



# Immune Modifying Therapy (IMT) for Rheumatic Disorders and Hepatitis B

Robert P. Perrillo, M.D.  
Baylor University Medical Center  
Dallas, Texas



**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**
- **Kenneth Sack, MD:** Professor of Clinical Medicine, Division of Rheumatology, University of California San Francisco



# Disclosures

- Dr. Perrillo is on the speaker's bureau for Gilead Sciences, Bristol Myers Squibb, and Roche Pharmaceuticals. He also is on the Advisory Board of Roche Pharmaceuticals

# Practice Variation For HBV Management Among Rheumatologists<sup>1</sup>

- Survey of > 1000 rheumatologists in 2010
- Frequency of routine screening for HBV:
  - 42% do before non-biologic DMARDs
  - 69% do before biologic DMARDs
  - Almost all screen when well known risk factors but fewer screen patients from endemic areas
- Lack of awareness of DMARD drug warnings common
- 7 % of respondents had witnessed reactivation with biologic DMARDs

# Practice Variation Among Rheumatologists (cont)

- Reported type of screening:
  - 92% use HBsAg testing
  - 51% use anti-HBs
  - 42% use anti-HBc
- 81% prefer that gastroenterologist or hepatologist treat



**Why are these varied HBV screening practices among rheumatologists important?**

# Chronic Hepatitis B: High Risk Groups

- Persons born in HBV high/inter- mediate risk regions of the world:
- Asia, Africa, Pacific Islands, Middle East, Eastern Europe, Mexico, Central America, Caribbean
- Men who have sex with men
- Pregnant women
- Hemodialysis patients
- HIV-positive persons
- Injection drug users
- Persons needing IMT
- Persons with elevated ALT or AST of unknown etiology
- Blood or tissue donors
- Infants borne to infected mothers
- Househols and sexual contacts of HBV-infected

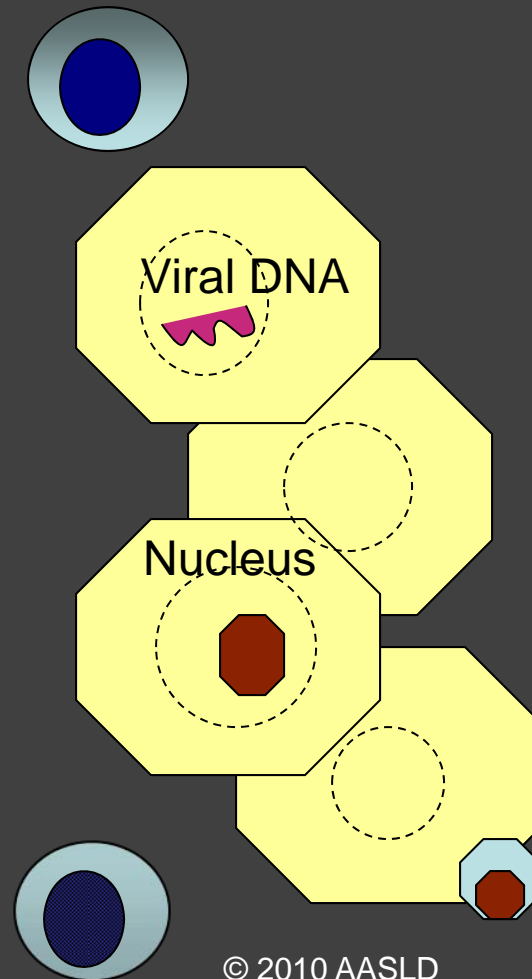
# Hepatitis B Reactivation

- Abrupt reappearance or increase of serum HBV DNA in patient with previously inactive or resolved HBV infection
- Often accompanied by reappearance or flare of liver disease = reactivated hepatitis
- Can lead to clinically apparent acute hepatitis, which can be severe or even fatal
- Reactivated hepatitis B often subclinical and may resolve spontaneously

# Viral and Immunologic Events Before Immune Modifying Therapy

HBV DNA +  
ALT NL

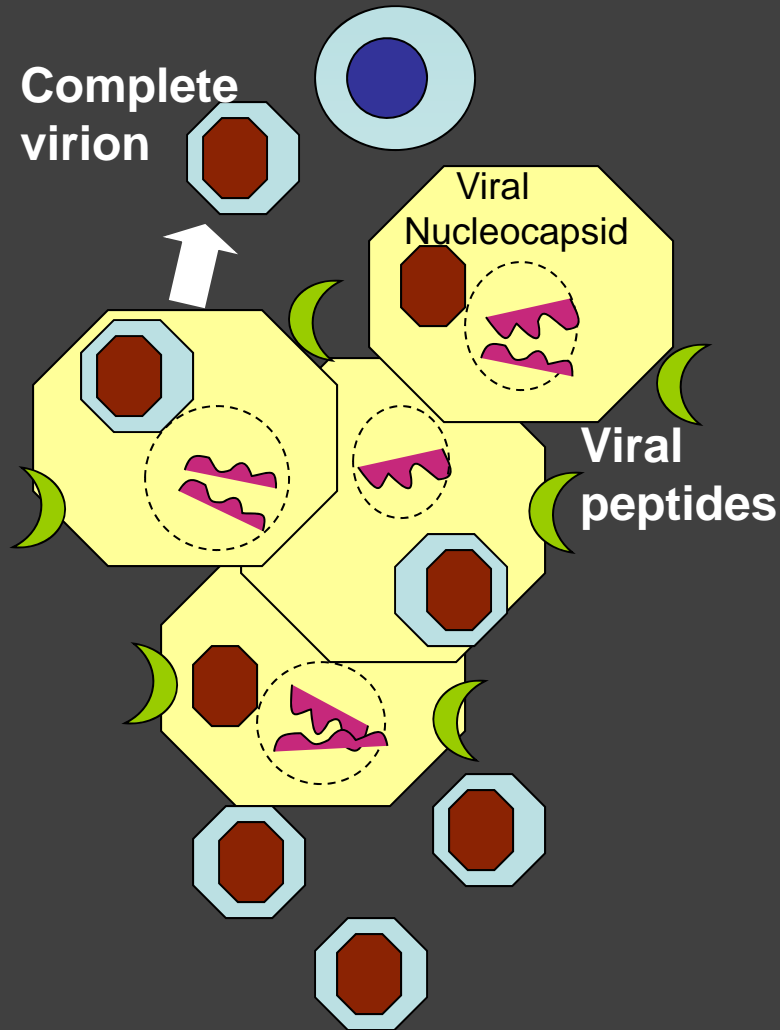
Lymphocyte



# Viral and Immunologic Events During Immune Modifying Therapy

HBV DNA ++++

ALT NL or slightly abnl

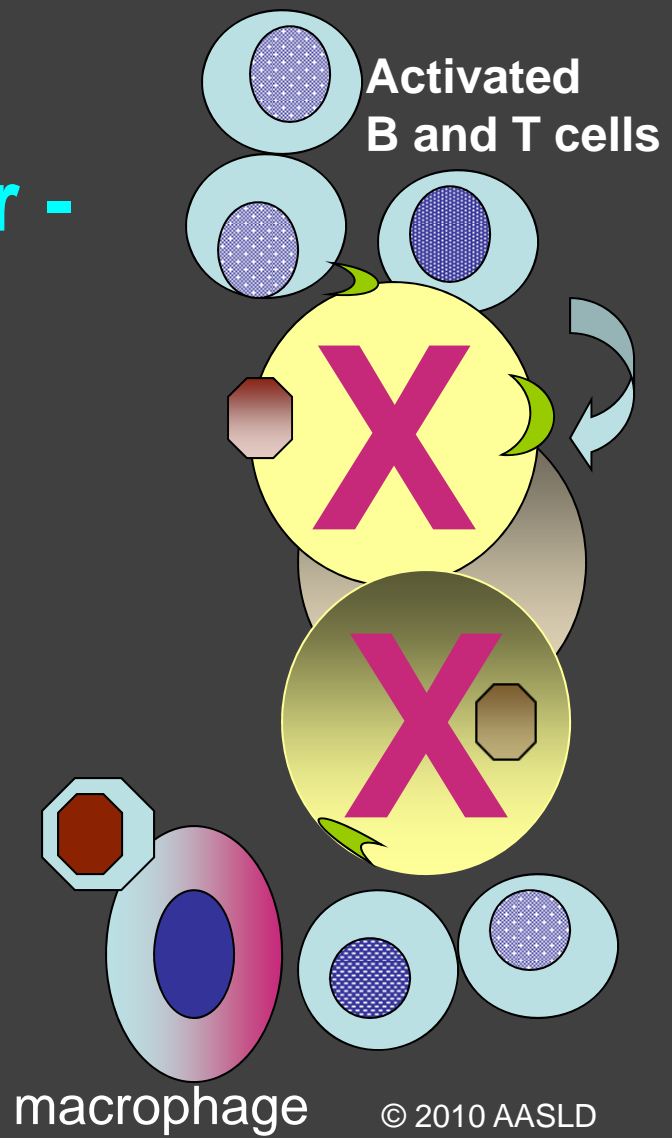




# Viral and Immunologic Events After Discontinuation of Immune Modifying Therapy

HBV DNA + or -

ALT very elevated



# Specific Effects of TNF- $\alpha$ on Hepatitis B



- TNF- $\alpha$  inhibits HBV transcription. <sup>1,2</sup>
- Impaired antiviral response in HBV producing animal model if TNF- $\alpha$  is inhibited. <sup>2,3</sup>
- TNF- $\alpha$  gene polymorphisms demonstrated to be linked to HBV persistence.<sup>3</sup>

# Reactivated Hepatitis B in Rheumatologic Practice

- Incidence not well defined with IMT
- Many cases minimally or totally asymptomatic
- Severe cases described in GI and oncologic literature with rituximab including fatalities and need for liver transplantation.
- Black box warnings for TNF- $\alpha$  inhibitors

# Reports of HBV Reactivation in Rheumatic Patients Treated with TNF- $\alpha$ Inhibitors or Rituximab– No Prophylaxis



Drug	Disorder	Age Sex	Pre-Rx Serology	Duration	Other Drugs	Anti-viral Prophylaxis	Outcome
<b>Inflix</b>	RA	49,M	HBsAg, anti-HBc and anti-HBs (+)	18 months	MTX 10mg/wk mg/wk, pred 8 mg	No	Mod hepatitis
<b>Etan</b>	RA	62, F	HBsAg/antiHBc (+)	2 years	MP 8 mg MTX 10-15/wk,	No	Mild hepatitis
<b>Etan</b>	RA	48, F	HBsAg (+), HBV DNA (-)	13 months	MTX	No	Mild hepatitis
<b>Inflix</b>	AS	43,M	HBsAg (+)/HBeAg (-)	14 wks (5 mg/kg)	None	No	Mild hepatis, DNA (+)
<b>Etan</b>	AS	73,M	HBs Ag (-) anti-HBc /anti-HBs (+)	14 months	pred 5 mg	No	Mild hepatitis
<b>Inflix</b>	AS	31, M	HBsAg/anti-HBe (+) HBV DNA (-)	3 infusions	MTX 15 mg/wk,	No	Severe hepatitis, HBV DNA (+)
<b>Inflix</b>	AS	35, F	HBsAg/anti-HBe (+), HBV DNA neg	3 infusions	None	No	Severe hepatitis, HBV DNA > 15 million copies
<b>Ritux</b>	Vasculitis	73,M	HBsAg (-), anti-HBc (+)	4 infusions (375 mg/m <sup>2</sup> )	Prednisolone 40 mg	No	Became HBsAg and HBV DNA (+). Died of renal failure 11 months later
<b>Adal</b>	RA	56,M	HBsAg (+), HBV DNA (-)	40 mg every other week	Methylprednisolone 4 mg/day, SSZ 2 gm/day	No	HBV DNA increased to 4,100 copies. LAM started successfully,



# HBV Reactivation in Rheumatic Patients Treated with TNF- $\alpha$ Inhibitors or Rituximab– Prophylaxis Given

Drug	Disorder	Age Sex	Pre-Rx Serology	Duration	Other Drugs	Anti-viral Prophylaxis	Outcome
Ritux	RA	56,F	HBs/anti-HBe (+), HBV DNA >4,000 copies	2 infusions (1000 mg)	None	Yes	Mild hepatitis, HBV DNA > 500 million copies but therapeutic response
Etan	RA	73,F	HBsAg /anti-HBc (+), HBV DNA (-)	25 mg twice week x 12 months	Prednisone 5 mg daily	Yes	No reactivated hepatitis
Inflix	RA	67,F	HBsAg (+), HBV DNA (-)	12 months before switch to etan	Prednisone 5 mg, MTX 10 mg/wk	Yes	No reactivated hepatitis

# Reactivated Hepatitis B: Associated Risk Factors

- Incidence not well defined with IMT
- Many cases minimally or totally asymptomatic
- Severe cases described in GI and oncologic literature with rituximab including fatalities and need for liver transplantation.
- Black box warnings for TNF- $\alpha$  inhibitors

# CASE 1: Severe Spondyloarthritis

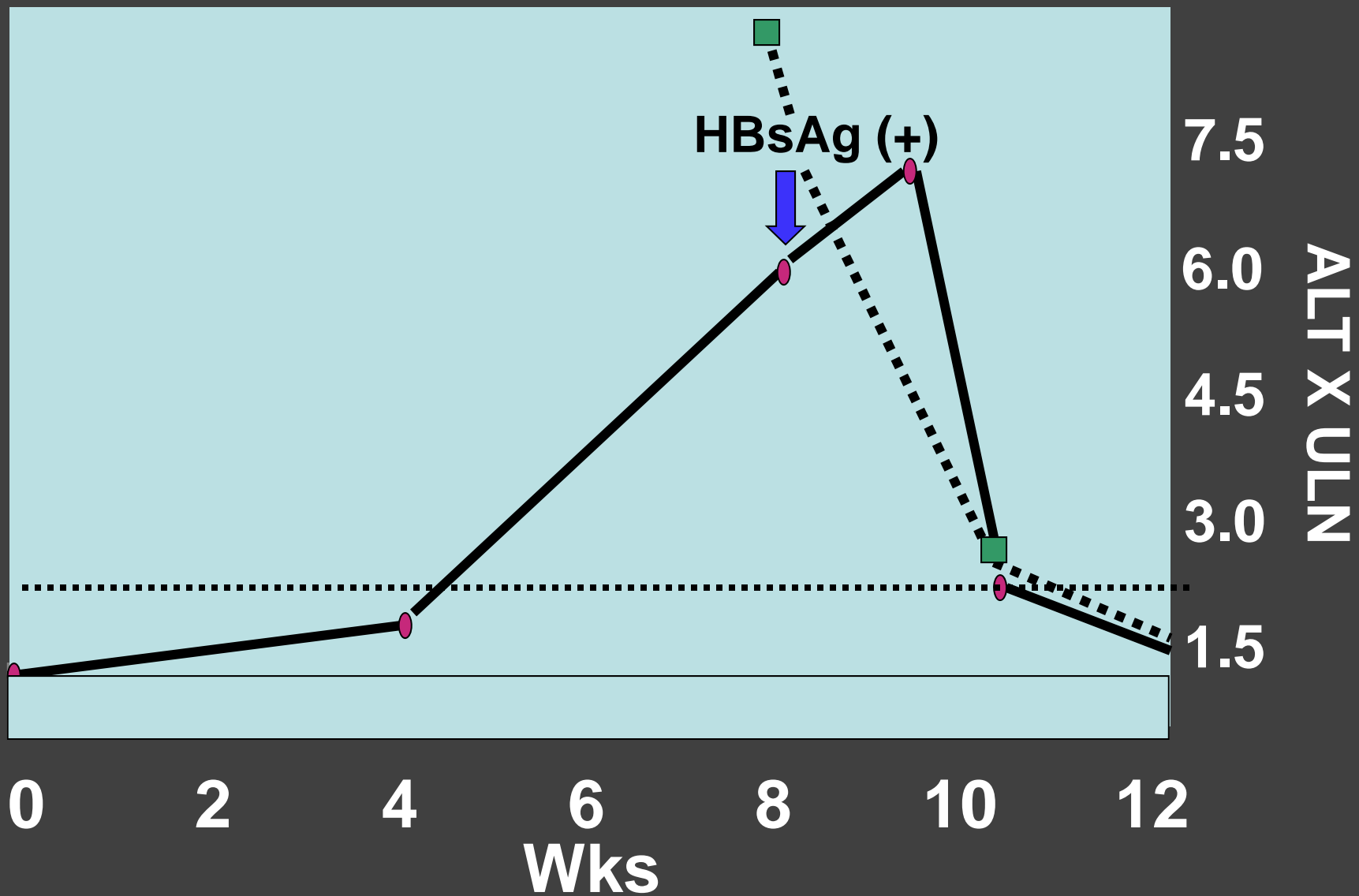
- 35 yo Caucasian female presents with severe spondyloarthritis associated with both back and chest pain. No prior history of liver disease.
- Incomplete response with NSAIDs with persistent elevation of sed rate (62 mm).
- The patient fails to respond to methotrexate (15 mg/wk) and sacroiliac injections of steroids

# CASE 1: What Do You Do?

- You want to start infliximab therapy
- Chose the *most appropriate* next step
  - A. Start infliximab and consult with GI or hepatology if ALT elevation occurs.
  - B. Screen for HBsAg, anti-HBc, and anti-HBs and start infliximab. Follow HBV DNA if HBsAg (+). Consider treatment if increasing.
  - C. Screen for HBsAg, anti-HBc and anti-HBs. Consider pre-emptive antiviral therapy if HBsAg or anti-HBc-positive.

# CASE 1: Clinical Follow Up

- Response if A chosen
- Patient started on infliximab (5 mg/kg) IV at weeks 0,2, and 6.
- ALT is monitored monthly.
  - Dramatic relief of joint symptoms after 2 courses of treatment.
  - At week 8, ALT > 6 x ULN and bilirubin 2.3 mg/dL (INR WNL).
  - GI recommends HBsAg testing which is (+). Entecavir started. Baseline HBV DNA 210,000 copies and nearly undetectable at week 4. Liver biopsy 4 weeks later shows minimal inflammation but stage 3 out of 4 fibrosis.

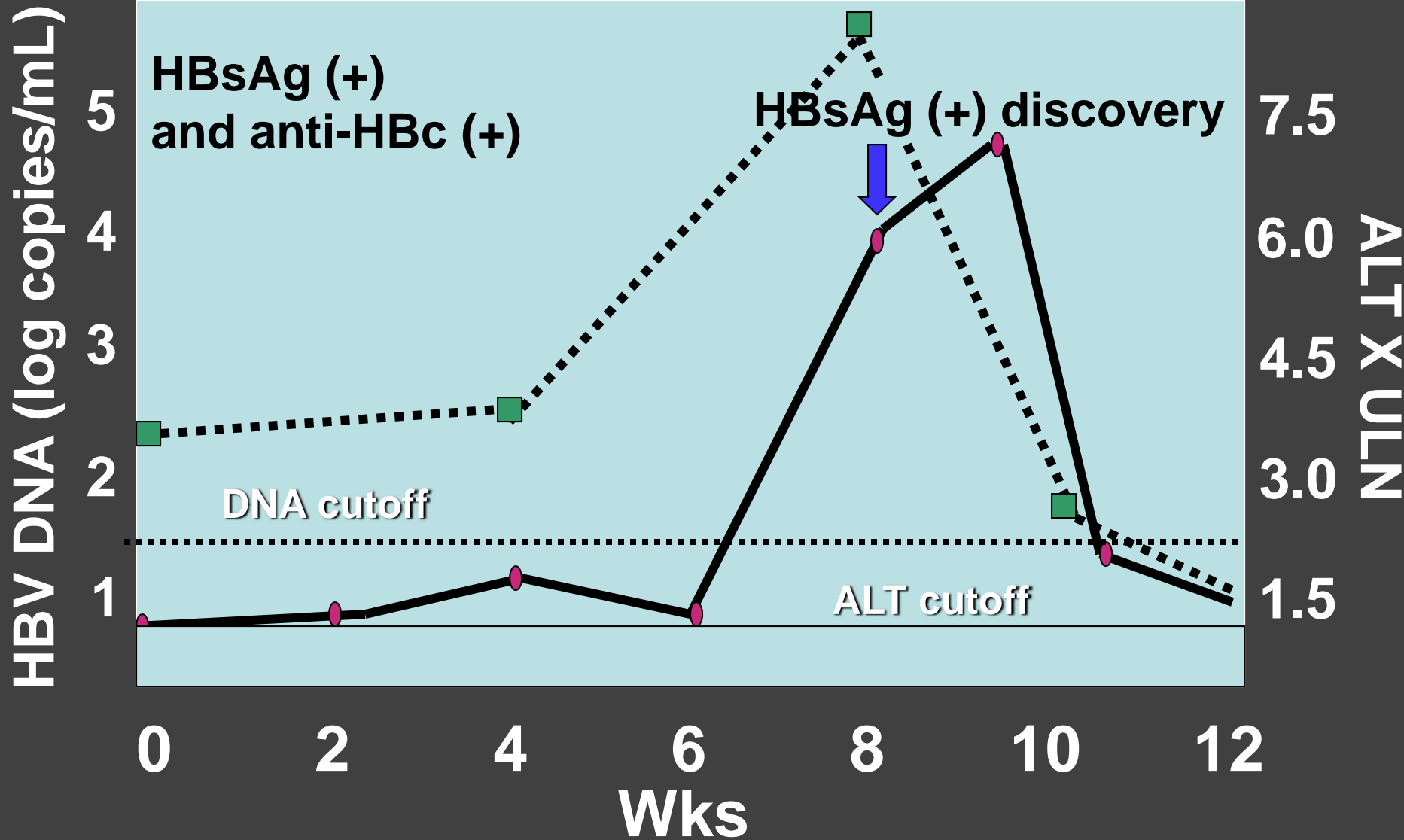


Infliximab

Entecavir

# Case 1: Clinical Follow Up

- **Response if Answer B Chosen**
- Patient screened for HBsAg, anti-HBc and anti-HBs.
- Infliximab started with monitoring of HBV DNA every 4 weeks.
  - Found to be HBsAg and anti-HBc (+).
  - Infliximab started with dramatic relief of joint symptoms after 2 courses of treatment
  - HBV DNA 3,000 copies at baseline and 210,000 copies at week 8. ALT essentially unchanged at week 4 but  $> 6 \times$  ULN at week 8; bilirubin now 2.3 mg/dL (INR WNL).
  - GI consult recommends starting entecavir and HBV DNA near LLOD 4 weeks later.

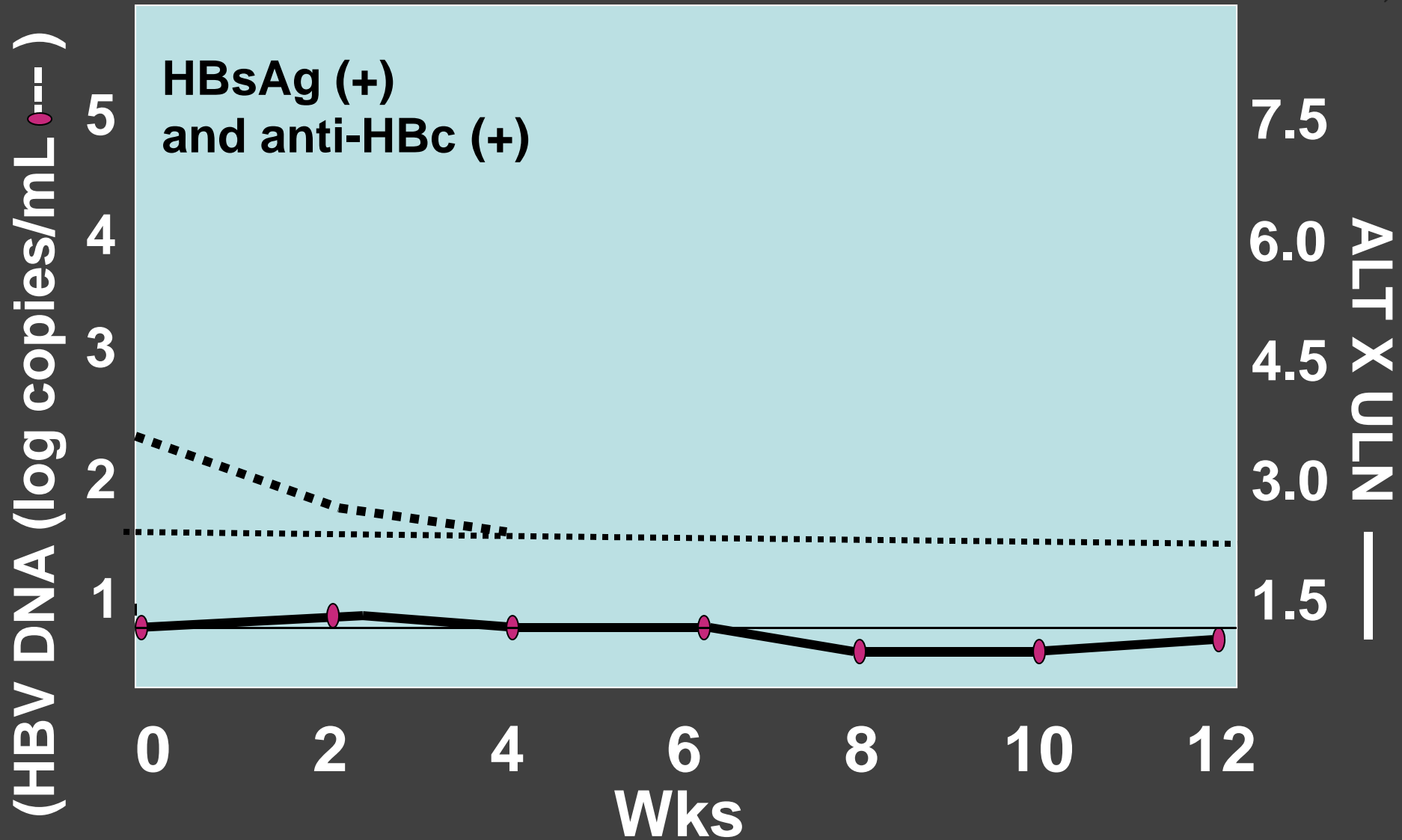


**Infliximab**

**Entecavir**

# CASE 1: Clinical Follow Up

- Response if Answer C Chosen
- Patient screened for HBsAg, anti-HBc, anti-HBs. Pre-emptive antiviral if HBsAg or anti-HBc (+).
  - HBsAg and anti-HBc (+). Anti-HBs (-).
  - Hepatology recommends HBeAg/HBV DNA testing and starting entecavir *before* infliximab begun.
  - HBeAg (-) and baseline HBV DNA 3,000 copies. Plan to continue entecavir until 6 months *after* discontinuation of infliximab.
  - Dramatic relief of joint symptoms after 2 courses of treatment.
  - HBV DNA non-detectable at week 4 and patient treated uneventfully.



**Infliximab**

**Entecavir**

# Interpretation of Hepatitis B Tests

## Positive Test

## Clinical Significance

HBsAg

Means patient is infected (acute or chronic); HBV DNA may not be positive in all chronic carriers

Hepatitis B surface antibody (anti-HBs)

Either vaccinated or natural immunity

Hepatitis B core antibody (anti-HBc)

1) Active infection when HBsAg also (+); (2) occult infection when HBsAg (-) and HBV DNA (+); (3) past infection or false (+) when HBsAg negative

Anti-HBs and anti-HBc

Best evidence for past immunity; lowest risk for HBV reactivation

HBeAg

Anti-HBe

Protein produced by virus; higher levels of viral replication when positive  
Inactive HBsAg carrier or chronic hepatitis with lower levels of HBV DNA

# What is Optimal Prophylaxis?

- **Timing of treatment**
  - Should be started at or 1 week before initiating IMT
- **Choice of antiviral**
  - Degree of antiviral potency
  - Degree of drug resistance
- **Duration of treatment**
  - Continue for 6 months after last dose of IMT
  - Some experts recommend treatment up to 12 months after last dose of IMT whenever baseline HBV DNA high

# Published Recommendations for HBV Screening of Patients to be Given IMT

1. [AASLD, 2009](#): HBsAg and anti-HBc screening should be done prior to onset of therapy.
2. [EASL, 2009](#): HBsAg and anti-HBc screening before initiation; vaccination against HBV for seronegative patients.
3. [APASL, 2005](#): Screen for HBsAg prior to start of therapy.
4. [CDC, 2008](#): Screen for HBsAg, anti-HBc, and anti-HBs prior to start of therapy.
5. [ACR, 2008](#): No screening recommendations.

# Recommendations



- 1) All patients who are to be treated with IMT should be screened for HBsAg, anti-HBs, and anti-HBc before starting treatment because:
  - A. HBsAg carriers have the highest risk of reactivation
  - B. Lack of anti-HBs identifies those needing vaccination
  - C. Serious flares of hepatitis reported in anti-HBc (+) persons (occult infection) if IMT prolonged and/or very potent

Therefore, the AASLD Special Interest Group for Hepatitis B strongly endorses the screening recommendations above for these patients.

# Recommendations (cont)

- 2) Greater attention needs to be given to patients who are borne in areas of the world that are intermediate to high risk for hepatitis B (see Slide # 6).
- 3) All HBsAg carriers undergoing IMT need pre-emptive treatment with antivirals; those with anti-HBc alone should be considered for treatment based on the type of IMT. If either is positive, consultation with a hepatologist or other specialist is recommended.