Isolated Hepatitis B Core Antibody in People with HIV Infection

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No financial conflicts of interest or relationships to disclose.
Topics

• Virology & Definition

• When isolated anti-HBc is encountered

• Clinical significance – occult HBV infection

• HBV immunization in these patients

• Practical considerations
Hepatitis B virus

Virology

www.hivandhepatitis.com
Natural History of Acute Resolved HBV
Core Antibody

Anti-HBc does not react to the core of the intact virion since the core is completely surrounded by the envelope. Thus, anti-HBc does not play a direct role in controlling or preventing HBV infection.

From [http://depts.washington.edu/hepstudy](http://depts.washington.edu/hepstudy) (now Hep B Online)
Isolated Hepatitis B Core Antibody

- **Definition:** *Anti-HB core Ab(+) but anti-HBs and HBs antigen negative*
- **Common profile** – found in 20-45% in persons with HIV
- **Factors** associated with isolated core Ab:
  - Chronic hepatitis C infection
  - Older age
  - CD4 count <100 cells/mm³
  - HIV suppression on ART: *less likely* to be isolated core

Isolated Hepatitis B Core Antibody in HIV

Seen in 1 of these 4 scenarios:

1) “Window phase” of acute HBV infection between loss of HB surface antigen and emergence of anti-HB surface Ab;

2) Remote resolved HBV infection with waning of anti-HB surface Ab to level <10 IU;

3) Chronic infection, i.e. occult HBV with HB surface Ag that has escaped detection either due to low production or mutations in envelope protein rendering sAg undetectable by routine assays;

4) Finally, false positive → actually never exposed to HBV

Isolated Hepatitis B Core Antibody
Clinical significance

• Isolated core Ab appears to be a stable pattern over time in most (84%) individuals
  – If retested, still present (i.e. false positive seems unlikely)
  – If it changes, transitions to/from pattern of natural immunity (anti-HBs and anti-HBc positive) were typical
  – Transition to/from chronic HBV infection (gain or loss of HBsAg) was rare

• Not associated with:
  – ALT/AST elevations (independent of HCV coinfection)
  – Liver stiffness by FibroScan (independent of HCV coinfection)

French, J Infect Dis 2007;195;1437-42.
Isolated Hepatitis B Core Antibody in HIV

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Isolated Hepatitis B Core Antibody
Occult Hepatitis B in HIV

- Defined by negative surface Ag, (+)HBV DNA level
- Not common – prevalence variable, depending on geography, population & assays
  - US-based case series: prevalence ~2-10% among isolated core pts
  - True prevalence may be underestimated due to
    ✓ Cross-sectional nature of many studies
    ✓ Fact that patients may be on HBV-active antivirals
- HBV viral levels detected typically low (<1000 IU/mL range)

Reactivation of occult HBV infection in an HIV/HCV Co-infected patient successfully treated with sofosbuvir/ledipasvir: a case report and review of the literature

Gabriele Fabbri, Ilaria Mastrorosa, Alessandra Vergori, Valentina Mazzotta, Carmela Pinnetti, Susanna Grisetti, Mauro Zaccarelli, Adriana Ammassari and Andrea Antinori
Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports


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Background: Rituximab has been associated with hepatitis B virus reactivation (HBV-R). However, the characteristics and scope of this association remain largely undefined.

Methods: We completed a comprehensive literature search of all published rituximab-associated HBV-R cases and from the Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) MedWatch database. Literature and FDA cases were compared for completeness, and a meta-analysis was completed.

Results: One hundred and eighty-three unique cases of rituximab-associated HBV-R were identified from the literature (n = 27 case reports, n = 156 case series). The time from last rituximab to reactivation was 3 months (range 0–12), although 29% occurred >6 months after last rituximab. Within FDA data (n = 118 cases), there was a strong signal for rituximab-associated HBV-R [proportional reporting ratio = 28.5, 95% confidence interval (CI) 23.9–34.1; Empiric Bayes Geometric
A 50 year-old man with HIV, CD4 678 cells/mm³ and VL is undetectable on ART (abacavir-lamivudine-dolutegravir). His hepatitis B profile demonstrates isolated anti-HBc. LFTs are normal.

**What would you do next?**

A. Check HBV DNA level to evaluate for occult HBV.

B. Start complete HBV immunization series with standard dose.

C. Give one standard dose and check anti-HBs titer in 4 weeks to determine next steps.

D. Check anti-HBe antibody to determine next steps.
Isolated Hepatitis B Core Antibody
HBV Immunization

• Immunization can presumably help distinguish the latter 3 scenarios:

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Vaccine Response</th>
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<tbody>
<tr>
<td>Resolved HBV, waned sAb</td>
<td>Anamnestic response</td>
</tr>
<tr>
<td>Occult (chronic) HBV</td>
<td>No response</td>
</tr>
<tr>
<td>False positive</td>
<td>Primary response</td>
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</tbody>
</table>

• BUT most isolated core Ab patients with HIV do NOT mount an anamnestic response
## Isolated Hepatitis B Core Antibody

### HBV Immunization

<table>
<thead>
<tr>
<th>Study</th>
<th>Anamnestic Response</th>
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</thead>
<tbody>
<tr>
<td>Gandhi JID 2005</td>
<td>24% (7/29)</td>
</tr>
<tr>
<td>Jongjirawisan JAMT 2006</td>
<td>7% (2/28)</td>
</tr>
<tr>
<td>Chakvetadze, CID 2010</td>
<td>32.5% (13/40)</td>
</tr>
<tr>
<td>Kaech, J Infect 2012</td>
<td>22% (8/37)</td>
</tr>
<tr>
<td>Piroth, JID 2016</td>
<td>8% (8/54)</td>
</tr>
</tbody>
</table>
HBV Immunization of Isolated Core Ab

Seroprotective Response

- **40 mcg x 3**
  - 89% at 28 weeks
  - **24/27**
  - **8 (15%)** had anamnestic response (>100 IU/L)

- **20 mcg x 1**
  - 46% at 4 weeks
  - **25/54**

- **81%** at 18 months
  - **21/26**

Practical Considerations
What do the guidelines say?

DHHS OI Guidelines on Hep B (last update June 2019):
• Do not routinely check HBV DNA in patients with isolated core Ab
• Vaccinate with one standard dose of HBV vaccine
• Check anti-HBs titers 1 to 2 months after
• If sAb <100 IU/L, then give full vaccine series (level BII)

HIVMA 2020 Primary Care Guidelines:
• Isolated core Ab patients should receive vaccination
Practical Considerations

Expert Opinion

- **Isolated cores:** Screen for occult HBV with HBV DNA level
  - Not on tenofovir, emtricitabine or lamivudine
  - ALT or AST elevated
  - Chronic hepatitis C – esp. pre-DAA
  - Not responding to HBV vaccination
  - When you’re worried re HBV reactivation

- **Hepatitis B Immunization for isolated anti-HBc:**
  - Vaccinate early
  - Always check anti-HBs 1-2 months after vaccination
  - Role of CpG-adjuvanted hep B vaccine...?
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