CMEO
BriefCase

Throwing a Curve Ball at Hepatitis B Serological Tests: Interpreting Results to Guide Next Steps

Supported by an educational grant from Gilead Sciences, Inc.

CME OUTFITTERS

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Patient Case: Samuel

- 54-year-old man with chronic hepatitis B (CHB) for 14 years who immigrated from Sierra Leone 8 years ago
- Maintained on tenofovir alafenamide (TAF) with stable HBV viral suppression for past 3 years
- Samuel presents today with abdominal pain, back pain, vomiting, and fatigue for the past 7 days

HBV = hepatitis B virus

Virtual Visit

Patient Case: Samuel

- Samuel's serologic results return:
  - Hemoglobin: 14
  - Hematocrit: 43%
  - Platelet count: 200,000
  - HBsAg positive
  - HBV DNA: 50 IU/mL
  - ALT: 520 u/L
  - AST: 340 u/L
  - Total bilirubin: 2.2 mg/dL
  - Alkaline phosphatase (ALP): 164 IU/L
  - Albumin: 3.4 mg/dL
  - Creatinine: 1.1 mg/dL

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; dL = deciliter; HBsAg = hepatitis B surface antigen; IU = international unit; L = liter; mg = milligram; mL = milliliter; u = units

Audience Response

If Samuel has been adherent to his TAF, what could be the likely cause of the acute infection?

A. Herbal supplements could be interacting with his TAF
B. Alcoholic hepatitis
C. Hepatitis B reactivation
D. Hepatitis A
E. Hepatitis Delta (D)
F. I don’t know

Virtual Visit

Audience Response

What would be your next step?

A. Send Samuel to the emergency department
B. Ask Samuel about his sexual partners
C. Ask Samuel about any herbal supplements that he may be taking that could interact with his TAF
D. Expand testing to include hepatitis A, Delta (D), and E
E. I don’t know

Virtual Visit

Learning Objective

Implement routine screening protocols for hepatitis B in the primary care setting to derive guideline-directed care, as well as improve the detection of hepatitis D.

Hand in Hand: Hepatitis B and Delta

- Hepatitis delta virus (HDV) is a serious co-infection of HBV that is estimated to affect 48-72 million people with CHB worldwide[1]
- HBV-HDV co-infection is most prevalent in Central Asia, Eastern Europe, Central Latin America, and West and Central Africa[2]
- HDV requires HBV for replication, thus HDV infection only occurs in the presence of HBV[2]

1. Shen DT, et al. *Gut.* 2020;69(4):786-788. 2. Kumar P, et al. *Prev Chronic Dis*. 2020;17:E159.

Transmission of HDV

- Sex with an infected partner
- Injection drug use that involved sharing needles, syringes, or drug-preparation equipment
- Birth to an infected mother (rare)
- Contact with blood from or the open sores of an infected person
- Needle sticks or exposures to sharp instruments
- Sharing items (e.g., razors, toothbrushes) with an infected person

Centers for Disease Control and Prevention (CDC). CDC Website. 2020. https://www.cdc.gov/hepatitis/hdv/hdvfaq.htm#section2. Accessed April 29, 2021.

HDV Symptoms Present Much Like Other Viral Hepatitis Infections

- Fever
- Fatigue
- Loss of appetite
- Nausea
- Vomiting
- Abdominal pain
- Dark urine
- Clay-colored bowel movements
- Joint pain
- Jaundice

Most symptoms typically appear 3 - 7 weeks after initial infection

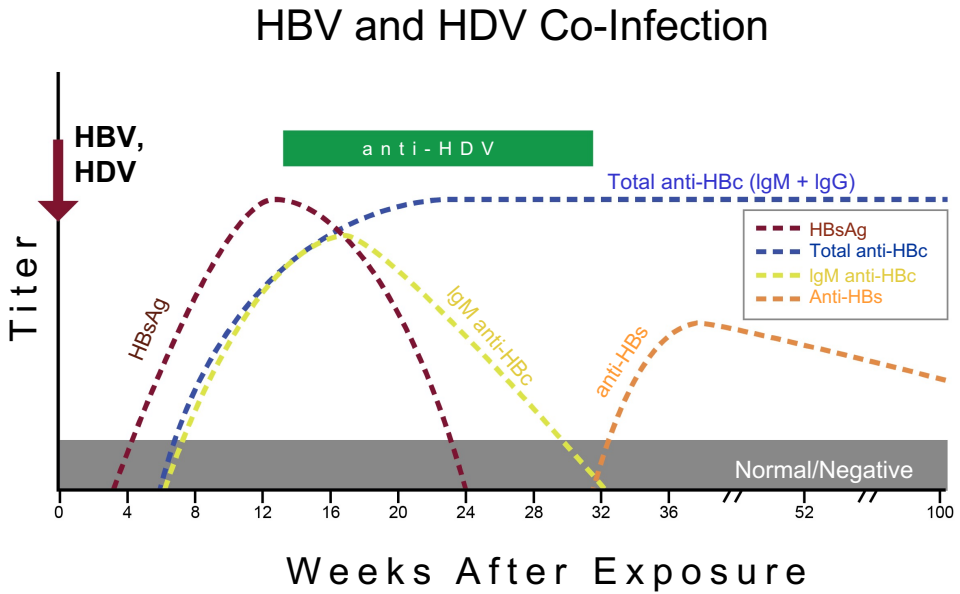
Farci P, et al. *Semin Liver Dis.* 2012;32(3):228-236.

What additional serologic tests should be ordered to determine if Samuel has HDV?

A. Total anti-HDc (IgM + IgG) and anti-HDV
B. Hepatitis Delta antigen (HDAg), Total HDV antibody (IgM + IgG), HDV RNA
C. HBsAg, anti-HDV, Total anti-HBc (IgM + IgG)
D. Hepatitis Delta antigen, Total HDV antibody (IgM + IgG), HDV DNA
E. I don’t know

HBV and HDV Co-Infection

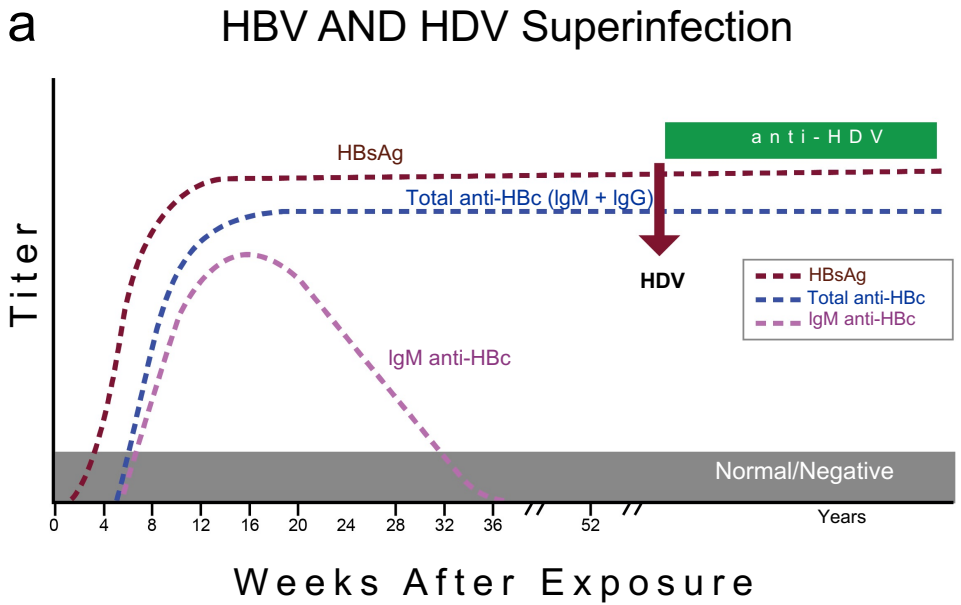
- Results in an acute HBV and HDV infection
- Resembles classic acute HBV except that a biphasic course of ALT may be seen several weeks apart
- Most patients recover during the acute co-infection
- Only 5% go on to develop chronic infection (persistence of infection beyond 6 months)



1. Masood U, et al. Hepatitis D. [Updated 2021 Jan 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021. https://www.ncbi.nlm.nih.gov/books/NBK470436/. Accessed April 29, 2021. 2. Centers for Disease Control and Prevention (CDC). CDC Website. https://www.cdc.gov/hepatitis/resources/professionals/training/serology/training.htm. Accessed April 29, 2021.

HBV and HDV Superinfection

- Individuals who are chronic carriers of HBsAg may develop a superinfection with HDV
- May present as acute severe hepatitis from a different cause
- May be mistaken as an acute flare of CHB
- Clinical course more severe
- 90% may progress to chronic HDV resulting in more severe morbidity and complications



1. Masood U, John S. Hepatitis D. [Updated 2021 Jan 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021. https://www.ncbi.nlm.nih.gov/books/NBK470436/. Accessed April 29, 2021. 2. Centers for Disease Control and Prevention (CDC). CDC Website. https://www.cdc.gov/hepatitis/resources/professionals/training/serology/training.htm. Accessed April 29, 2021.

Correct Serologic Tests to Order

What additional serologic tests should be ordered to determine if Samuel has HDV?

A. Total anti-HDc (IgM + IgG) and anti-HDV
B. Hepatitis Delta antigen (HDAg), Total HDV antibody (IgM + IgG), HDV RNA
C. HBsAg, anti-HDV, Total anti-HBc (IgM + IgG)
D. Hepatitis Delta antigen, Total HDV antibody (IgM + IgG), HDV DNA
E. I don't know

Treatment Options

- No FDA-approved treatment for HDV infection is available
- High-dose IFN-alpha 2a has shown a survival benefit
  - 9 million IU 3x weekly
- Pegylated-IFN alfa
  - 1.5 μg/kg or 180 μg subcutaneously weekly
  - Undetectable HDV RNA at the end of treatment in 19% - 57% with sustained response in 17% - 43% at 6 months of follow-up
  - However, sustained viral clearance persists in 28% at 1 year
  - Patients with higher HBV DNA loads seem to respond faster than HDV viremia only
  - Tolerance and outcomes not improved with addition of ribavirin, adefovir, or entecavir

IFN = interferon

Hercun J, et al. *Gastroenterol Clin North Am*. 2020;49(2):239-252.

Emerging Treatments for HDV

Drug Name	Mechanism of Action	Clinical Status
Bulevirtide	Entry inhibitor	Approved in Europe, Phase III FDA Breakthrough Therapy Designation FDA Orphan Drug Designation
Lonafarnib	Prenylation inhibitor	Phase III FDA Breakthrough Therapy Designation FDA Orphan Drug Designation FDA Fast Track Designation
Lambda (Pegylated IFN)	Immune response stimulator	Phase III Ready FDA Breakthrough Therapy Designation FDA Orphan Drug Designation FDA Fast Track Designation
REP 2139	HBsAg inhibitor	Phase II
Ezetimibe	NTCP inhibitor	Phase II

NTCP = sodium-taurocholate cotransporting polypeptide

Hepatitis B Foundation. 2020. https://www.hepb.org/research-and-programs/hepdeltaconnect/drug-watch/. Accessed April 29, 2021.

Treatments for HDV in Late Stages of Development

Bulevirtide

- Combined with pegylated IFN-alpha 2a or TDF led to HDV viral suppression
- A third of people taking bulevirtide with TDF maintained an undetectable HDV viral load after discontinuing
- Treatment generally well tolerated[1]

Lonafarnib

- Reduced viral load and can be safely boosted with ritonavir to allow for higher and more effective doses
- Has been studied with and without IFN Lambda and IFN-alpha 2a
- Acceptable gastrointestinal side effects[2]

Lambda (Pegylated IFN)

- Phase II LIFT open label study of 26 adult patients with chronic HDV treated with Lambda 180 mcg weekly in combination with lonafarnib 50 mg + ritonavir 100 mg BID for 24 wk + 24 wk follow-up
- 95% achieved > 2 log decline in HDV RNA at 24 wks
- 53% undetectable HDV RNA
- Generally well tolerated[3]

BID = twice daily; mcg = micrograms

1. Wedemeyer H, et al. *J Hepatol*. The Digital International Liver Congress; 2020. Abstract No. AS072. 2. Wedemeyer H, et al. 67th Meeting of the American Association for the Study of Liver Diseases; 2019. Abstract 230. 3. Koh C, et al. American Association for the Study of Liver Diseases; 2019. No. L08.

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Recognize the presentation of an acute hepatitis flare and factors that may link the acute infection to hepatitis delta
- Implement appropriate serologic testing to uncover the source of the HBV flare
- While there are no FDA - approved treatments for hepatitis delta, become familiar with the safety and efficacy data of agents in late stages of development

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https://www.cmeoutfitters.com/liver-hub/

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Hepatitis B Patient Education Hub

A robust hub of patient education and resources for your patients to learn more about hepatitis B.

https://www.cmeoutfitters.com/hbv-patient-education-hub/

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