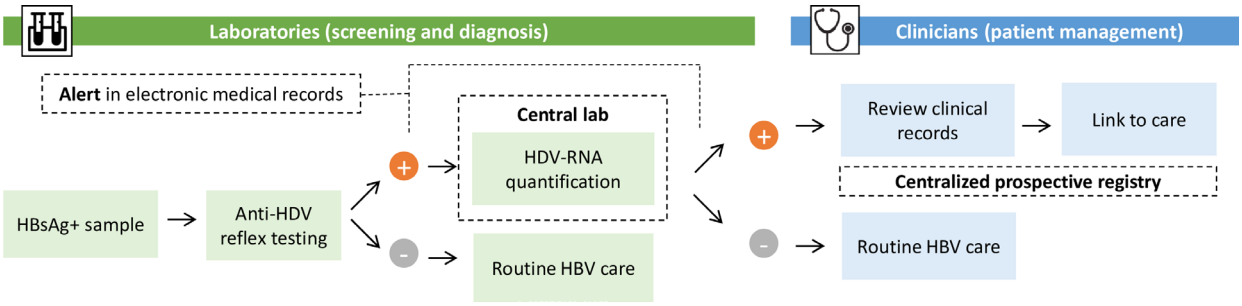

Figure 2 Protocol circuit from HBsAg-positive sample determination to linkage to care.

will be sent to Vall d'Hebron University Hospital for reflex HDV-RNA quantification. The techniques to determine HDV-RNA will consist of one automated standardised test (Vircell, Spain).[12] In HDV-RNA negative cases, quantification will be re-assessed once again in a 3 month period to corroborate negative viraemia. If the result is undetectable again, the individual will continue following routine HBV care, as well as those anti-HDV-negative.

All anti-HDV-positive individual's medical records will be evaluated by a physician or expert nurse in connection with the reference hospitals to assess whether they have been linked to care or not. If they are not linked to care, the nurse will call or send them a letter to make an appointment with a reference hepatologist. In individuals who are already linked and receiving adequate follow-up, no further interventions will be undertaken (figure 2).

Monitoring and evaluation

A non-open access centralised digital platform will be designed to collect data at baseline and during monitoring of all anti-HDV positive individuals. The electronic platform will collect data on baseline demographics, stage of infection, risk factors, disease awareness, previous diagnosing, linkage to care and therapy. This platform will enable sharing data between all laboratory staff, nurses and clinicians involved in the project, creating a transversal collaboration among all experts.

The total duration of the study will be 18 months. The first 2 months will be devoted to training all participant centres and to designing and setting up the medical records alert. The next year will be dedicated to reflex testing execution and subject assessment (including HDV-RNA quantification, patient monitoring and linkage to care). The last 4 months will be for data analysis and manuscript elaboration in leading peer-reviewed journals.

Statistical analysis

Data will be compared between anti-HDV+subjects with and without viraemia, and those anti-HDV+known and new. Normally distributed quantitative variables will be compared using Student's t-test and expressed, as mean±SD. Variables with a non-normal distribution will be analysed using the Mann–Whitney U test and expressed as median and IQR. Categorical variables will be compared using the $\chi 2$ test or Fisher's exact test when frequencies are less than 5%, and expressed as frequencies and percentages. Statistical significance will be set at a p value of <0.05.

All statistical analyses will be carried out using IBM SPSS 2.0 (SPSS Inc, Armonk, NY, USA).

Patient and public involvement

The research question was developed based on clinical needs and public health priorities. Surveys or interviews with HDV patients will help understand their challenges, including stigma and barriers to care. Patients will become involved after screening, particularly during linkage to care, where their communication preferences will be asked during consultations.

In this laboratory-based screening, recruitment will not involve direct patient selection since the HBsAg-positive population will already be identified. However, patients will contribute to the conduct of the study by reviewing informational materials for post-screening and participating in outreach strategies for vulnerable populations. Patients will be informed of their status in a sensitive and supportive manner, ensuring clear communication of the next steps, such as referrals to specialists or further follow-ups.

ETHICS AND DISSEMINATION

This study complies with the criteria of the Vall d'Hebron Hospital Ethics Committee (reference number PR(AG)628/2023) and the Spanish Agency of Medicines and Medical Devices, and will be conducted according to the principles of the Declaration of Helsinki, Good Clinical Practice guidelines and local regulatory requirements. Informed consent forms will be provided to participating individuals and all data will be anonymised.

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