Hepatitis B virus (HBV) and Hepatitis D virus (HDV) Laboratory-based Reflex Testing Case Studies

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Introduction
A global laboratory survey was undertaken by the Coalition for Global Hepatitis Elimination and the University of North Carolina in collaboration with WHO to investigate the scope, use, and implementation experience of reflex viral load for HBV DNA and also reflex HDV serology and HDV RNA testing.

Methods and Materials
A comprehensive web-based survey was conducted using SmartSheet to gather quantitative and qualitative data on HBV DNA and HDV reflex testing. The survey was shared with over 1,000 participants. Reflex laboratory testing was defined as either immediate HBV DNA testing and/or reflex HDV serology testing of persons with positive HBsAg test results using an existing blood specimen, based on a single clinical interaction and one blood sample or immediate testing of positive HDV serology samples for HDV RNA. The survey was in five sections and those that offered reflex testing for either HBV DNA and/or HDV serology addressed reasons for offering reflex testing, specimen collection process, testing protocol, costs, the impact on care, and key challenges in implementation.

A total of 26 laboratories from 19 countries responded to the survey—8 (42%) were from high-income countries, and 11 (58%) were from low-middle-income countries.

Six labs performed HBV DNA reflex testing (China, Ghana, Myanmar, Nigeria, Italy, and Spain) and 8 HDV serology reflex tests (USA, China, Egypt, Malawi, Italy, and Spain). Of the six labs performing HBV DNA reflex testing, all reported initiating this option to improve linkage to care.

All six reported securing buy-in from administrators as a critical step in implementation, followed by training clinicians (n=2) and laboratory staff (n=4).

Eight sites performed HDV serology testing, and three performed reflex HDV serology in positive HBsAg samples.

Four laboratories reported performing HDV RNA molecular testing and three reflex testing of positive HDV serology samples.

Italy and Spain have labs that reported testing in all five categories of testing surveyed (1-HBV DNA, 2-HDV serology, 3-reflex HDV serology, 4-HDV RNA molecular, 5-reflex HDV RNA molecular).

Three of the five labs reported securing a reliable supply of high-quality and approved tests as challenging.

Key steps to initiating HBV DNA reflex testing
1. Developing guidance for testing algorithm
2. Evaluations proposed to的成本
3. Equipment (new purchase or software)
4. Securing agreement by administrators
5. Securing agreement by payers
6. Setting up automated lab forms to report labs to clinicians
7. Setting up automated lab forms to enter test
8. Training for clinicians
9. Training for lab staff
10. Training for phlebotomists

Table 1. HBV and HDV reflex testing locations

<table>
<thead>
<tr>
<th>Country</th>
<th>Performing HBV reflex testing</th>
<th>Performing HDV reflex testing</th>
<th>Implementing reflex HDV RNA molecular testing</th>
<th>Implementing reflex HDV serology testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hospital Universitat La Pau, Spain</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Germany</td>
<td>No</td>
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<td>Spain</td>
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<tr>
<td>Egypt</td>
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<td>National Health Laboratory, Myanmar</td>
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<td>France</td>
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<tr>
<td>Italy</td>
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<td>Spain</td>
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<tr>
<td>Total case studies</td>
<td>6</td>
<td>8</td>
<td>5</td>
<td>3</td>
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</table>

Conclusions
- Reflex HBV DNA and HDV reflex testing are occurring in diverse settings globally (both high-income countries and low- and middle-income countries)
- Motivations for initiation of reflex testing: Improving patient management and care and understanding of burden of HBV and HDV
- Investments required: Securing buy-in from administrators identified as most important step
- Key challenges:
  - Training of laboratory staff for both reflex HBV DNA and reflex HDV testing
  - Supply of required tests (access to approved tests for HDV)
  - Additional evidence is needed from diverse settings on public health and economic impact of implementing reflex HBV DNA and reflex HDV testing to further build the case
  - Concerns about additional costs of reflex testing exist
- For labs implementing HBV DNA reflex testing, protocols are well-established and can be shared for scale-up

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