

# Is there a need for universal double reflex testing of HBsAg-positive individuals for hepatitis D infection?

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## Abstract

Hepatitis D virus (HDV) can infect HBsAg-positive individuals, causing rapid fibrosis progression, early decompensation, increased hepatocellular carcinoma risk, and higher mortality than hepatitis B virus (HBV) mono-infection. Most countries lack high-quality HDV prevalence data, and the collection techniques employed often bias published data. In recent meta-analyses, HDV prevalence in HBsAg-positive patients reaches 5%-15% and is even significantly higher in endemic areas. Since HBV vaccination programs were implemented, HDV prevalence has decreased among younger populations. However, owing to immigrant influx, it has increased in some Western countries. The current practice of HDV screening in HBsAg-positive individuals is stepwise, based on physician's discretion, and limited to at-risk populations and may require numerous visits. Double reflex testing, which includes anti-HDV testing in all HBsAg-positive individuals and then HDV RNA testing for anti-HDV-positive ones, is uncommon. Reflex testing can identify more HDV infection cases and link identified patients to further care and follow-up. Moreover, laboratory-based double reflex screening is less biased than physician-led testing. Therefore, health-care providers should learn about reflex testing, and federal and provincial hepatitis control programs should implement laboratory-based double reflex testing to obtain reliable HDV prevalence estimates. The test's cost-effectiveness depends on the number of HBV-positive patients screened to identify one HDV-positive patient. Such testing may be viable in areas with low HBsAg but high HDV prevalence. However, its economic impact on areas with low HDV prevalence needs further study.

**Key Words:** Anti-hepatitis D virus antibody; HBsAg; Hepatitis D virus RNA; Hepatitis B; Hepatitis D; Reflex testing

**Core Tip:** Most countries lack high-quality hepatitis D virus (HDV) prevalence data, and published data are often biased by the collection techniques employed. Currently, HDV diagnosis practice is stepwise. It relies on physician's discretion and requires numerous visits. Generally, only HBsAg-positive patients highly at risk for HDV are screened. Double reflex testing involves anti-HDV testing of all HBsAg-positive individuals, followed by HDV RNA testing for those who test positive for anti-HDV. This test approach is gaining attention because of the severe implications of HDV coinfection, and emerging as an effective strategy for identifying undiagnosed cases.

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## INTRODUCTION

Hepatitis D significantly increases the risk of rapid fibrosis progression, early decompensation, hepatocellular carcinoma, and higher mortality than HBV mono-infection[1]. Most countries have no quality prevalence data, and published data are often biased. Meta-analyses indicate that 5%-15% of HBsAg-positive patients have been exposed to hepatitis D virus (HDV), accounting for 12-70 million individuals[2-4]. However, these meta-analyses focused on regions or pockets with a high infection probability. Recently, the adjusted HDV prevalence was lower in most countries and territories than previously reported[5]. In addition, many countries have no nationwide reports of HDV prevalence. The study (crude) prevalence of hepatitis D is not the same as the country prevalence because only those suspected to harbor HBV are tested and reported. Therefore, the reported HDV pockets do not represent country prevalence.

Since hepatitis B vaccination programs were implemented, the epidemiological landscape of hepatitis D has changed. In 2021, the global HDV prevalence was approximately at 262240000 and only a fraction of these infections were newly diagnosed[6]. However, the true prevalence of HDV remains uncertain because of the lack of awareness, limited access to reliable diagnostic tests for HDV antibody and HDV RNA, and high screening cost, resulting in the diagnosis of only 20%-50% of the true population infected with the HDV[1]. Most of the diagnosed population comprises immigrants and refugees in the West and residents of several Asian nations[7]. Although the HDV prevalence is generally decreased in the younger population resulting from robust HBV vaccination programs in some countries, it has increased in Western countries because of the influx of immigrants, as mentioned above.

Early detecting hepatitis D is important because it has implications for public health. With early treatment, disease progression and complications may be prevented. In one study, delaying HDV screening for more than 5 years was independently associated with worsened liver-related outcomes[8]. In addition, knowledge of HDV coinfection influences treatment decisions because certain newly developed antiviral medications are effective against both HBV and HDV, including bulevirtide[9]. Identifying and managing HDV-positive individuals help reduce the risk of disease transmission, particularly in high-risk settings such as healthcare facilities and households. Screening programs also contribute to public health education by increasing awareness of the risks associated with HBV and HDV coinfection.

Double reflex testing involves anti-HDV testing of all HBsAg-positive individuals, followed by HDV RNA testing for those who test positive for anti-HDV. Owing to the severe implications of coinfection, this test has gained attention, emerging as an effective diagnostic strategy. However, the current practice of diagnosing HDV is stepwise, relying on the physician's discretion and requiring several visits. HDV cases must be identified for timely care management. Reflex testing simplifies the process for both healthcare providers and patients and reduces the bias inherent to physician-led testing.

The universal screening of HBsAg-positive patients helps identify more individuals with HDV infection. If implemented in national hepatitis control programs, it will be more cost-effective in areas with a reported lower prevalence of hepatitis B but a higher prevalence of hepatitis D. The cost-effectiveness depends on the number of HBV-positive patients screened to obtain one patient with hepatitis D. However, considering that the number of newly diagnosed HBV cases has decreased globally, the strategy of reflex testing may be easily implemented by the healthcare systems. Cost-effectiveness studies may be needed in areas with high HDV *vs.* low HDV prevalence.

Several pieces of evidence support double reflex testing. A study conducted at the University of Naples Hospital Federico II in Italy highlighted the impact of implementing reflex testing for HDV in HBsAg-positive individuals. Before reflex testing was introduced, only 16.4% of HBsAg-positive participants were tested for anti-HDV, but after implementation, the percentage increased to 100%. Although the anti-HDV positivity prevalence decreased (from 16.6% to 10.7%), the absolute number of identified anti-HDV-positive patients rose from 14 to 52, with a higher prevalence in immigrant populations, leading to the possibility of more targeted interventions[10]. Therefore, reflex testing substantially improves the detection of HDV infection.

In Spain, one study assessed the impact of HDV reflex testing over 8 years by comparing the previous scenario with the current one (7.6% testing rate) using a proposed universal reflex testing strategy. Results revealed that implementing

reflex testing increased anti-HDV detection; thus, more patients received treatment and achieved undetectable HDV-RNA levels. Liver complications and associated costs were also significantly reduced; thus, reflex testing could decrease the clinical and economic burden of chronic hepatitis D by 35%-38% by 2030[11]. Such modeling could be used to support the drive for double reflex testing with long-term savings, contributing to the increased upfront cost.

Guidelines for HDV screening vary internationally. The European Association for the Study of Liver recommends testing all HBsAg-positive individuals[12]. The American Association for the Study of Liver Diseases focuses on patients at high risk of HDV infection or with active liver disease despite low HBV-DNA levels[13]. However, a United States study showed that a risk-based screening approach would miss 18% of HDV-positive patients because of unreported or negative risk factors[14]. Therefore, reflex anti-HDV testing followed by HDV-RNA testing is now increasingly advocated in the United States. Despite Factors such as awareness, reliable test availability, and cost-effectiveness in different epidemiological settings can influence the adoption of such a program[1]. However, the Chronic Liver Disease Foundation has recently recommended universal HDV screening for all HBsAg-positive patients[15].

## CONCLUSION

Double reflex testing is highly recommended in hepatitis D-endemic regions. Modeling should be initially employed to project the cumulative savings attained from this program, which can, in turn, justify the economic impact of increased testing. Furthermore, low-HBV-prevalence and high-HDV-prevalence countries should consider double reflex testing as the preferred strategy[6]. Reflex testing for HDV in HBsAg-positive individuals significantly improves HDV infection detection and management and eases the burden on physicians. Therefore, healthcare providers need to be educated on this program, and government-based hepatitis control programs should implement it.

## FOOTNOTES

**Author contributions:** Abbas Z conceived the theme; A review of the literature was done by Abbas Z and Abbas M; Both authors approved the final version of the manuscript.

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