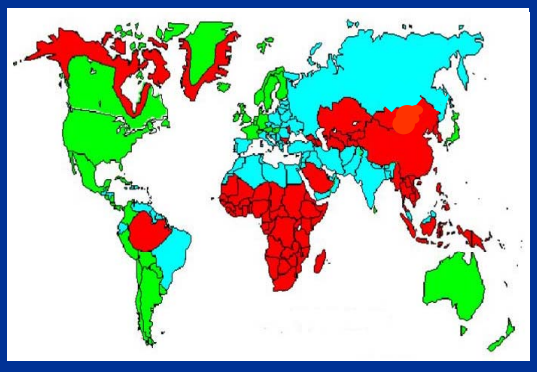
Treatment of Chronic Hepatitis B

Bruce R. Bacon, M.D.
James F. King MD Endowed Chair in Gastroenterology
Professor of Internal Medicine
Division of Gastroenterology and Hepatology
Co-Director, Saint Louis University Liver Center
Saint Louis University School of Medicine
St. Louis, Missouri

Global Burden of HBV

- **>350 million persons worldwide have chronic disease**
- **800,000 – 2 million in the U.S. have chronic disease**



WHO. Available at: http://www.who.int/csr/disease/hepatitis/HepatitisB_whocdscsrlyo2002_2.pdf. Accessed 02/03/11.
Gish RG, Gadano AC. J Viral Hepat. 2006;13:787-798.

Burden of Chronic Hepatitis B in the U.S.

- U.S. prevalence: 0.8 – 2 million
- 65% are unaware of their infection status
- Deaths directly related to HBV infection (2006): 3,000
- Incidence of acute HBV infection is declining in the U.S., but number of people living with chronic HBV infection may be increasing as a result of immigration from highly endemic countries
- Asian and Pacific Islander (API) Americans make up only 4.5% of the U.S. population, but account for >50% of Americans with chronic HBV infection

IOM (Institute of Medicine). 2010. Hepatitis and liver cancer: A national strategy for prevention and control of hepatitis B and C. Washington, DC: The National Academies Press.
Gish RG, and Gadano AC. J Viral Hepat. 2006;13:787-98.

Groups at High Risk for HBV Infection Who Should be Screened

- Individuals born in areas of high (≥8%) or intermediate (2%-7%) prevalence rates for HBV including immigrants and adopted children
- U.S. born persons not vaccinated as infants whose parents were born in regions with high HBV endemicity
- Household and sexual contacts of HBsAg (+) persons
- Persons who have ever injected drugs

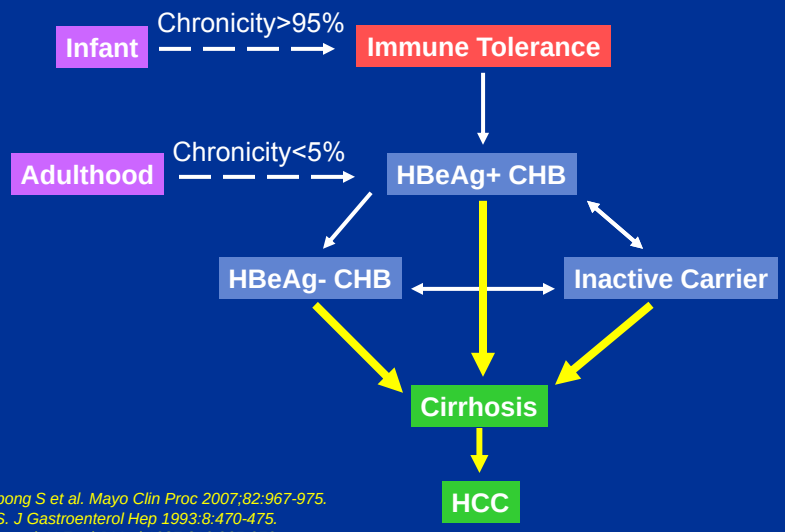
Lok ASF, McMahon BJ. Hepatology 2009;50:1-36.

Groups at High Risk for HBV Infection Who Should be Screened (con't.)

- Persons with multiple sexual partners or history of sexually transmitted disease
- Men who have sex with men
- Inmates of correctional facilities
- Individuals with chronically elevated ALT or AST
- Individuals infected with HCV or HIV
- Patients undergoing renal dialysis
- All pregnant women
- Persons needing immunosuppressive therapy

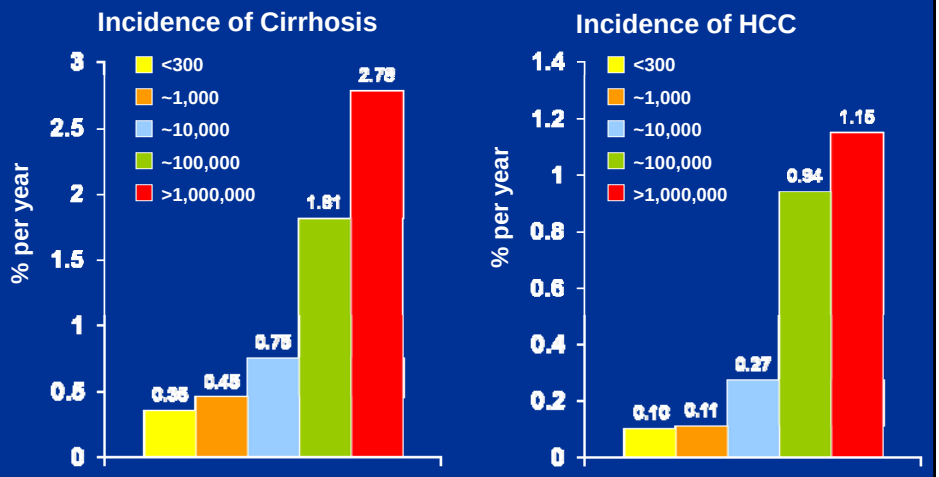
Lok ASF, McMahon BJ. Hepatology 2009;50:1-36.

Natural History of HBV Infection



Pungpapong S et al. Mayo Clin Proc 2007;82:967-975.
Chen DS. J Gastroenterol Hep 1993:8:470-475.
Seeff LB et al. N Engl J Med 1987;316:965-970.

Adverse Liver Outcomes in Chronic Hepatitis B: Relationship to HBV DNA Levels



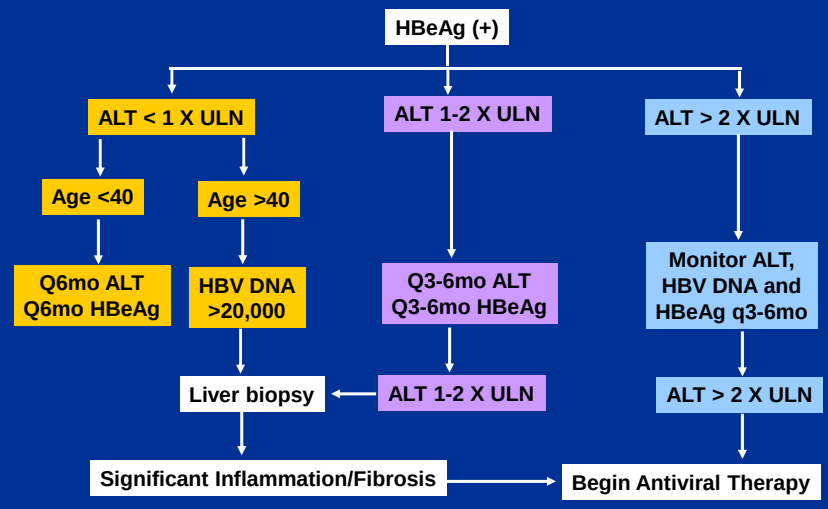
1. Iloeje UH et al. Gastroenterology 2006;130:678-686.
2. Chen C-J et al. JAMA 2006;295:65-73.

Chronic HBV Patients with Normal ALT May Have Significant Liver Disease

- 18% of patients with chronic HBV and persistently normal ALT (n=59) had significant fibrosis (stage 2+); 34% had grade 2 or 3 inflammation[1]
- 42% of chronic HBV patients with normal ALT (n=38) had significant fibrosis, 24% had cirrhosis, and 26% had significant inflammation[2]

1. Lai M et al. J Hepatol 2007;47:760-767.
2. Goebel T et al. Hepatology 2008;48(Suppl S1):743A.

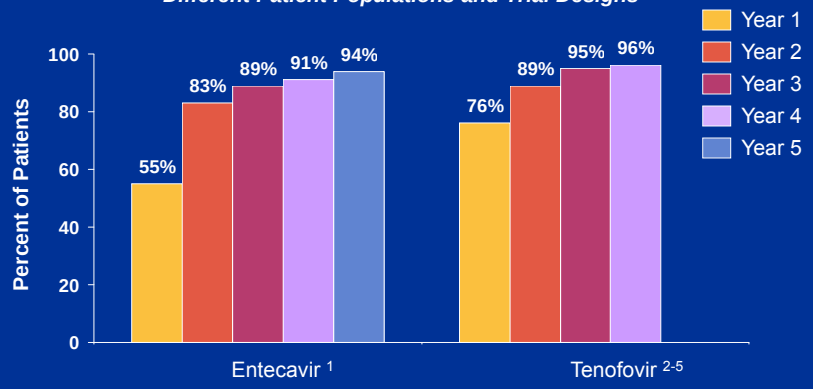
HBeAg (+) Hepatitis B: Algorithm for Treatment



Jafri S-MR, Lok AS-F. Clin Liver Dis 2010;14:425-438.

HBeAg (+) Hepatitis B: HBV DNA Undetectable During Continued Nucleos(t)ideTreatment

Not Head to Head Trials, Different Patient Populations and Trial Designs



1. Chang TT et al. Hepatology. 2010;51:422-430.
2. Marcellin P et al. N Engl J Med. 2008;359:2442-2455.
3. Heathcote EJ et al. Hepatology. 2008;48(suppl 1):376A.
4. Heathcote E et al. Hepatology. 2009;50(suppl 4):533A-534A.
5. Heathcote E et al. Hepatology 2010;52(suppl S1):556A-557A.

HBeAg (+) Hepatitis B Treatment Duration: Nucleos(t)ide Analogs

- AASLD guidelines recommend that treatment should be continued for at least 6 months after the patient has achieved both HBeAg seroconversion [HBeAg (-); anti-HBe (+)] and undetectable serum HBV DNA
- Some patients remain viremic after HBeAg seroconversion and reversion to HBeAg positivity occurs in up to 50% of patients when treatment is stopped
  - Thus, many patients will enter the inactive carrier phase and remain in that phase for months, years, or decades after HBeAg seroconversion

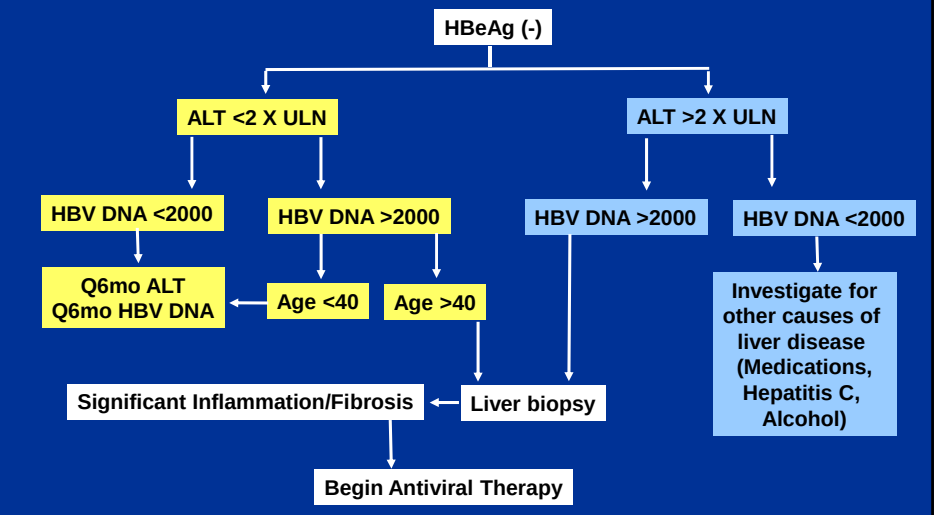
Jafri S-MR, Lok AS-F. Clin Liver Dis 2010;14:425-438.

HBeAg (+) Hepatitis B Treatment Duration: Nucleos(t)ide Analogs (con't.)

- Treatment can be discontinued in patients who complete consolidation therapy after HBeAg seroconversion; continued monitoring is required
- Lifelong treatment is recommended for patients who had decompensated cirrhosis
- Lifelong treatment may be considered for patients who had compensated cirrhosis
  - Treatment may be stopped in those with documented reversal of cirrhosis and those with confirmed HBsAg loss; continued monitoring is required

Jafri S-MR, Lok AS-F. Clin Liver Dis 2010;14:425-438.

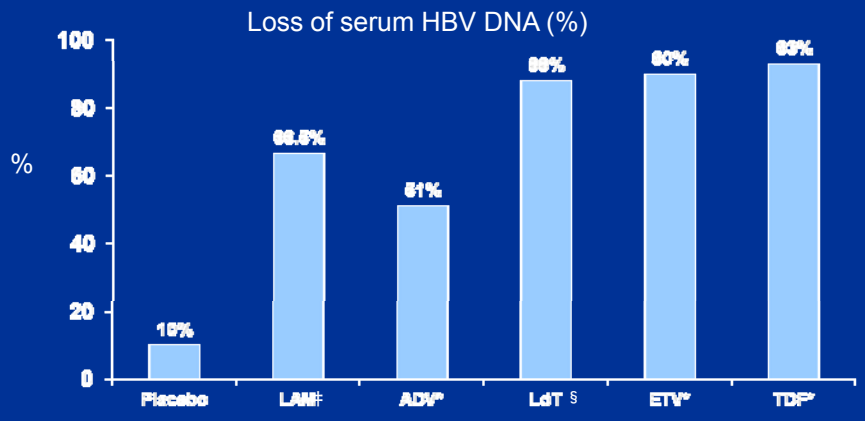
HBeAg (-) Hepatitis B: Algorithm for Treatment



Jafri S-MR, Lok AS-F. Clin Liver Dis 2010;14:425-438.

Antiviral Therapy for HBeAg (-) CHB: Loss of Serum HBV DNA

Not Head to Head Trials, Different Patient Populations and Trial Designs



*Treatment Duration: *, 48 wks; ‡, 48-52 wks; §, 52 wks.*
PLB = Placebo; LAM = Lamivudine; ADV = Adefovir;
ETV = Entecavir; LdT = Telbivudine; TDF = Tenofovir

Adapted from Lok ASF, McMahon BJ. Hepatology. 2009;50:1-36.

HBeAg (-) Hepatitis B Treatment Duration: Nucleos(t)ide Analogs

- AASLD guidelines recommend that treatment with nucleosi(t)ide analogs in HBeAg (-) hepatitis B patients should be continued until the patient has achieved HBsAg clearance
- Life-long treatment is recommended for patients with decompensated cirrhosis

Lok ASF, McMahon BJ. Hepatology. 2009;50:1-36.

AASLD Recommendations for HCC Surveillance of HBV Carriers

- HBV carriers at high risk for HCC should receive an US examination every 6 – 12 months including:
  - Asian men >40 years of age
  - Asian women >50 years of age
  - Persons with cirrhosis
  - Persons with a family history of HCC
  - Africans >20 years of age
  - Any carrier >40 years with persistent or intermittent ALT elevation and/or HBV DNA level >2,000 IU/mL
- Periodic surveillance with serum AFP should be considered for high risk HBV carriers living in areas where U.S. is not readily available

Lok ASF, McMahon BJ. Hepatology. 2009;50:1-36.

The Problem of Nucleos(t)ide Resistance in Chronic Hepatitis B

Factors Affecting the Development of Resistance

- Non-compliance
- Pretreatment HBV DNA levels
- Potency of the antiviral agent
- Rapidity of viral suppression
- Prior exposure to oral nucleoside or nucleotide antiviral therapy
- Duration of treatment
- Degree of genetic barriers to resistance to the individual drug
- Pharmacologic barrier: Blood and tissue levels

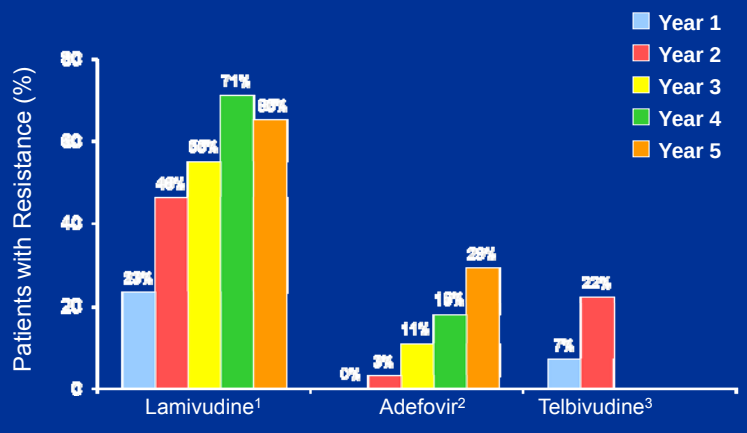
Adapted from Keeffe EB et al. Clin Gastroenterol Hepatol. 2008;6:1315-1341.

Consequences of Antiviral Resistance

- Virologic breakthrough; loss of initial virologic, biochemical, and histologic response
  - Can lead to hepatitis flares and hepatic decompensation, death, or urgent transplant
- Cross-resistance limits future treatment options
  - Subsequent requirement for dual therapy
- Transmission to treatment-naïve persons poses a potential public health problem
- Vaccine failure

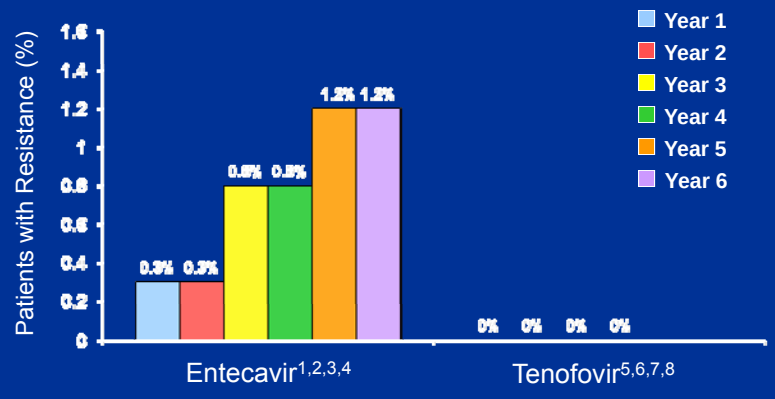
Adapted from Lok ASF, McMahon BJ. Hepatology. 2009;50:1-36.

Increased Resistance with Long-Term Treatment in Nucleoside-Naïve Patients



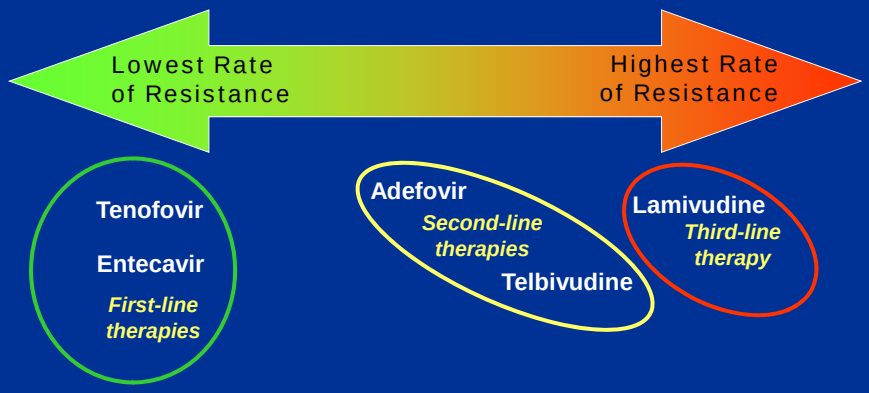
1. Lok ASF et al. *Gastroenterology* 2003;125:1714-1722.
2. Hadziyqnnis SJ et al. *Gastroenterology* 2006;131:1743-1752.
3. Tyzeka® (telbivudine) Prescribing Information. Novartis Pharmaceuticals, East Hanover, NJ. April, 2009.

Minimal Resistance with Long-Term Treatment in Nucleoside-Naïve Patients



1. Colonno RJ et al. *Hepatology* 2006;44:1656-1665.
2. Colonno et al, *Hepatology* 2006, 44 (Suppl 1):229A
3. Colonno RJ et al. *J Hepatol.* 2007;46(Suppl 1):S294.
4. Tenney DJ et al. *Gastroenterology* 2009;136 (Suppl 1):A-865.
5. Viread® (Tenofovir) Prescribing Information. Gilead Sciences, Foster City, CA. May. 2009.
6. Snow-Lampart A et al. *Hepatology* 2008;48(Suppl 1):745A.
7. Snow-Lampart A et al. *Hepatology* 2009;50(Issue S4):732A.
8. Heathcote E et al. *Hepatology* 2010;52(Suppl S1):556A-557A.

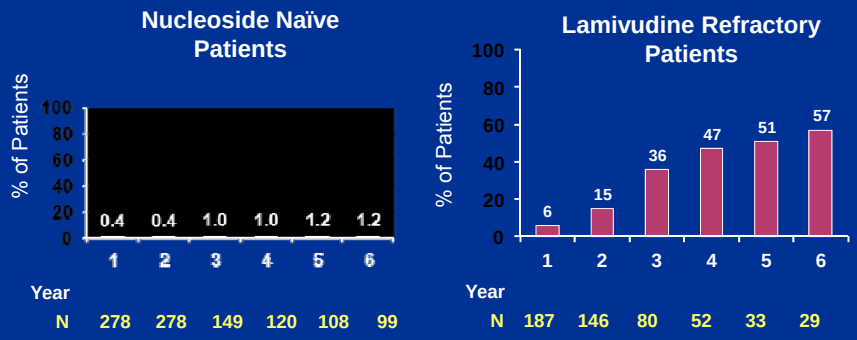
Nucleos(t)ide Resistance Profile: First-Line Treatment Options Have the Lowest Resistance Rates



Resistance does not appear to emerge during treatment with IFN α-2b or PEG-IFN α-2a

Adapted from Keeffe EB et al. *Clin Gastroenterol Hepatol.* 2008;6:1315-1341.

Entecavir Resistance in Nucleoside Naïve and Lamivudine Refractory CHB Patients



Colonno RJ et al. *Hepatology.* 2006;44:1656-1665.
Colonno et al. *Hepatology.* 2006;44(suppl 1):229A.
Colonno RJ et al. *J Hepatol.* 2007;46(suppl 1):S294.
Tenney DJ et al. *Gastroenterology.* 2009;136(suppl 1):A-865.

What Is HBV Reactivation?

- HBV reactivation is a well-characterized syndrome marked by the abrupt reappearance or rise of HBV DNA in the serum of a patients with previously inactive or resolved HBV infection
  - Often, but not always, accompanied by reappearance of disease activity or a flare of hepatitis in previously minimal or inactive disease
  - May occur spontaneously or as a result of immunosuppression
- The complex virological and biological features of reactivation often cause confusion and delayed recognition
  - Different studies often use different markers and criteria for diagnosing HBV reactivation
- There is no consensus on the definition in terms of which patients should be considered at high risk for reactivation based on their HBV serologic markers

Hoofnagle JH. Hepatology. 2009;49(5, Suppl):S156-S165.

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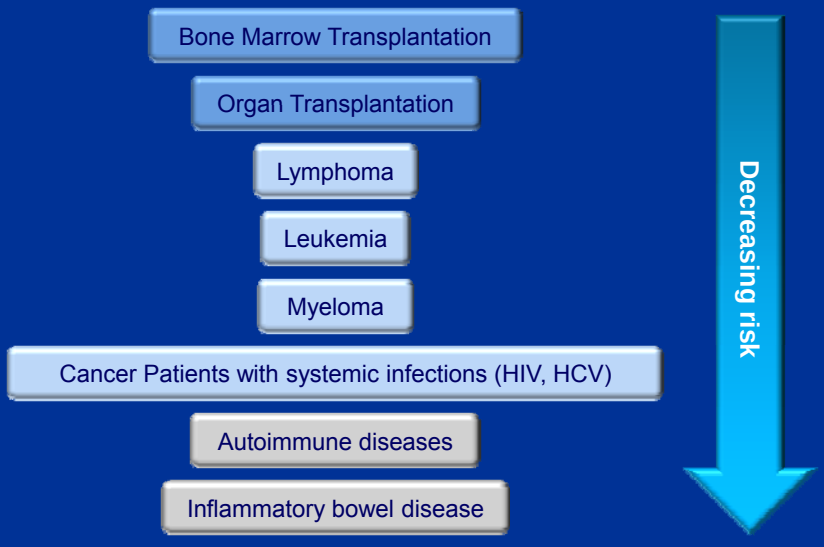
Overview of HBV Reactivation

- Frequency of HBV reactivation is not well-defined[1]
- Risk for reactivation appears to be high among patients undergoing chemotherapy[1]
  - For patients with lymphoma, incidence of HBV reactivation has been reported between 24%-67%
- Among patients with breast cancer, incidence of reactivation has been reported to be as high as 41% to 56%[1]
- Reactivation is not limited to chemotherapy, and has been described in the treatment of patients with rheumatic, dermatological, and gastroenterological disorders[2]

[1] Lubel JS, et **al**. J Gastroenterol Hepatol. 2010;25:864-871.
[2] Hoofnagle JH. Hepatology. 2009;49(5, Suppl):S156-S165.

Risk of HBV Reactivation by Diseases



Manzano-Alonso ML, Castellano-Tortajada G. World J Gastroenterol. 2011;17(12):1531-1537.

HBV Reactivation in Oncology Patients

- Reactivation may occur during or after chemotherapy
- Without prophylaxis for HBV, reactivation occurs in up to 85% of HBsAg+ , Non-Hodgkin's Lymphomas patients
- Those who received steroid containing chemotherapies had an associated HBV related death of 30 to 50%
- With appropriate antiviral prophylaxis, chemotherapy related reactivation of HBV is significantly decreased

Reactivation has occurred in patients who are HBsAg+ or anti-HBc+ only.

Loomba R, et al. Ann Intern Med. 2008;148:519-528.
Evens AM, et al. Ann Oncol. 2011;22(5):1170-1180.

HBV Reactivation in Lymphoma Patients Receiving Chemotherapy Without Antiviral Prophylaxis

- First large prospective study in Hong Kong studied 100 lymphoma patients receiving chemotherapy
  - 48% (13/27) of the HBsAg+ patients developed reactivation during or shortly after chemotherapy
  - 4% (2/51) of the HBsAg-/HBcAb+ patients, developed an extreme form of HBV reactivation, called “reverse seroconversion”
  - 46% (7/15) of the reactivation cases developed jaundice
  - 3/7 patients with jaundice developed hepatic failure and 1 was fatal

Lok ASF, et al. Gastroenterology. 1991;100:182-188.

Immunosuppressive Therapies

- Immunosuppressive therapies used in:
  - Chronic Inflammatory disorders
  - Chemotherapy
- TNF alpha antagonists

Immunosuppressive therapies have been implicated in HBV Reactivation across multiple disease processes.

Perrillo RP. Gastroenterology. 2001;120(4):1009-1022.

HBV Reactivation in Dermatologic and Rheumatologic Conditions

- Dermatologic Conditions[1]
  - 41.3% of patients with systemic sclerosis treated with corticosteroid
  - Corticosteroid therapy can cause immunosuppression
- Rheumatologic Conditions[2]
  - 25% of patients are receiving biologic therapies
  - Use of biologic therapies can cause immunosuppression

Patients undergoing treatment with any immunosuppressant agent should be screened for HBV prior to initiation of therapy.

[1] Hunzelmann N, et al. Arthritis Res Ther. 2009;11:R30.
[2] Cush JJ, Dao KH. Medscape Education. Available at: http://www.medscape.org/viewarticle/553515. Posted: March 30, 2007. Accessed 14 July, 2011.

HBV Reactivation in Inflammatory Bowel Disease

- HBV reactivation has been documented in patients being treated with immunosuppressive agents for inflammatory bowel disease[1]
- Immunosuppressive side effect of agents can lead to HBV reactivation in chronically infected patients[1]

HBV Seroprevalence in Patients Treated for IBD[2]

	HBsAg+	Anti-HBc+ Only
Crohn's	1%	7.2%
Ulcerative Colitis	0.8%	8.1%

Patients undergoing treatment for inflammatory bowel disease should be screened for HBV at diagnosis.

[1] Esteve M, et al. Gut. 2004;53:1363-1365.
[2] Gisbert JP, et al. Aliment Pharmacol Ther. 2011;33:619-633.

HBV Reactivation in Hematopoietic Stem Cell Transplantation

- HBV Reactivation is more common in stem cell transplantation than seen with standard cancer chemotherapy
- Incidence of HBsAg seroreversion post-transplantation
  - 2 years: 40%
  - 5 years: 70%

All patients candidates for stem cell transplantation should be screened for HBV prior to conditioning chemotherapy regimen.

Lubel JS, Angus PW. J Gastroenterol Hepatol. 2010;25:864-871.

HBV Reactivation with Organ Transplantation

- HBV reactivation has been described in patients who have received transplantation with heart, liver and kidneys[1,2]
- Liver transplantation[2]
  - Occurs due to organ donor being HBsAg or anti-HBc positive
  - Most dramatic examples of reverse HBsAg seroconversion occur with anti-HBc+ / HBsAg- donor organs to HBsAg- recipients
  - HBV reactivation rate: 70%

Reactivation of HBV in kidney and heart transplant recipients ranges from 50 to 94% without antiviral prophylaxis.[2]

[1] *Lubel JS, Angus PW. J Gastroenterol Hepatol. 2010;25:864-871.*
[2] *Hoofnagle JH. Hepatology. 2009;49(5, Suppl):S156-S166.*

Risk of Reactivation With Rituximab

- Reactivation flares of HBV have been well documented in patients receiving rituximab[1,2]
- Currently, rituximab is commonly used to treat[2,3]
  - Non-Hodgkin's Lymphoma
  - Chronic Leukocytic Leukemia
  - Rheumatoid Arthritis
  - Lupus Nephritis

[1] *Leung C, et al. Oncologist. 2011;16(5):579-584.*
[2] *Zell JA, et al. Anticancer Drugs. 2005;16:83-85.*
[3] *Özgönenel B, et al. Am J Hematol. 2006;81:302.*

Conclusions

- HBV is common and most patients are unaware that they are infected
- Guidelines for screening have been developed
- Treatment is safe and highly effective at suppression
- Resistance is not a common problem
- Advanced fibrosis is reversible with successful treatment
- Reactivation can be a devastating problem