



Hepatitis B and Immune-Modulatory Drugs in Gastrointestinal Disorders

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**AASLD and the Hepatitis B Special Interest Group
Thank the Following for Their Contribution in
Providing Peer
Review of This Slide Module:**

2010 AASLD Practice Guidelines Committee

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Disclosures

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2008 CDC Guidelines for HBV Screening

New Recommendations

- Persons born in countries with $\geq 2\%$ HBsAg prevalence
- US-born persons not vaccinated as infants whose parents were born in regions with high HBV endemicity ($\geq 8\%$ HBsAg prevalence)
- Persons with behavioral exposures to HBV
 - Injection drug users, men who have sex with men
- Persons needing immune-modulatory therapy
 - Chemotherapy, organ transplantation, immunosuppression and biologics for rheumatologic or gastroenterologic disorders
- Persons with elevated ALT/AST of unknown etiology



Consequences of Immune-Modulatory Therapies in Patients with Chronic HBV Infection

- **Reactivation** of inactive disease
 - = **ALT flare** → in response to increasing HBV DNA levels
 - **Acute liver failure** → with liver-related death or need for liver transplantation
- **Accelerated course** with greater risk of progression to cirrhosis among those receiving long-term immunosuppressive therapy



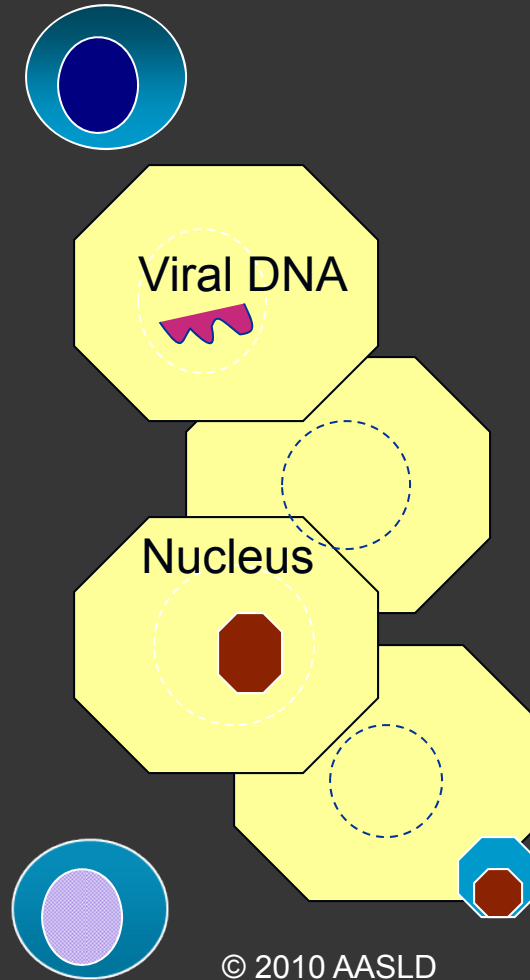
How is HBV affected by immune modulatory therapies?

Viral and Immunologic Events Before Immune Modifying Therapy

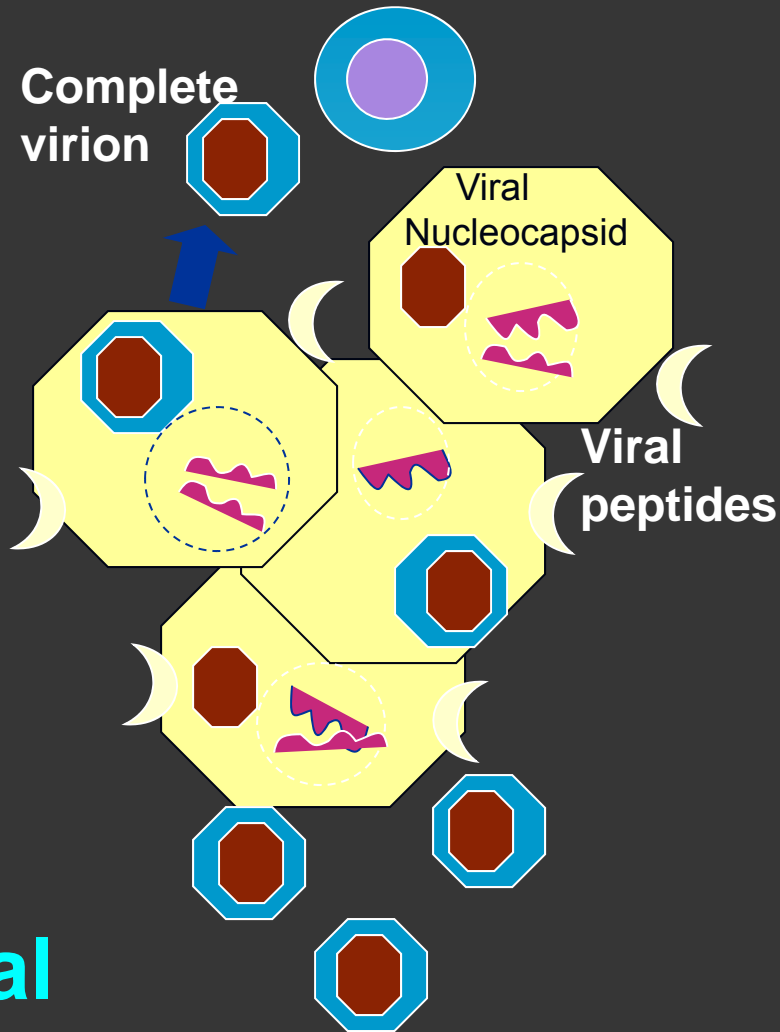


HBV DNA +
ALT normal

Lymphocyte



Viral and Immunologic Events During Immune Modifying Therapy



HBV DNA +++++

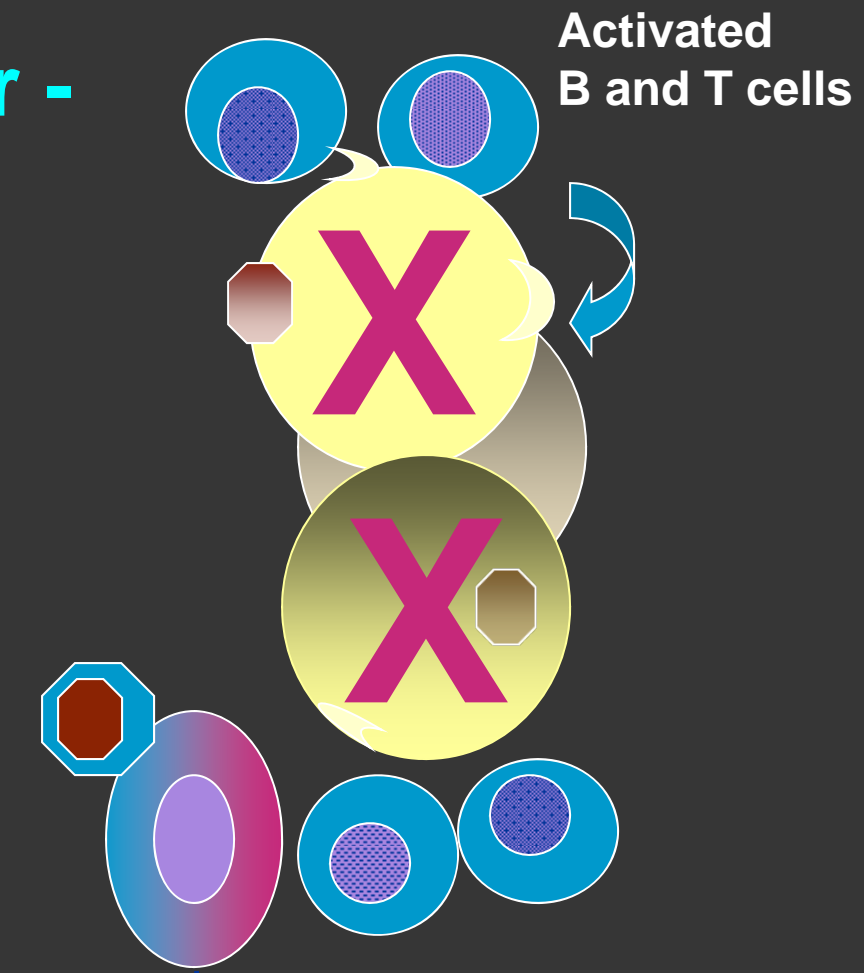
ALT normal or slightly abnormal



Viral and Immunologic Events After Discontinuation of Immune Modifying Therapy

HBV DNA + or -

ALT very elevated



macrophage

Clinical Aspects of Hepatitis B Reactivation

- Reappearance or increase of serum HBV DNA
- Often followed by reappearance or flare of liver disease = reactivated hepatitis
- Reactivated hepatitis B often subclinical and may resolve spontaneously
- Infrequently can lead to clinically apparent hepatitis with jaundice and symptoms
- Rarely this reactivated hepatitis can be severe or even fatal

Specific Effects of Prednisone on Hepatitis B

- Immune suppressive effects
- HBV genome contains a corticosteroid-response receptor on hepatitis B core protein → upregulates HBV replication⁽¹⁾
 - e.g. Prednisolone increases intracellular viral DNA and RNA levels approximately twofold in cell culture system ⁽²⁾



Specific Effects of Purine Synthesis Inhibitors on Hepatitis B

- Inhibitors of purine synthesis
 - Azathioprine
 - Methotrexate
 - Mycophenolate mofetil
- Primary effect is presumably by inhibition of T and B cell proliferation including immunoglobulin production
- Azathioprine is associated with increased intracellular viral DNA and RNA levels *in vitro* ⁽¹⁾

Specific Effects of TNF- α on Hepatitis B

- TNF- α inhibits HBV transcription
- Impaired antiviral response in animal models of HBV if TNF- α is inhibited
- TNF- α gene polymorphisms demonstrated to be linked to HBV persistence

Other Immune Modulatory Drugs

- There are several other biologic modifiers whose specific actions on HBV infection are less well-defined:
 - co-stimulation blockers e.g. Abatacept
 - anti-integrins: e.g. Natalizumab
- Presumably, these drugs have the capacity to impair immune control of HBV, but direct data are lacking



How often does HBV reactivation occur in the treatment of GI disorders?

Reactivation of Hepatitis B: Frequency in GI Patients

- Incidence not well defined –case reports only
 - N=28 cases in literature
- Outcomes vary from asymptomatic liver enzymes elevation to fatal fulminant hepatitis
- Most common drugs reported – anti-TNF drugs
 - Infliximab and adalimumab
- Duration of prior drug exposure ranges from single dose to months of continued therapy



Factors Linked with Risk of HBV Exacerbation

- Potency and type of immune-modulatory therapy
 - More reports with infliximab or adalimumab but reporting bias possible
 - No comparative studies of anti-TNF versus other classes
 - Black box warning regarding HBV for anti-TNF drugs
- HBV DNA levels
 - Higher risk when serum HBV DNA is detectable
- HBsAg positive (vs anti-HBc positive)



Risk of HBV Reactivation in HBsAg-neg and anti-HBc pos Patients

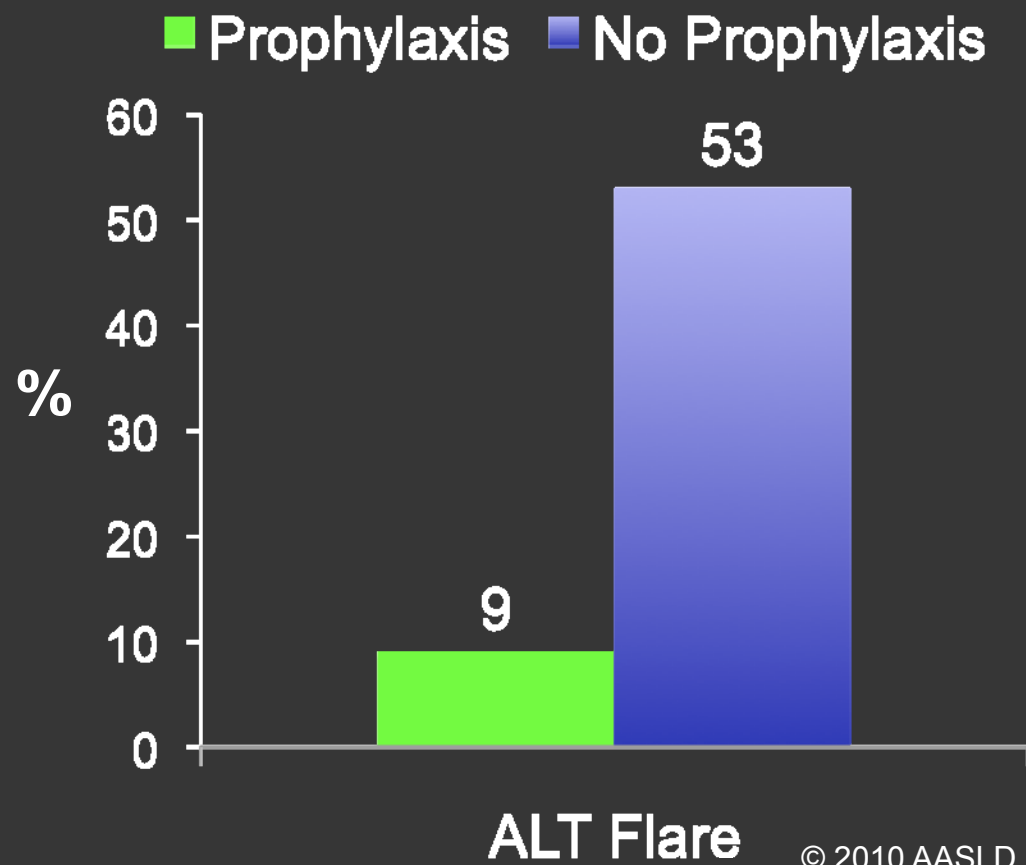
- Risk of reactivation is low but not zero
- In oncologic studies:
 - Incidence of HBV reactivation was 3% ⁽¹⁾
 - Higher risk if HBV DNA detected pre-treatment
 - Presence of anti-HBs NOT protective against HBV reactivation
- In GI and rheumatologic studies using immunosuppressive drugs, cases of reactivation have been rarely described



What is optimal management strategy for patients needing immune-modulatory therapy?

Antiviral Prophylaxis Reduces Risk of HBV Exacerbation

Systematic Review of Lamivudine in Chemotherapy in HBsAg+ Patients



- Endpoint = ALT flare defined by ALT increase ≥ 3 -fold
- 80% reduction in ALT flares in prophylaxis group
- Consistent effects across controlled studies

Prophylactic Therapy in Patients on Immune Modulatory Drugs

Prophylactic antiviral therapy reduces or eliminates the risk of HBV reactivation

Available antivirals are safe and well-tolerated in patients with chronic diseases

All HBsAg+ patients should receive antiviral prophylaxis



Antiviral Prophylaxis Decisions



Case #1: Recently Diagnosed Crohn's Disease

- 35 yo male with ileocolonic Crohn's disease diagnosed 1 year ago
- Referred to you for refractory symptoms: diarrhea, weight loss, severe anemia
- Prior therapies include mesalamine and budesonide
- You plan to treat with infliximab
- Prior to starting you obtain HBV and HCV testing as well as PPD



HBV results are as follows:

**HBsAg-negative; anti-HBc positive;
anti-HBs negative**

- What is recommended at this point?
 1. No further testing needed – proceed with infliximab therapy
 2. Obtain HBV DNA and if positive, start prophylactic therapy
 3. Start prophylaxis – no need to do further testing



HBV results are as follows: HBsAg-negative; anti-HBc positive; anti-HBs negative

- What is recommended at this point?
 1. No further testing needed – proceed with infliximab therapy

Infliximab has the potential to reactivate HBV and although the risk is lower in those who are anti-HBc positive (vs HBsAg positive), severe cases of infliximab induced reactivation have been reported in HBsAg negative cases in the IBD literature ⁽¹⁻³⁾



HBV results are as follows:

**HBsAg-negative; anti-HBc positive;
anti-HBs negative**

- What is recommended at this point?
2. Obtain HBV DNA and if positive, start prophylactic therapy

This is one option BUT the absence of HBV DNA prior to infliximab treatment is insufficient to predict the course of HBV during and after infliximab treatment AND ongoing monitoring of HBV DNA is needed.



HBV results are as follows: HBsAg-negative; anti-HBc positive; anti-HBs negative

- What is recommended at this point?
3. Start prophylaxis – no need to do further testing

This option is most likely to prevent reactivation and an ALT flare as shown in patients treated for malignancy and isolated cases of IBD reported in the GI literature.

Occult HBV Infection

Anti-HBc positive \pm anti-HBs

- Low risk for reactivation
- Presence of detectable HBV DNA associated with higher risk of reactivation – recommend treatment in this subgroup
- If HBV DNA negative, options include:
 - Treat as you would HBsAg positive (easy but over-treating many)
 - No treatment, but monitor HBV DNA levels and treat if become detectable (interval for monitoring not established but every 3 months may be considered)



Case 2:

Newly Diagnosed Ulcerative Colitis

- 38 yo Asian-American female presents with diarrhea (7-8 liquid stool per day) for past 3 weeks and 1 week of hematochezia
- No significant past or family history; no recent travel; no new medications. Stool cultures negative
- Flexible sigmoidoscopy reveals friable, hemorrhagic mucosa involving entire left colon and biopsies consistent with ulcerative colitis
- Your initial plan includes treatment with prednisone and 5-ASA enemas



HBV results are as follows: HBsAg-positive; anti-HBc positive; anti-HBs negative

- What is recommended at this point?
 1. Proceed with prednisone therapy without HBV prophylaxis
 2. Obtain HBV DNA and if positive, start HBV prophylactic therapy
 3. Start HBV prophylaxis



HBV results are as follows:

HBsAg-positive; anti-HBc positive; anti-HBs negative

- What is recommended at this point?
 1. Proceed with prednisone therapy without HBV prophylaxis

This is likely to cause HBV reactivation since prednisone is particularly apt to increase HBV DNA replication and 30-40% of patients have ALT flares after a 4-6 week course of corticosteroids.



HBV results are as follows:

**HBsAg-positive; anti-HBc positive;
anti-HBs negative**

- What is recommended at this point?
2. Obtain HBV DNA and if positive, start prophylactic therapy

This is not recommended, not only because of delays in receiving the results of HBV DNA testing, but also this patient has an increased risk of reactivation due to HBsAg positive status



HBV results are as follows:

**HBsAg-positive; anti-HBc positive;
anti-HBs negative**

- What is recommended at this point?
3. **Start prophylaxis**

This is the strategy likely to be most successful in preventing an increase in HBV DNA and thereby prevent reactivation of HBV and all that follows

Testing Requirements in Patient Undergoing Any Immune-Modulatory Therapy

Required Screening tests

- HBsAg
- Anti-HBc total
- Anti-HBs*

Secondary and Follow Up Tests

- HBV DNA quant if:
- Anti-HBc positive
- OR
- HBsAg positive

* To guide decisions regarding vaccination

Serologic Profiles

| HBsAg | Anti-HBc | Anti-HBs | Interpretation | Recommendation |
|-------|----------|----------|--------------------------------------|---------------------------------|
| + | + | - | Chronic hepatitis | Needs prophylaxis |
| - | + | - | Prior HBV infection | Consider prophylaxis |
| - | + | + | Prior HBV infection | Consider prophylaxis* |
| - | - | - | No prior or current infection | Consider vaccination (1) |

* Risk may be lower than anti-HBc alone but studies are limited



Therapies Requiring HBV Testing Prior to Start of Treatment

- Prednisone
- Azathioprine, methotrexate, mycophenolate mofetil
- Anti-TNF drugs
- Other biologics
 - Abatacept
 - Natalizumab

Timing of Prophylactic Antiviral Therapy

- **Initiation of treatment**
 - Should be started at same time or 1 week before initiating immune modulatory drug
- **Duration of treatment**
 - Continue for 6-12 months after last dose of immune modulatory drug
 - For patients on long-term immunosuppressive therapy, HBV prophylaxis should be continued indefinitely

Prophylactic Treatment Choices

| Drug Name | Dose and Route | Preferred Drugs* |
|-------------|----------------|------------------|
| Lamivudine | 100 mg QD | |
| Adefovir | 10 mg QD | |
| Entecavir | 0.5 mg QD | ✓ |
| Telbivudine | 600 mg QD | |
| Tenofovir | 300 mg QD | ✓ |

✓ Preferred because drugs have high antiviral potency and low risk of drug resistance

Important Factors in Selecting the HBV Prophylactic Drug

- In treatment-naïve patients:
 - Entecavir and tenofovir are preferred drugs
- If prior HBV treatment:
 - Drug-resistant HBV more likely and selection of the HBV drug must take this into account
- If pregnant:
 - Tenofovir or lamivudine are preferred drugs
- All drug doses need to be adjusted if renal dysfunction

Monitoring of Patients on Long-Term Antiviral Prophylaxis

- HBV DNA levels every 3-6 months to exclude virologic breakthrough
 - If increase in HBV DNA on treatment, may indicate:
 - drug resistance or
 - non-compliance
- All nucleoside analogues have black box warning regarding lactic acidosis (potential risk for nucleoside analogue)

Recommendations (1)

Screening

1. All patients who are going to be treated with immune-modulatory drugs should be screened for HBsAg, anti-HBc, and anti-HBs
 - HBsAg + patients have the highest risk of reactivation
 - HBsAg neg and anti-HBc positive patients have much lower risk of reactivation

The AASLD Special Interest Group for Hepatitis B strongly endorses the screening recommendations of the CDC for these patients



Recommendations (2)

Management of HBsAg+ Patient

- All should receive antiviral prophylaxis
- Tenofovir and entecavir preferred drugs for long term prophylaxis
 - Previous antiviral history may modify choices
- Start: 1 week prior or same time as the immunomodulatory drug is started
- Stop: 6-12 months after last dose of immunomodulatory drug is given



Recommendations (3)

Management of Anti-HBc+ Patient

- Prophylactic antiviral therapy is not routinely recommended as risk of reactivation is low
 - If unable to monitor HBV DNA levels regularly, prophylaxis is the safest strategy
- If HBV DNA detectable, antiviral prophylaxis is recommended
- If HBV DNA undetectable
 - Monitor HBV DNA levels every 1-3 months; if ↑ then start antiviral prophylaxis
- If chose to treat without knowledge of HBV DNA, use same strategy as HBsAg+ patient