Recommendations for Hepatitis B Viral Infection Testing and Monitoring among HCV-Infected Veterans Being Considered for DAA Treatment

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Background:

1. Reactivation of hepatitis B virus (HBV) is defined as an increase in hepatitis B viral replication (HBV DNA) associated with an increase in liver damage. Reactivation is detected by an increase in HBV DNA level or HBsAg detection (in someone previously HBsAg (-) and anti-HBc (+)), and is usually associated with an increase in ALT, with or without an increase in bilirubin.
2. In HCV-infected patients who are ready to start DAA treatment, those who are also HBsAg (+) are at the **highest risk** for HBV reactivation and should be initiated on HBV treatment prior to starting DAA therapy. Consideration can also be given to initiating HBV treatment in Childs-Pugh B and C cirrhotics who are anti-HBc positive only, but HBsAg negative.
3. HBV reactivation is very rare among HBsAg (-) and anti-HBc (+)patients who are not immunocompromised. Only three cases have been reported to date, although one of them developed fulminant hepatic failure requiring a liver transplantation.
4. Reactivation of HBV usually **occurs within 4-8 weeks** after starting DAAs (mean = 52 days) but can occur at any time, even after DAA treatment has completed.

Baseline assessment for HBV

1. History
    a. Is patient known to have documented HBV or documented immunity from prior vaccination? If unknown, check HBV serology and immunize if necessary. Each patient should have documented HBV serology prior to HCV treatment.
    b. Assessment for cirrhosis; patients with cirrhosis are at a higher risk for decompensation if a flare occurs.
2. HBV serologic tests
    a. **HBsAg** (hepatitis B surface antigen)
    b. **anti-HBc total** (hepatitis B core antibody, also known as HBcAb)
    c. **anti-HBs** (hepatitis B surface antibody, also known as HBsAb)
    d. HBV DNA (not required in those with anti-HBs)
3. Other baseline laboratory tests
    a. Liver Panel (albumin, total protein, total bilirubin, direct bilirubin, alkaline phosphatase, ALT, AST)
    b. CBC/platelets
    c. INR
    d. hepatitis A antibody (total)
    e. HIV

Table 1: Interpretation of HBV Serologic Tests and Recommendations for Monitoring and Treatment during DAA Treatment

Tests	Results	Interpretation	Next Steps/ Monitoring	Treatment
HBsAg **anti-HBc** **anti-HBs**	Negative Negative Negative	Susceptible to HBV infection	Immunize* for HBV	**HCV**: Start DAA treatment. **HBV**: Immunize*; DAA treatment can be given concurrently with immunization.
HBsAg **anti-HBc** **anti-HBs**	Negative Negative Positive	Immune due to HBV vaccination	No additional HBV monitoring	**HCV**: Start DAA treatment. **HBV**: No HBV treatment.
HBsAg **anti-HBc** **anti-HBs**	Negative Positive Positive	Recovered from HBV; immune due to natural infection	Monitor **ALT** while on DAA treatment at weeks 4, 8, and 12 and at 12 weeks post-treatment; if ALT does not normalize or rises on therapy, check HBV DNA and HBsAg	**HCV**: Start DAA treatment. **HBV**: No HBV treatment. If HBV DNA detectable, treat with entecavir or tenofovir**
HBsAg **anti-HBc** **anti-HBs**	Positive Positive Negative	Chronic HBV	Check HBV DNA, HBeAg and anti-HBe Monitor ALT while on DAA at weeks 4, 8, and 12, and at 12 weeks post-treatment. Monitor HBV DNA every 3 months.	**HCV and HBV**: Start DAA concurrently with or after starting HBV treatment** After completing DAA treatment, reassess need for continued HBV therapy per AASLD HBV guidelines*** or consult with an expert.
HBsAg **anti-HBc** **anti-HBs**	Negative Positive Negative	Possible interpretations: 1. Distantly immune and test not sensitive enough to detect very low level of anti-HBs in serum 2. Susceptible, with a false positive anti-HBc 3. Recovering from acute HBV infection 4. Undetectable level of HBsAg present in the serum but is actually chronically infected	Check HBsAg or HBV DNA (one or both of these should be performed within the prior 12 months); note: this should *not* delay start of DAA treatment and can be ordered at start of DAA treatment. Monitor ALT at weeks 4, 8, and 12 and at 12 weeks post-treatment; if ALT does not normalize or rises on therapy, check HBV DNA and HBsAg. Strongly consider checking HBV DNA between weeks 4-8 of DAA treatment (**particularly in cirrhotics**). If HBV DNA is detectable, check HBsAg and HBeAg	**HCV**: Start DAA treatment **HBV**: HBV treatment not routinely recommended *However:* a) If HBV DNA is detectable or HBsAg is positive prior to DAA treatment ***or*** becomes detectable during DAA treatment, initiate HBV treatment**. b) Consider HBV prophylaxis in patients with decompensated cirrhosis (CTP class B and C) regardless of HBV DNA or HBsAg status c) For patients on an immunosuppressant agent HBV treatment may be indicated. After completing DAA treatment, reassess need for continued HBV therapy per AASLD HBV guidelines*** or consult with an expert.
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	Positive Positive Positive Negative	Acute hepatitis B infection	Recheck HBsAg, anti-HBc and anti-HBs in six months. Recheck liver panel in 6 months	**HCV**: If possible, wait 6 months for HBV to recover. **HBV**: Symptomatic support (no specific HBV treatment). Monitor for at least 6 months to determine recovery (vs. chronic infection).

* Hepatitis B vaccine (e.g., Engerix-B, Recombivax HB or TwinRx), series of 3 doses; recheck anti-HBs ≥1 month after the third vaccination

**HBV treatment: entecavir 0.5mg-1mg/day or tenofovir 300 mg/day. In HIV/HBV/HCV-coinfected patients, the antiretroviral regimen should include tenofovir, or if not tolerated, entecavir should be added during DAA therapy.

*** AASLD Guidelines for Treatment of Chronic Hepatitis B

Table 2. Summary of AASLD HBV Treatment Criteria

ALT*	HBV DNA (IU/mL)	HBeAg	Other factors which should be present	Treatment Recommended per AASLD HBV Guideline**
≥ 2x ULN	>2,000	negative		yes
≥ 2x ULN	>20,000	positive		yes
>ULN but <2x ULN	>2,000	negative	Evidence of histological disease	yes
>ULN but <2x ULN	>20,000	positive	Evidence of histological disease	yes
>ULN but <2x ULN	<2,000 <20,000	negative positive	Any **one** of the following: Age>40 Family history of HCC Previous HBV therapy Extrahepatic manifestations	yes
Normal or elevated	>2,000	negative or positive	Cirrhosis	yes
Normal or elevated	>100,000	positive or negative	Age>40	yes
Normal or elevated	positive or negative	positive or negative	Immunosuppressants	yes
Normal	Any detectable	positive or negative		No (Immune Tolerant)

*ULN for men = 30 U/L; ULN for women = 19 U/L

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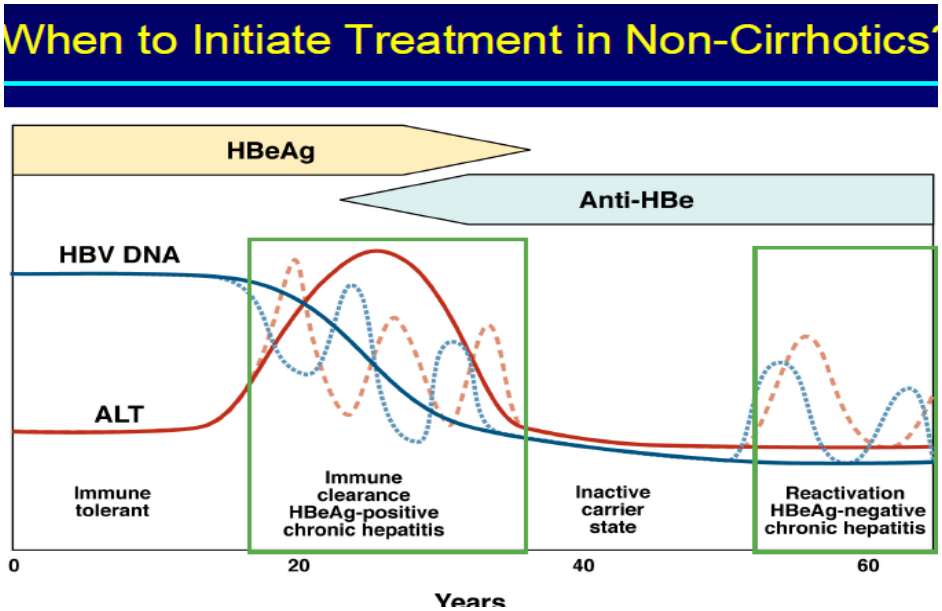
AASLD HBV guidelines available at: www.aasld.org/sites/default/files/guideline_documents/hep28156.pdf



Source: Anna Lok, DDW 2016 (Yapali S, et al. Clin Gastro Hepatol 2014)

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