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Liver International – Research Letter

A call for the comprehensive diagnosis of viral hepatitis as a key step towards its elimination

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Lay Summary:

The global elimination of viral hepatitis elimination is within reach, and will be facilitated by improving testing tools. With a single blood sample, it is now possible to screen and to perform a comprehensive diagnosis for hepatitis B, hepatitis C, hepatitis D, and other blood-borne viruses like HIV to link those in need to treatment and care. Automated electronic alerts, for those testing positive to engage with specialist, can also improve linkage to care. Further, to add extra value to the patient and health system, with the same blood sample, it is possible to undertake an initial evaluation of liver disease by calculating a non-invasive fibrosis score, such as FIB-4, thereby contributing to a complete liver health assessment. Today, a single blood sample can reveal silent and preventable liver diseases that may improve liver health outcomes.

Together, the hepatitis B, C and D viruses (HBV, HCV and HDV) represent a major public health threat, due to their high morbidity and mortality. Globally, there are around 296 million people with chronic HBV (of whom an estimated 3-5% have HDV) and 58 million with chronic HCV(1). In recent years, the number of viral hepatitis infections have declined, facilitated by the elimination policies launched by the World Health Organization (WHO) in 2016, aiming for a 90% reduction in incidence and a 65% reduction in mortality by 2030 compared to 2015(2). Despite this decrease, forecasts suggest that we are currently not on track to achieve the global elimination targets by 2030(3).

Successful measures aimed at meeting these targets, have been hindered by the COVID-19 pandemic, which has severely affected health services and undermining care for other diseases. This has augmented the late diagnosis of viral hepatitis, thus increasing the likelihood of liver related complications. As countries recover from COVID-19, we must resume and strengthen efforts aimed to eliminate viral hepatitis, using innovative strategies to optimize testing, linkage to care, and treatment(4).

For HCV, reflex testing for a definitive diagnosis, which consists of conducting all necessary serological and molecular analysis in a single blood specimen, followed by effective communication of results through an electronic alert, is the key in preventing care-continuum drop-off(4) and facilitating treatment access for diagnosed patients. Reflex RNA testing simplifies diagnosing by minimizing the number of needed healthcare visits and loss to follow-up and it has proven to be cost effective. This strategy has become standard practice in the UK and Spain(5), with guidelines recommending its use for all HCV antibody-positive tests.

In this regard, the professional associations in Spain (the Spanish Association for the Study of the Liver, the Viral Hepatitis Study Group of the Spanish Society of Infectious Diseases and Clinical Microbiology and the Spanish Society of Digestive Pathology), a country close to eliminating HCV infection, have developed a consensus for the comprehensive diagnosis of chronic viral hepatitis (Figure 1). The main objective of this consensus is to establish a series of recommendations that allow for the complete diagnosis of chronic viral hepatitis in a single analytical extraction(6). Likewise, via this research letter, we aim to make a series of recommendations for health professionals, services, and programs, in order to prevent infections and facilitate early diagnosis, the dissemination of information on hepatitis and, finally, improvement in healthcare models, guaranteeing follow-up and access to treatment.

The single analytical extraction diagnostic algorithm could be applied to both a biological sample obtained by venipuncture or a dried blood specimen, facilitating access to the most vulnerable

populations. The comprehensive diagnosis of viral hepatitis using a single blood extraction is advantageous, since it minimizes the need for specimen draws to one per patient. It also allows for reduction of care fragmentation by minimizing the number of healthcare encounters needed to reach a diagnosis to one, which may help to increase early disease detection and prevent virus associated hepatic comorbidities and mortality. This reduced fragmentation of health care also addresses provider-level barriers to viral hepatitis care, by decreasing the need for referral and coordination with external health services and facilitates linkage of those diagnosed to effective health management, enhancing treatment uptake and cure rates(7).

In the case of HCV screening, the blood specimen could be further used to test for the presence other pathogens, enabling the diagnosis of associated infections, as HCV often overlaps with other chronic conditions caused by blood-borne viruses, such as HIV and HBV. Given WHO's movement towards more population-centric models of care(8), these recommendations are aligned with integrated strategies for viral hepatitis, HIV and sexually transmitted infections. The systematic use of such an approach will enable obtaining reliable estimates of the prevalence of different diseases and, consequently, to establish global, national and regional plans to facilitate their control and elimination. This will facilitate the achievement of WHO objectives relating to diseases other than HCV.

It is worth remembering that chronic viral hepatitis is largely neglected as it is associated with substance use and linked to social stigma, with a higher prevalence occurring among lower socioeconomic groups. The social gradient in screening uptake might result in unequal access to care and increased mortality rates among those most vulnerable. The comprehensive diagnosis of viral hepatitis and HIV would help to minimize the impact of these social inequities.

The implementation of such a protocol appears to be relatively simple. However, further work is required to optimize and embed this strategy into health systems and improve HCV infection outcomes. Recently, our working group conducted a survey (*unpublished data*), which was mailed to 130 hospitals in Spain (response rate 37%), to assess their potential to implement these recommendations. While all centers can test for HIV, HBV, and HCV, it was found that only 67% can test for HDV antibodies and 31% can identify HDV-RNA. Reflex-testing is conducted for HCV in 88% of the centres, 62% for HBV, 50% for HDV, and only 41% for HBV-HDV. Even though 90% of centers consider both HBV and HCV serology should be performed on HIV-positive patients in the same sample, only 18% of HBsAg-positive and/or anti-HCV-positive subjects have it done. Therefore, necessary tasks include: 1) educating all professionals involved in hepatitis patient care to implement this innovative strategy, 2) improving the availability of reflex testing for HCV detection so as to enable it to become standardized in clinical practice, 3) increasing the

integration of HBV and HIV testing in HCV infected patients, and 4) for those with HBV, integrating double reflex testing for HDV infection, as HBV-HDV co-infection causes severe liver disease and promising treatment is available(9).

To further leverage the single analytical extraction diagnostic algorithm for viral hepatitis, fibrosis assessment could also be performed using the same blood sample. Non-invasive tests, such as FIB-4, can easily and even automatically be calculated to rule cirrhosis in or out, for those with HCV infection in need of hepatocellular carcinoma screening and follow-up. As for those with HBV infection, fibrosis assessment is needed prior to treatment initiation. Furthermore, novel intelligent diagnostic tools(10) can help to uncover preventable liver diseases on a large scale and fit in well within the comprehensive diagnosis of viral hepatitis.

Figure caption:

Figure1. Pathway and recommendations for a comprehensive diagnosis of viral hepatitis with a single blood sample. *Ab: Antibody; HBsAg: hepatitis B virus antigen; HCV: hepatitis C virus; HDV: hepatitis D virus; HIV. human immunodeficiency virus*.

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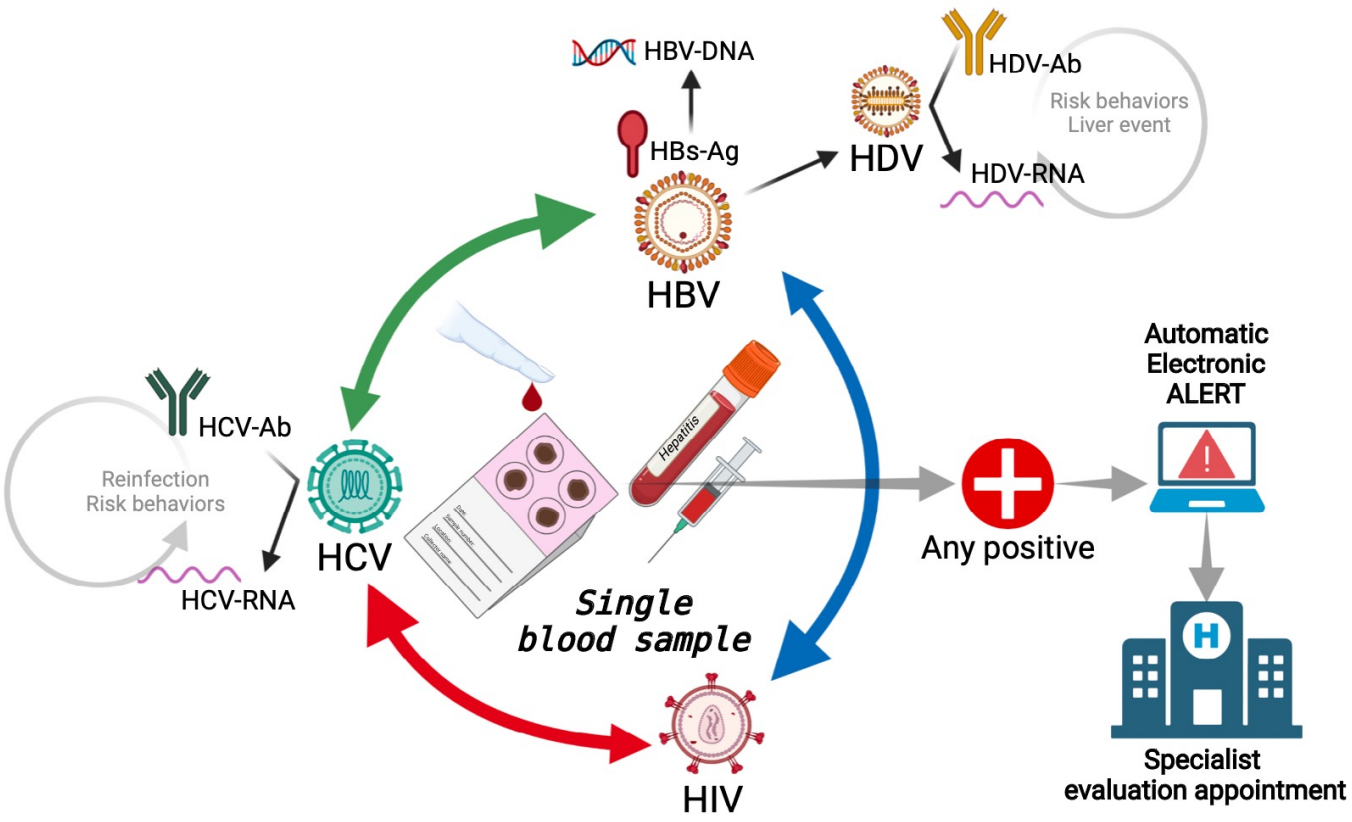

Key bullet points for compehensive viral hepatitis diagnosis and management

Hepatitis B

a) In all subjects in whom the hepatitis B virus surface antigen (HBsAg) is detected for the first time, it is recommended that at least, it is recommended to perform the determination of DNA-HBV automatically in the same sample.
b) In the same way, co-infections by the hepatitis D virus (HDV) and hepatitis C virus (HCV) must be ruled out automatically, by detecting antibodies against HDV and HCV (anti-HDV and anti-HCV), respectively.

Hepatitis C

a) In all subjects in whom positive anti-HCV is detected for the first time, the presence of HCV-RNA or HCV core antigen must be determined in the same sample.
b) In addition, in those anti-HCV positive patients previously diagnosed and cured, but with risk behaviors, HCV viremia should be repeated, at least yearly.

Hepatitis D

a) In all patients in whom anti-HDV is positive, HDV-RNA should be determined.
b) In HBsAg-positive patients, anti-HDV serology should be repeated if there are risk factors for HDV infection or any alteration of liver enzymes/events.

Additional Recommendations:

a) All patients with hepatitis B, C and/or D should be referred to and evaluated by a physician experienced in viral hepatitis.
b) In all patients with chronic viral hepatitis, HIV infection must be ruled out.
c) HBsAg and anti-HCV must be performed in all patients with positive HIV serology.
d) The integration of the results of Point-of-Care tests and supervision by a Microbiology laboratories is recommended, as well as the inclusion of these results in patient's medical records.
e) The integration of screening programs for the detection of patients with active infection.
f) The implementation of automated alert systems to inform the primary care physician and/or specialist of the existence of viral hepatitis.
g) The creation of automated appointment systems for the patient in a specialized out-patient clinic.