



# Enfermedades Infecciosas y Microbiología Clínica

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## Detection of previously undiagnosed or lost to follow-up hepatitis C infections by implementing an opportunistic screening in an emergency department



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### ABSTRACT

**Objectives:** This study aimed to evaluate the effectiveness of an opportunistic hepatitis C virus (HCV) screening program in identifying new cases and ensuring their follow-up (linkage to care) in our health area.

**Methods:** We conducted a prospective study from June 2023 to May 2024 in an emergency department (ED) of Catalonia (Spain), screening patients aged 30–70 years who had blood samples collected as part of routine clinical practice. Patients with positive anti-HCV antibodies were confirmed with HCV RNA testing, and those with active infection were referred to the gastroenterology department for care.

**Results:** Out of 15,245 eligible patients, 5184 were screened for HCV, marking a 192% increase compared to the previous year. Of total serologies, 3973 were requested in patients aged between 30–70 years and the rest by routine clinical practice. Anti-HCV antibodies were detected in 120 patients (3.02%), and 13 (0.33%) had active HCV infection. The mean age of viremic patients was 49.62 years and 76.92% were male. Identified risk factors included drug use (63.64%) and being from countries with high HCV prevalence (18.18%). Advanced liver fibrosis was found in 25% of patients.

**Conclusions:** Opportunistic screening in the ED significantly increased HCV testing and identified a higher prevalence of active infection compared to the general population. These findings support expanding screening guidelines to reach broader populations, improving early diagnosis and linkage to care for HCV.

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## Detección de infecciones por hepatitis C no diagnosticadas o perdidas en el seguimiento mediante la implementación de un cribado oportunista en un servicio de urgencias

### RESUMEN

**Objetivo:** Evaluar la eficacia de un programa de cribado oportunista del virus de la hepatitis C (VHC) en la identificación de nuevos casos y su seguimiento (vinculación al sistema sanitario) en nuestra área de salud.

#### Palabras clave:

Hepatitis C crónica  
VHC  
Cribado oportunista  
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Fibrosis hepática  
Oportunidades perdidas  
Vinculación al sistema sanitario

**Métodos:** Estudio prospectivo realizado entre junio de 2023 y mayo de 2024 en el servicio de urgencias de un hospital universitario de Cataluña (España). Se incluyeron pacientes de entre 30 y 70 años a quienes se extrajeron muestras de sangre como parte de la práctica clínica habitual. Los casos positivos para anticuerpos frente al VHC se confirmaron mediante detección de ARN del VHC, y los pacientes con infección activa fueron referidos al servicio de gastroenterología para vincularlos al sistema sanitario.

**Resultados:** De los 15.245 pacientes elegibles, se cribó a 5.184, lo que supone un incremento del 192% respecto al año anterior. Del total de serologías realizadas en el servicio de urgencias, 3.973 fueron en pacientes con edades entre 30-70 años, y las restantes fueron realizadas por práctica clínica habitual. Se detectaron anticuerpos frente al VHC en 120 pacientes (3,02%), de los cuales 13 (0,33%) presentaban infección activa. La edad media de los pacientes con viremia fue de 49,62 años, y el 76,92% eran hombres. Los principales factores de riesgo fueron el consumo de drogas (63,64%) y ser originarios de países con alta prevalencia de VHC (18,18%). El 25% de los pacientes presentaban fibrosis hepática avanzada.

**Conclusiones:** El cribado oportunista en el servicio de urgencias incrementó notablemente el número de serologías de VHC realizadas e identificó una prevalencia de infección activa superior a la estimada para la población general. Los resultados respaldan la necesidad de ampliar las directrices de cribado para abarcar poblaciones más amplias, favorecer el diagnóstico precoz y la adecuada vinculación a la atención sanitaria.

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## Introduction

Despite recent progress, hepatitis C virus (HCV) infection remains a global health challenge.<sup>1</sup> The World Health Organization (WHO)'s Global Hepatitis Strategy aims to achieve a 90% reduction in new HCV infections and a 65% reduction in HCV-related mortality by 2030.<sup>2</sup> In Europe, the incidence of HCV was estimated at 8.9 cases per 100,000 population in 2019, with a male-to-female ratio of 2.1:1.<sup>3</sup> Between 2015 and 2019, the Strategic Plan for Tackling Hepatitis C (PEAHC, for its Spanish acronym) evaluated the prevalence and incidence of HCV in Spain, creating a registry of patients with hepatitis C and establishing measures to mitigate its impact on the National Health System.<sup>4</sup> In a seroprevalence survey conducted between 2017 and 2018, the Spanish Ministry of Health estimated a 0.17% prevalence of active HCV infection in the general population. Among these patients, 29.4% were unaware of their infection and 63.5% had previously known exposures or risk factors.<sup>5</sup> In a more recent study conducted in 2020, the estimated incidence of HCV in Spain was 2.4 cases per 100,000 population, mostly affecting adults aged 55–64 years.<sup>6</sup>

Screening is a fundamental tool in the fight to eliminate HCV, since it has been shown to reduce disease prevalence in its earliest stages.<sup>7</sup> The 2018 European Centre for Disease prevention and Control (ECDC) guidelines recommend the implementation of comprehensive national testing strategies and appropriate linkage to care of individuals affected.<sup>8</sup> Although the Spanish PEAHC plan has helped significantly in reducing the number of HCV-related hospitalizations,<sup>9</sup> a considerable proportion of patients remain unaware of their condition.<sup>5,10</sup>

The Spanish Association for the Study of the Liver (AEEH, for its Spanish acronym) recommends testing for anti-HCV antibodies in the entire population aged between 40 and 70 years, linking to care all patients with active HCV infection.<sup>11</sup> Several cost-effectiveness studies support the feasibility of this approach, highlighting its healthcare saving and positive impact on national productivity.<sup>12–14</sup> Furthermore, international guidelines recommend universal HCV screening for all adults over 18.<sup>15</sup> Numerous projects for the active retrieval and treatment of patients with HCV in Europe and Spain<sup>16–20</sup> have demonstrated their contribution to the WHO elimination targets and the effectiveness of these approaches, despite the disruptive impact the COVID-19 pandemic.<sup>21–23</sup>

The recommendations of the 2020 Spanish Ministry of Health screening Guidelines indicate HCV testing in people with known

exposures or risk factors.<sup>24</sup> This places the emergency department (ED) in an ideal position for identifying new cases of hepatitis in this population,<sup>25,26</sup> as high-risk groups, such as people who inject drugs or migrants from countries with high HCV prevalence, tend to seek medical care primarily through EDs due to their poor linkage to the healthcare system.<sup>27,28</sup> In fact, recent studies on the diagnosis of HCV and other blood-borne viruses in EDs confirm that this strategy is feasible, effective and cost-effective.<sup>29–31</sup>

Although the latest HCV report from the Ministry of Health does not include data from Catalonia,<sup>6</sup> a study conducted in patients attending the ED of a university hospital in Barcelona revealed a 0.73% prevalence of active HCV infection. Notably, 44% of the diagnosed patients were unaware of their infection and 60% had no known risk exposures.<sup>32</sup> These findings illustrate the need to improve HCV screening in this region, especially in the setting of the ED. In this study, we analyzed the results of an opportunistic HCV screening program in the ED of Bellvitge University Hospital (HUB, for its Spanish acronym). The primary objective was to identify new patients and link them to the healthcare system.

## Methods

### Health area covered by the study

HUB, located in the city of Hospitalet de Llobregat (Barcelona), serves as the local or regional referral center for approximately 350,000 inhabitants. HUB is also the third-level high-tech referral hospital for the South Metropolitan Territorial Management area of Catalonia (Spain), acting as the referral hospital for highly complex pathologies for a population of nearly 2,000,000 inhabitants.

### Study design and patient identification and retrieval

Patients included in the study were adults aged between 30 and 70 years old who attended the ED between June 2023 and May 2024 and had a blood sample taken in accordance with routine clinical practice. All patients included gave tacit consent for the anti-HCV test. Exclusion criteria were: (1) patient refusal to the test or (2) having a HCV test performed in the previous 3 months. In order to implement this screening, a pre-configured computer test ordering system was created to facilitate the serology testing process upon request by the responsible physician. This system has also been used in our hospital to expedite test requests for at-risk patients at the physician's discretion (outside of opportunistic screening).

Continuous training was also provided to all healthcare staff working in the ED. The medical records of the patients identified were reviewed and analyzed by the study authors. Patients with a positive RNA result were contacted by phone through the ED and linked to care in the gastroenterology department.

### Variables

The data collected included sociodemographic variables (age, sex and nationality of origin), risk factors (history of drug use, individuals from countries with moderate/high HCV prevalence,<sup>33</sup> and history of incarceration) and clinical characteristics, like liver fibrosis stage and coinfection with human immunodeficiency virus (HIV) or hepatitis B virus (HBV). The liver fibrosis stage of the patients retrieved was determined with serological markers using the AST to Platelet Ratio Index (APRI) score and the fibrosis index based on four factors (FIB-4).<sup>34</sup> For some patients, data of elastography (Fibroscan®) classified according to the METAVIR scoring system was available.<sup>35</sup> Patients with advanced fibrosis or cirrhosis were classified according to the criteria established by Zioli et al. (2005),<sup>36</sup> and staging was completed with abdominal ultrasound.

### Diagnostic kits

In this study, HCV antibodies were detected using the Elecsys Anti-HCV II reagent kit on the Cobas e801 analyzer (Roche). The presence of active infection was confirmed by quantitative reverse transcriptase polymerase chain reaction (RT-PCR) assay using the Alinity m HCV AMP kit on the Alinity analyzer (Abbott).

### Statistical analysis

A comprehensive descriptive analysis was performed for quantitative variables. Normally distributed variables were summarized using means and standard deviations (SD), while non-normally distributed variables were expressed as medians and interquartile ranges (IQR). For categorical variables, proportions with confidence intervals (CI) were used.

## Results

### Number of serology tests in the FOCUS program

During the first year of program implementation (June 2023 to May 2024), 5184 serology tests were requested in our ED (Fig. 1), reflecting a 192% increase compared to the 1776 tests performed in the ED in the previous 12 months by clinical request prior to the implementation of the screening. Of the total number of serology tests, 4382 (84.5%) were performed within the framework of the FOCUS program, either through direct request by suspicion (at the physician's discretion but using FOCUS pre-configured computer test ordering system) or following the inclusion criteria for opportunistic screening (Fig. 1).

### Patients identified through opportunistic screening

During the study period, 128,200 patients attended the ED, 15,245 (11.89%) of whom met the inclusion criteria (Fig. 1). Of these, serology tests were requested for 3973 patients (26.06%), while in 11,272 cases (73.94%) the clinician failed to request the test despite the inclusion criteria being met. Anti-HCV antibodies were detected in 120 patients, indicating a seroprevalence of 3.02%. Of these patients, 97 (80.83%) were already aware of their past infection (with or without treatment). Among patients with anti-HCV antibodies, 13 were diagnosed with active HCV infection (RNA positive), which represents 0.33% of the total number of

**Table 1**  
HCV screening results by age, sex and nationality (June 2023–May 2024).

	Patients screened	Anti-HCV-positive	HCV RNA-positive
Total, N	3973	120 (3.02%)	13 (0.33%)
Age, n (%)			
30–39	862 (21.70%)	19 (15.83%)	4 (30.77%)
40–49	992 (24.97%)	25 (20.83%)	2 (15.38%)
50–59	1015 (25.55%)	32 (26.67%)	4 (30.77%)
60–70	1104 (27.79%)	44 (36.67%)	3 (23.08%)
Age, mean ± SD	50.53 ± 11.42	53.32 ± 10.96	49.62 ± 12.78
Sex, n (%)			
Men	2241 (56.41%)	76 (63.33%)	10 (76.92%)
Women	1732 (43.59%)	44 (36.67%)	3 (23.08%)
Nationality, n (%)			
Spanish	n.d.	94 (78.33%)	9 (69.23%)
Other	n.d.	26 (21.67%)	4 (30.77%)

HCV: hepatitis C virus; n.d.: not determined; SD: standard deviation.

patients screened. Twelve of these patients (92.31%) were linked to health care. Out of the 13 patients identified with active infection, nine (69.23%) were previously unaware of their condition and the remaining four (30.77%) had been lost to follow-up. The number needed to screen (NNS) was 33.1 (95% CI: 28.15–40.19) to detect one anti-HCV positive, and 305.6 (95% CI: 198.10–668.31) to detect one patient with active infection.

### Sociodemographic characteristics

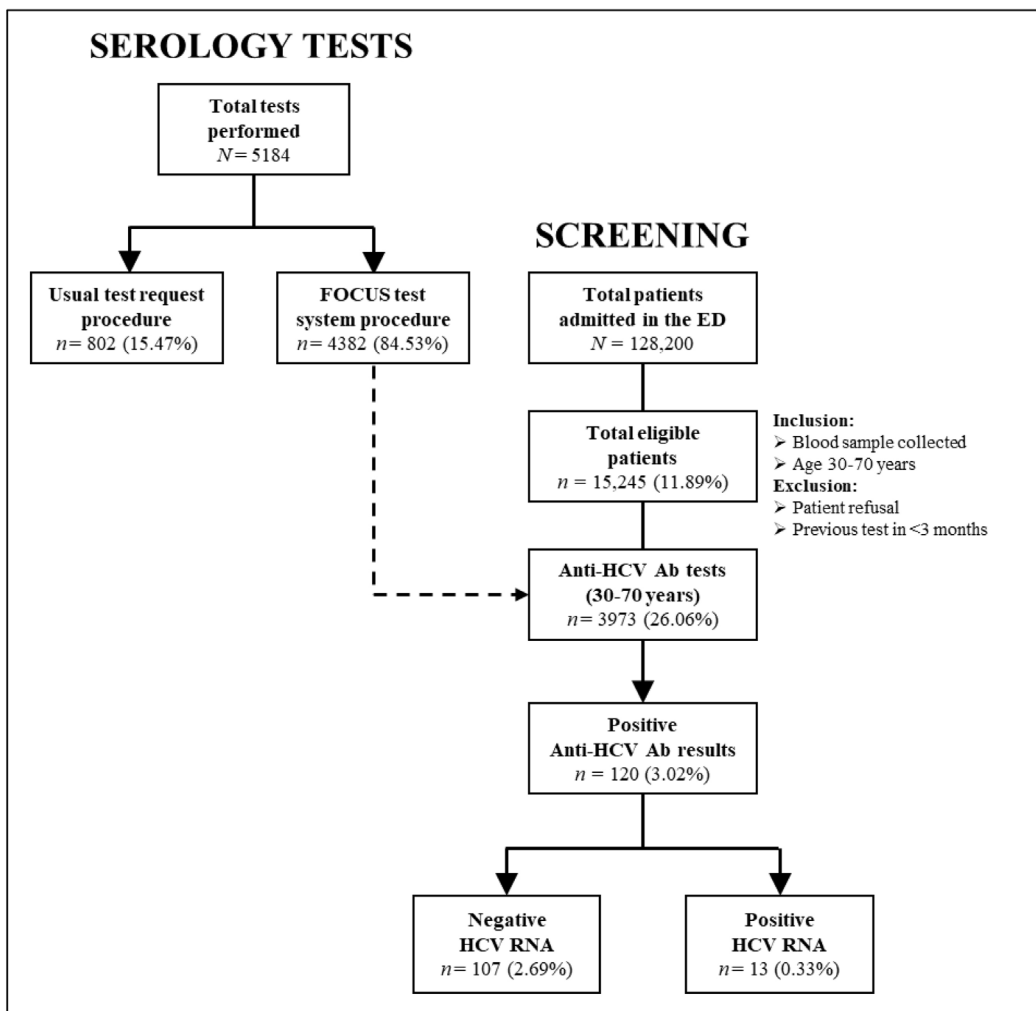
Table 1 presents the sociodemographic data of the population according to the serology and viremia results. The mean age of the infected patients was 49.62 ± 12.78 years, 76.92% (n = 10) were men, and 30.77% (n = 4) had a nationality of origin other than Spanish.

### Risk exposure assessment

Eleven viremic patients (84.62%) presented previous exposures to risk factors in their medical records (Table 2). Among the risk practices, exposures or conditions described as criteria for screening in the Clinical Guidelines,<sup>15</sup> more than a half were related to injection or inhaled drug use (n = 7, 63.64%). Other risk factors included HIV or HBV coinfection (n = 2, 18.18%) and individuals originating from countries with moderate or high HCV prevalence (n = 2, 18.18%). Three patients (23.08%) had no risk factors noted in their medical record.

### Liver fibrosis stage

Regarding the liver fibrosis stage, 12 patients (92.31%) had laboratory data available for calculating the APRI and FIB-4 scores (Table 2). Of these patients, 6 (50%) had an APRI score < 0.5 (no liver fibrosis or moderate liver fibrosis), 2 (16.67%) had a score between 0.5 and 1.5 (indeterminate), 1 (8.33%) between 1.5 and 2.0 (advanced fibrosis), and 3 (25%) had a score > 2.0 (cirrhosis). Similar results were obtained in the analysis of the FIB-4 index, where 7 (58.33%) patients had a score < 1.45 (no liver fibrosis or moderate liver fibrosis), 2 (16.67%) had a score between 1.45 and 3.25 (indeterminate) and 3 (25%) scored > 3.25 (advanced fibrosis). Data from 6 viremic patients (46.15%) who underwent transient elastography (FibroScan®) showed that 5 (83.33%) of the patients had liver fibrosis stages between F0 and F2, while 1 patient (16.67%) had advanced stage liver disease (F3–F4).



**Fig. 1.** Flowchart showing the number of serology tests performed between June 2023 and May 2024, total number of patients seen in the ED, patients eligible for opportunistic screening, and the results of the anti-HCV Ab and HCV RNA tests. Ab: antibodies; ED: emergency department; HCV: hepatitis C virus.

*Previous missed diagnostic opportunities*

The majority of viremic patients (n = 12, 92.31%) had previously attended medical consultations (Table 3). Of these, 7 (53.85%) had previously visited EDs prior to their diagnosis (4.57 ± 4.35 times on average), with dates of previous visits going back as far as 5 years. Most patients had also had prior encounters in other healthcare settings, such as primary care visits (n = 9, 69.23%) or hospitalization (n = 3, 23.08%).

**Discussion**

Opportunistic screening programs, especially in EDs, help identify patients unaware of their HCV infection.<sup>8,25,26,29,30</sup> The FOCUS program has helped not only to increase the number of serology tests performed in the target population (patients aged 30–70 years who had a blood sample taken in our ED), but also in the overall population. This has indirectly increased the screening of individuals aged < 30 years and >70 years as a result of the pre-configured computer test ordering system created for the implementation of screening, which has served to expedite tests requested at the physician’s discretion outside of this process (based on risk factors). Specifically, the introduction of the FOCUS project in the ED of our hospital nearly tripled the number of HCV tests compared to the previous year.

The results of our study underscore the effectiveness of opportunistic screening in identifying new HCV cases and improving the scope of diagnosis. Linkage to care is crucial to ensure that all patients diagnosed receive the necessary treatment.<sup>37</sup> In our study, 12 of the 13 patients with active infection were linked to medical care, demonstrating the effectiveness of the follow-up system implemented. Dedicated staff played a key role in this process, ensuring that patients were properly informed and referred to the gastroenterology department.

The prevalence of active HCV infection in this study was 0.33%, which is almost twice the 0.17% prevalence estimated for the general Spanish population.<sup>24</sup> Another opportunistic screening conducted at a university hospital in Barcelona with patients aged > 16 years<sup>32</sup> also reported a prevalence of active HCV infection (0.73%) higher than that estimated in the national seroprevalence study.<sup>24</sup> Therefore, both studies highlight the higher proportion of previously undiagnosed infections in the population of the Barcelona metropolitan area attending EDs, revealing a significant opportunity to improve HCV detection in the general population through opportunistic screening strategies.

Analysis of patient medical records identified exposure factors or at-risk situations associated with HCV infection. In our study, 76.92% viremic patients presented risk factors such as injection or inhaled drug use and origin from countries with high HCV prevalence.<sup>33</sup> This identifies particularly vulnerable groups in our

**Table 2**

Risk factors recorded in the medical records and liver status of patients with HCV viremia identified during screening.

	Patients diagnosed RNA+ by screening, n (%)
Total ED	13 (0.33%)
Patients without risk factors in the medical record	3 (23.08%)
Patients with risk factors	10 (76.92%)
Types of risk factors identified	11
HIV or HBV coinfection	2 (18.18%)
Injection or inhaled drug use	7 (63.64%)
Individuals from countries with moderate/high HCV prevalence	2 (18.18%)
History of incarceration	0
APRI score at diagnosis	12 (92.31%)
<0.5 (no liver fibrosis or moderate liver fibrosis)	6 (50%)
0.5–1.5 (indeterminate)	2 (16.67%)
1.5–2.0 (advanced fibrosis)	1 (8.33%)
>2.0 (cirrhosis)	3 (25%)
FIB-4 score at diagnosis	12 (92.31%)
<1.45 (no liver fibrosis or moderate liver fibrosis)	7 (58.33%)
1.45–3.25 (indeterminate)	2 (16.67%)
>3.25 (advanced fibrosis)	3 (25%)
Fibrosis staging by transient elastography	6 (46.15%)
F0 (no fibrosis) or F1 (mild fibrosis)	4 (66.67%)
F2 (moderate fibrosis)	1 (16.67%)
F3 (advanced fibrosis)	1 (16.67%)
F4 (cirrhosis)	0

APRI: AST to Platelet Ratio Index; ED: emergency department; FIB-4: Fibrosis-4 Index; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; N.D.: not determined.

**Table 3**

Missed opportunities for diagnosis of patients diagnosed through the screening program.

Patients who sought medical care in the previous 5 years, n (%)	Patients diagnosed during screening (n = 13)
Any healthcare setting	12 (92.31%)
Primary care	9 (69.23%)
Emergency department	7 (53.85%)
Hospitalization	3 (23.08%)
Hospital outpatient clinics	3 (23.08%)

health area and may explain the high prevalence observed in our hospital.

Additionally, the fact that over 20% of newly detected cases had no record of risk factors underlines the need to expand screening guidelines to include a broader population. Strict adherence to Ministry of Health and AEEH screening recommendations (age- and risk-based testing only)<sup>2,11</sup> would have resulted in failure to diagnose some viremic patients in our study. This underscores the limitations in current guidelines and the need to adopt a more inclusive and proactive approach to HCV screening. In fact, liver fibrosis data revealed that a high percentage of patients had advanced fibrosis or cirrhosis at diagnosis, indicating that they were identified late in the course of the infection.<sup>38</sup>

In this regard, previous missed diagnostic opportunities were evident in our analysis. The majority of viremic patients (92.31%) had a history of previous healthcare system encounters, including multiple visits to EDs and other healthcare settings. These patients could have been diagnosed earlier should a testing procedure had been in place in these settings, highlighting the importance of implementing more comprehensive systematic screening strategies to avoid late diagnosis and improve long-term health outcomes. This is consistent with recent studies on HCV screen-

ing cost-effectivity in EDs, which demonstrate that this strategy is practical and cost-effective.<sup>29–31</sup>

Our study presents some limitations. Its unicentric nature entails that we should not extrapolate the results obtained to other places or health areas. In addition, only 26.1% of eligible patients were screened, which could introduce selection bias. Since screening was not randomized, certain patient subgroups may have been over- or underrepresented. However, this limitation is common in ED-based screening studies and is primarily due to the opportunistic nature of testing. To improve coverage and reduce clinician-dependent variability, we strongly advocate for an opt-out screening strategy (where all eligible patients are screened unless they explicitly decline) and the automation of HCV test ordering, ensuring that all eligible patients are systematically screened. This would enhance efficiency, minimize missed testing opportunities, and provide a more representative sample of the ED population.

In conclusion, HCV detection rates in the ED resulted in a significantly higher measured prevalence compared to the general population, suggesting that many infections would remain undiagnosed if only Ministry of Health screening guidelines were followed. Opportunistic ED-screening has proven to be effective in identifying more patients without disrupting workflow. Our findings support expanding screening guidelines to broader populations, optimizing efforts toward HCV elimination.

### Data sharing statement

The data that support the findings of this study are available on request from the corresponding author. Data are not publicly available due to privacy or ethical restrictions.

### Ethical approval

The design of this project is based on good clinical practices, following the recommendations of the WHO and the Department of Health of the Catalan Institute of Health (ICS). This study complies, both in its composition and in its standard operating procedures, with current Spanish and European legislation. The project was carried out in accordance with the principles of the Declaration of Helsinki and complied with the European Union General Data Protection Regulation, ensuring the removal of all personal identifiers from the results.

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We received funding from the Gilead Sciences FOCUS program to support viral hepatitis screening and linkage to the first medical appointment after diagnosis. FOCUS funding does not support activities beyond the first medical appointment and is agnostic as to how organizations approach subsequent patient clinical management.

### Conflicts of interest

Alba Carrodegas and José Luis González-Sánchez own stock in and are employees of Gilead Sciences. The remaining authors declare no conflicts of interest associated with the research, authorship, and publication of this article. Data collection and management were conducted independently, with additional oversight from independent data monitoring agencies.

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