

HEPATITIS B REACTIVATION GUIDE

HEPATITIS B REACTIVATION

WHAT IS REACTIVATION?

- Clinical guidelines on hepatitis B reactivation (HBVr) tend to differ but generally consist of the following characteristics
 - The sudden increase in hepatitis B DNA or ALT levels despite chronic or past infection status
 - Change in the surface antigen biomarker (a previously negative to now positive test)
 - Hepatitis B Flares and/or liver failure
- Although reactivation can be spontaneous, it is best understood as a medical complication from certain drugs and treatment procedures.
- What can cause reactivation?
 - Certain drugs and therapies used to treat cancers
 - Certain drugs used to treat immune system disorders
 - Direct-acting antivirals to treat hepatitis C (HCV) and antiviral therapy for HIV

5% - 70%

may be at risk for reactivation



What puts someone at risk for reactivation?

- Undergoing immunosuppressive therapy, chemotherapy, or Hepatitis C therapy
- Born in an endemic country
- Current or resolved Hepatitis B infection
- Changes in HIV medications

UNDERSTANDING HBV REACTIVATION

Understanding how reactivation occurs can be overwhelming but consider the following example:

- Chickenpox is a common infection among children. It is caused by the varicella zoster virus.
- Even though the infection clears up over time and the physical symptoms go away, the virus remains in the body silently.
- This is why older adults are at risk for Shingles as it's caused by the same virus as it stays hidden in the body for several years.

Similar to the Shingles virus, the hepatitis B virus "sleeps" in the liver for a long period of time. Even though the virus is inactive, reactivation may be triggered by external factors (certain types of medication or co-infection with another disease) or spontaneously.

CLINICAL SYMPTOMS



Nausea



Jaundice



Fatigue



Liver pain



LABORATORY SIGNS

Elevated hepatitis B DNA levels along with liver enzymes (ALT, AST, AP, GGT) indicate rapid replication of the virus

Hepatitis flares, liver dysfunction (indicated by changes in Bilirubin, Albumin, & INR), and other signs of damage to the liver

HEPATITIS B BLOOD TESTS

UNDERSTANDING THE HBV TRIPLE PANEL

Interpretation & Action Needed	HBsAg Hepatitis B Surface Antigen	HBsAb (anti-HBs) Hepatitis B Surface Antibody	HbCAb Hepatitis B Core Antibody
Not Immune- Not Protected Not infected but still at risk. <u>Vaccine needed.</u>	—	—	—
Immune controlled- Protected Recovered from a previous infection. <u>No vaccine needed.</u>	—	+	+
Immune- Protected Not infected and no prior infection. <u>Vaccinated.</u>	—	+	—
Infected Current infection and transmissible. <u>More testing needed.</u>	+	—	+
Exposed Prior exposure to the virus. <u>More testing needed.</u>	—	—	+

WHAT ROLE DOES THE CORE ANTIBODY PLAY IN REACTIVATION?

- The core antibody test is useful in identifying a past exposure to the HBV virus. A past exposure means that the virus is "sleeping" in the liver.
- It is possible to test negative for surface antigen and positive for core antibody. This means that the virus is present but currently inactive.
- Since past HBV exposure is crucial to understanding risk factors, it is important for all individuals to be aware of their current or past HBV infection status.
 - In patients with core antibody positivity, HBV DNA can still be found in small amounts in the liver and other organs
 - Some types of medication can suppress the body's ability to respond to threats and cause an increase in the trace amounts of HBV DNA, resulting in reactivation.

WHO IS AT RISK?

WHAT IS IMMUNOSUPPRESSION THERAPY?

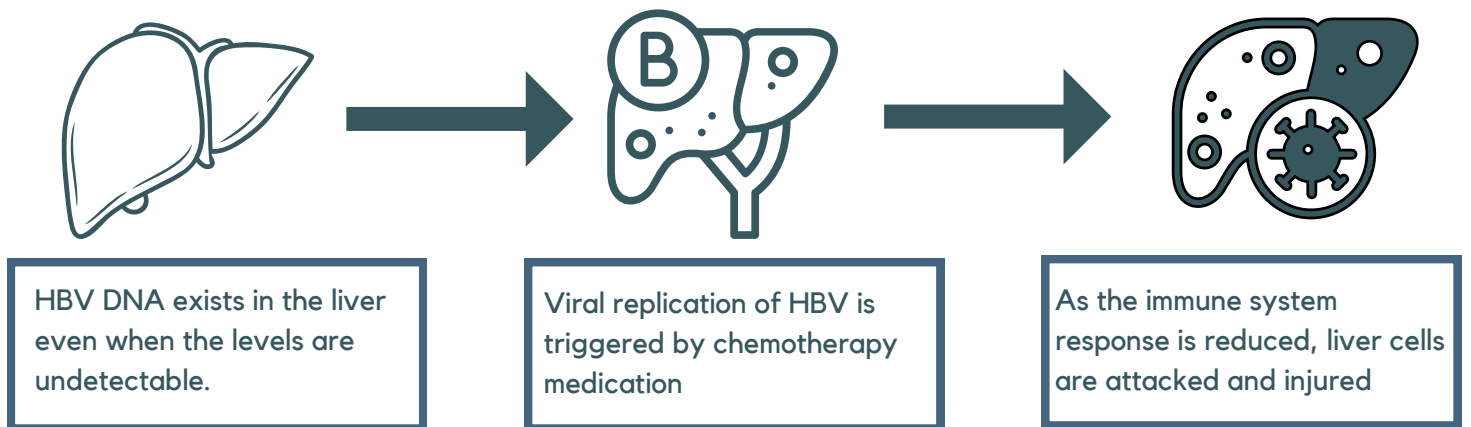
Most HBVr cases are associated with immunosuppression therapy. Immunosuppression therapy treats autoimmune conditions in which the immune system cannot distinguish between foreign invaders and healthy cells and tissues. The body accidentally attacks and kills healthy cells and tissues. It is also used in cancer therapies and organ transplantation procedures.

CHEMOTHERAPY & HBVr

Chemotherapy is used to kill harmful cancer cells with the goal to either destroy the cancer or control its progression. The drugs used can trigger HBVr as the immune system is significantly weakened.

- 1 Immunosuppressive treatment for cancer or autoimmune disorder
- 2 Chemotherapy treatment for cancer
- 3 Treatment for HCV and HIV in people who also have HBV
- 4 Transplant related immunosuppression
- 5 Spontaneous reactivation among individuals with an autoimmune disorder

HOW DOES CHEMOTHERAPY CAUSE REACTIVATION?



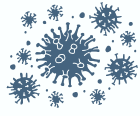
REACTIVATION AMONG HCV AND HIV POSITIVE INDIVIDUALS

For individuals who are co-infected with hepatitis C, it is possible that medication for HCV may trigger reactivation. The complex interaction of the two viruses combined with the direct-acting antiviral treatment may cause elevation in HBV DNA levels, reappearance of other clinical HBV symptoms, or significant liver injury resulting in the need for transplantation. Currently, the risk for reactivation with HCV treatment is higher among those who are surface antigen positive and lower in those who are core antibody positive.

Some cases of HBVr have been reported among HIV-positive individuals starting antiretroviral therapy. In some instances, withdrawal was the identified cause for HBVr. However, research is limited as to why the antiretroviral therapy for HIV causes an increase in HBV DNA levels.

MORE RISK FACTORS

Virological



- High HBV DNA
- Chronic infection with hepatitis B
- Hepatitis B envelope antigen positivity (HBeAg)
- HBV genotype
- Co-infection with other viruses (HCV or HDV)

Host



- Older age
- Male
- Cirrhosis
- Health conditions requiring immunosuppressive medication

Medication Related



The following medications are risk factors for reactivation but it is not an exhaustive list. Please consult with a healthcare provider about hepatitis B screening before starting treatment with any medication.

- **Rituximab**
 - used to treat autoimmune diseases and cancers
- **Ofatumumab**
 - used to treat cancers
- **Doxorubicin**
 - used to treat hematologic and nonhematologic cancers
- **Corticosteroids**
 - used to treat rheumatological disorders
- **TNF- α Inhibitors**
 - used to treat chronic inflammatory diseases
- **Tyrosine Kinase Inhibitors**
 - used to treat cancer malignancies
- **Bortezomib**
 - used to treat bone marrow cancer
- **Direct-Acting Antivirals for Hepatitis C**
 - used to treat hepatitis C
- **Pre-Exposure Prophylaxis (PrEP)**
 - preventative medicine used to reduce the risk of contracting HIV

HOW TO PREVENT REACTIVATION?

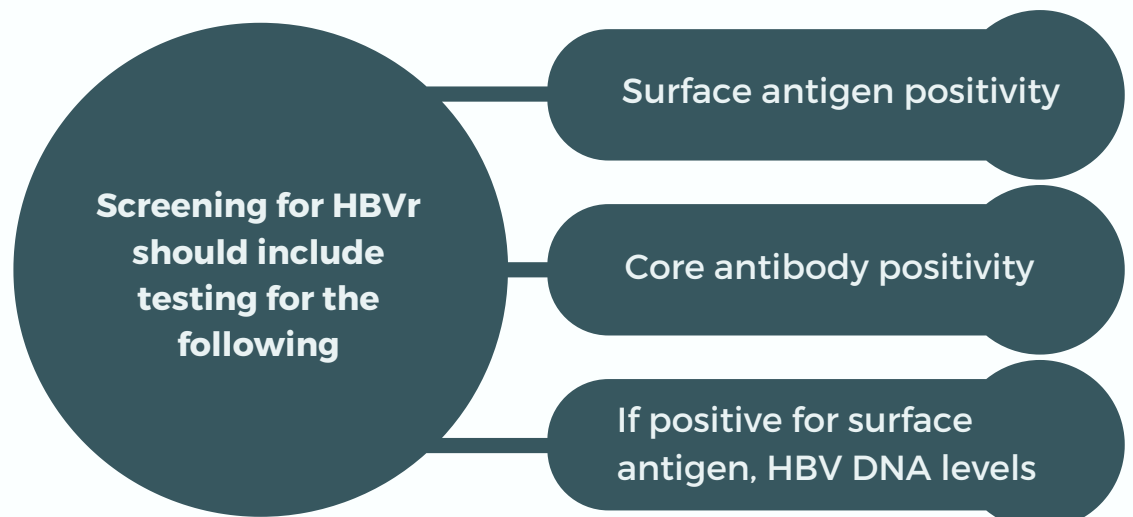
The risk of reactivation with hepatitis B continues to be studied by researchers and medical professionals. Several methods and strategies have been identified to ensure the prevention of reactivation when treating at-risk populations.

SCREENING STRATEGIES

It is recommended to test all patients undergoing immunosuppressive therapy, chemotherapy and HCV therapy for HBV surface antigen, HBV surface antibody, HBV core antibody, and HBV DNA prior to the start of the treatment. These tests will also help determine if vaccine is needed.

Pre-exposure prophylaxis (PrEP) is a type of a medication used to prevent the exposure of HIV through sex or injection drug use. It is important to test for HBV serological markers before initiating PrEP and during the course of treatment to detect any changes to the HBV DNA.

Continuous screening and monitoring may also be needed if an individual tests positive for core-antibody only in order to detect changes in HBV DNA levels during the course of the therapy.



THE SCENARIO

John Smith is an older man living in Philadelphia. He attended a hepatitis B screening event. He noticed that the results indicated that he tested negative for surface antigen but positive for hepatitis B core antibody. He was happy that he did not have the infection.

Several years later, John is scheduled to start immunosuppressive therapy for early-stage lymphoma. During the course of his therapy, his doctor stops treatment and notifies him that his hepatitis B virus has reactivated. John is confused as he recalled that he never had an HBV infection.

THE PROBLEM



Prior to starting the immunosuppressive therapy for his lymphoma, his doctor did not test for any of the HBV serological markers to detect risk for HBV reactivation. Knowing John's HBV infection status prior to the start of the therapy may have prevented reactivation.

When John received his test results from the hepatitis B screening event, he did not fully understand the meanings of the different HBV serological markers. John had tested positive for the core-antibody marker which meant that he had a past exposure to the virus and that a small amount of HBV DNA exists in the liver.



DISCUSSION



Awareness of HBV infection status

With over 70% of the U.S. population unaware of their HBV status, it is crucial to increase screening outreach. People must be aware of their HBV infection status (current or past) and must accurately understand their test results. A core antibody test is the best indication of a past hepatitis B infection



Identifying risk of HBV reactivation

There have been a lot of inconsistencies when it comes to creating and following public health recommendations and guidelines on HBVr prevention, diagnosis, and management. It is important for providers to be aware of the known risk between HBVr and immunosuppressive drugs before putting patients on treatment

REFERENCES

- Smalls, D. J., Kiger, R. E., Norris, L. B., Bennett, C. L., & Love, B. L. (2019). Hepatitis B Virus Reactivation: Risk Factors and Current Management Strategies. *Pharmacotherapy*, 39(12), 1190–1203. <https://doi.org/10.1002/phar.2340>
- Chang Y, Jeong SW and Jang JY (2022) Hepatitis B Virus Reactivation Associated With Therapeutic Interventions. *Front. Med.* 8:770124. doi: 10.3389/fmed.2021.770124
- <https://www.hepatitisb.uw.edu/mini-lectures/lecture/isolated-hepatitis-b-core-antibody>
- Myint, A., Tong, M.J. and Beaven, S.W. (2020), Reactivation of Hepatitis B Virus: A Review of Clinical Guidelines. *Clinical Liver Disease*, 15: 162-167. <https://doi.org/10.1002/cld.883>
- Pattullo V. (2016). Prevention of Hepatitis B reactivation in the setting of immunosuppression. *Clinical and molecular hepatology*, 22(2), 219–237. <https://doi.org/10.3350/cmh.2016.0024>
- Pei, R., Grund, S., Verheyen, J., Esser, S., Chen, X., & Lu, M. (2014). Spontaneous reactivation of hepatitis B virus replication in an HIV coinfecting patient with isolated anti-Hepatitis B core antibodies. *Virology journal*, 11, 9. <https://doi.org/10.1186/1743-422X-11-9>
- Mohareb, A. M., Larmarange, J., Kim, A. Y., Coffie, P. A., Kouamé, M. G., Boyd, A., Freedberg, K. A., & Hyle, E. P. (2022). Risks and benefits of oral HIV pre-exposure prophylaxis for people with chronic hepatitis B. *The lancet. HIV*, 9(8), e585–e594. [https://doi.org/10.1016/S2352-3018\(22\)00123-0](https://doi.org/10.1016/S2352-3018(22)00123-0)
- Jeng, W.-J., Chen, Y.-C., Chien, R.-N., Sheen, I.-S. and Liaw, Y.-F. (2018), Incidence and predictors of hepatitis B surface antigen seroclearance after cessation of nucleos(t)ide analogue therapy in hepatitis B e antigen–negative chronic hepatitis B. *Hepatology*, 68: 425-434. <https://doi.org/10.1002/hep.29640>