بسم الله الرحمن الرحيم

Hepatitis B virus reactivation associated with immunosuppressive therapy

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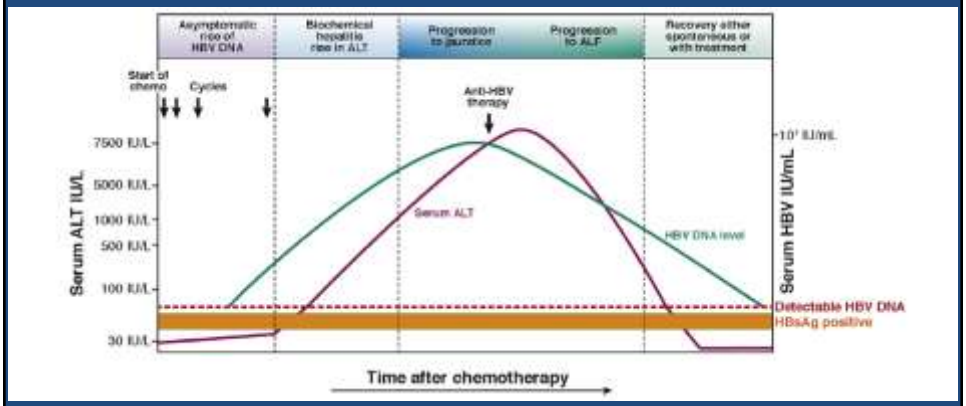
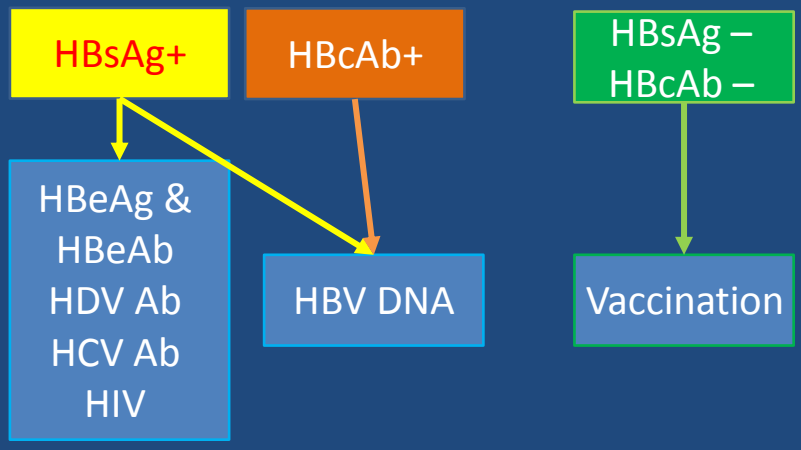
Course of HBV reactivation after receiving immunosuppressive therapy



Gastroenterology 2017;152:1297–1309

HBV reactivation

Patients should be tested for hepatitis B virus prior to initiating immunosuppressive therapy



Who is at risk for HBV reactivation

- Patients receiving chemotherapy
- Patients being treated for autoimmune disorders
- Patients undergoing transplantation

Annals of Internal Medicine® 2016

Hepatitis B Virus Reactivation and Prophylaxis During Solid Tumor Chemotherapy: A Systematic Review and Meta-analysis.

- Reactivation in chronic HBV without prophylaxis ranged from 4% to 68% (median, 25%)
- Patients with resolved HBV infection, none received HBV prophylaxis and reactivation risk ranged from 0.3% to 9.0%.

Table 2. Guidelines on screening for hepatitis B virus markers before immunosuppression or chemotherapy

Society	Who should be screened?	Screening tests
AGA	Patients at moderate or high risk of HBVr	HBsAg, anti-HBc + HBV DNA in case of positive results
EASL	All candidates for chemotherapy and immunosuppression	HBsAg, anti-HBc, and anti-HBs +HBV DNA in case of positive results

Clinical Medicine 2018 Vol 18, No 3: 212–8

How to assess risk

HBV serologic status | Type of immunosuppressive therapy

- HBV serologic status
  - HBsAg-positive
    - HBeAg-positive and/or high baseline levels of HBV DNA may be at highest risk
  - HBsAg-negative, HBc Ab positive
    - even if they are anti-HBs-positive

High hepatitis B virus (HBV) DNA viral load as the most important risk factor for HBV reactivation in patients positive for HBV surface antigen undergoing autologous hematopoietic cell transplantation

George K. K. Lau, Yu-hung Leung, Daniel Y. T. Fong, Wing-yan Au, Yok-lam Kwong, Albert Lie, Ji-liè Hou, Yu-mei Wan, Alvin Kwa, and Raymond Liang

Table 3. Results of univariate analysis of predictive factors for hepatitis due to HBV reactivation after transplantation

Characteristic	No. of patients	Relative hazard	95% CI	*P*
HBV DNA on PCR	137			
Positive	41	32.3	4.12-250	.001
Negative	96	1		
Precore A_{1896}	24			
Positive	5	0.7	0.14-3.03	.596
Negative	19	1		
HBsAg	137			
Positive	23	33.3	7.35-142.86	< .0001
Negative	114	1		
HBV DNA on Digene assay	119			
Detectable	10	62.5	16.67-250	< .0001
Undetectable	109	1		

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Table 4. Results of Cox proportional hazard analysis of HBV virologic factors predictive of hepatitis due to HBV reactivation in HBsAg-positive patients after autologous hematopoietic cell transplantation

Variable	Hazard ratio*	95% CI	*P*†
HBV DNA‡			
Detectable	9.35	1.65-52.6	.012
Undetectable	1		
Genotype			
C	1.47	0.16-13.50	.734
B	1		
BCP			
Positive	2.02	0.70-43.48	.448
Negative	1		
Pretransplantation ALT			
Elevated	5.49	0.07-6.25	.105
Normal	1		

How to assess risk

HBV serologic status

Type of immunosuppressive therapy

- Type of immunosuppressive therapy
  - Anti-CD 20 agents
    - rituximab
  - Glucocorticoids
    - Dose/duration
  - TNF alpha-inhibitors

Categorizing level of risk

HBV serologic status | Type of immunosuppressive therapy

- Risk of reactivation
  - **Very high risk:** >20 percent
  - **High risk:** 11-20 percent
  - **Moderate risk:** 1 to 10 percent
  - **Low risk**: <1 percent

Categorizing level of risk

HBV serologic status | Type of immunosuppressive therapy

- **Very high risk**
  - ***HBsAg-positive*** and are going to
    - receive anti-CD20 therapy (rituximab)
    - undergo hematopoietic cell transplantation.

Categorizing level of risk

HBV serologic status | Type of immunosuppressive therapy

- **High risk**
  - ***HBsAg-positive*** and are going to receive
    - high-dose glucocorticoids (≥20 mg/day for at least four weeks) or
    - anti-CD52 agent, alemtuzumab.

Categorizing level of risk

HBV serologic status | Type of immunosuppressive therapy

- **Moderate risk**
  - ***HBsAg-positive*** individuals if they are going to receive any of the following:
    - cytotoxic chemotherapy **without** glucocorticoids
    - anti-TNF therapy
    - anti-rejection therapy for solid organ transplants.

Categorizing level of risk

HBV serologic status | Type of immunosuppressive therapy

- **Low risk**
  - ***HBsAg-positive*** individuals if they receive methotrexate or azathioprine.
  - ***HBsAg-negative and anti-HBc-positive*** individuals if they receive high-dose glucocorticoids (eg, ≥20 mg/day) or the anti-CD52 agent alemtuzumab.

Categorizing level of risk

HBV serologic status | Type of immunosuppressive therapy

- **Very low risk**
  - ***HBsAg-negative and anti-HBc-positive*** patients receiving the following:
    - cytotoxic chemotherapy without glucocorticoids,
    - anti-TNF therapy
    - Methotrexate, or azathioprine.

Clinical manifestations of reactivation

- Most patients with HBV reactivation are asymptomatic, and the only manifestation is an increase in the HBV DNA level.
- Other patients can have a flare of their HBV infection

Diagnosis of reactivation

- HBV reactivation = increase in HBV DNA.
  - A ***detectable HBV DNA*** level when they previously had undetectable HBV DNA.
  - A rise in HBV DNA of more than ***2 $\log_{10}$*** iu/ml in patients who had HBV DNA present at baseline.
  - In some studies, HBV reactivation is defined as a ***≥10-fold*** increase in HBV DNA compared with baseline.
  - ***Reverse seroconversion*** (when a patient previously HBsAg-negative/anti-HBc-positive becomes HBsAg-positive).

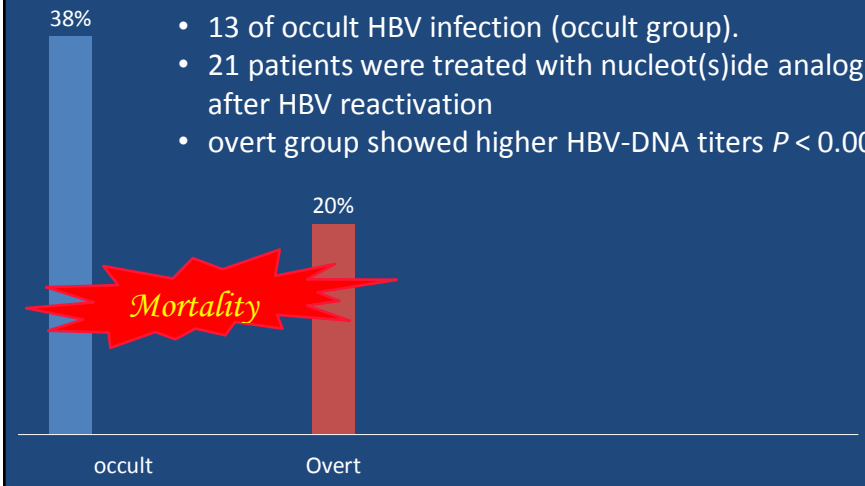
Treatment of HBV reactivation

- Severe hepatitis and/or hepatic failure can develop in up to 25 to 50 percent of patients with HBV reactivation
- We recommend antiviral treatment for all patients who develop HBV reactivation.
- Tenofovir or entecavir for patients who are treatment-naïve

Preventing HBV reactivation

HBV reactivation is life-threatening!!

- 23 patients with symptomatic HBV reactivation occurring during or after immunosuppressive
  - 10 with reactivation of overt HBV infection
  - 13 of occult HBV infection (occult group).
  - 21 patients were treated with nucleot(s)ide analogues after HBV reactivation
  - overt group showed higher HBV-DNA titers $P < 0.005$).



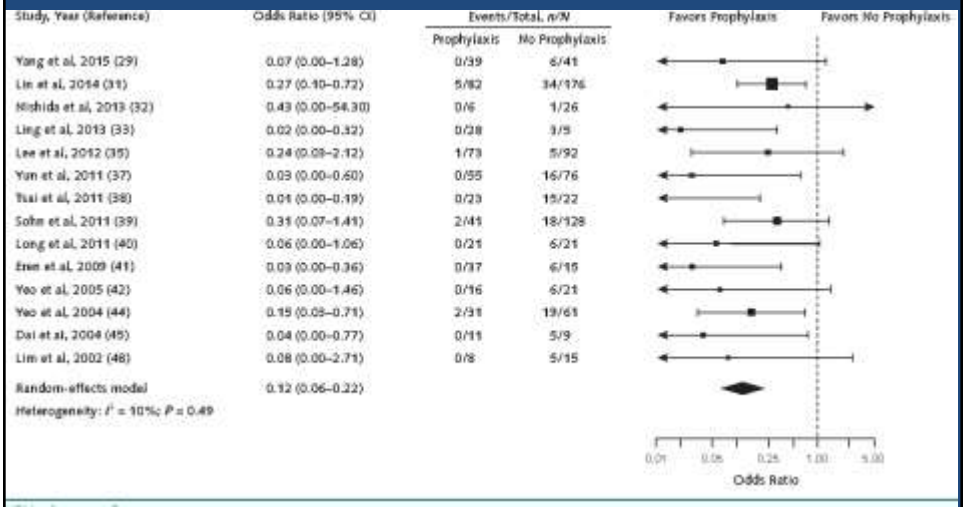
J. Med. Virol., 2011

Who should receive antiviral therapy

Annals of Internal Medicine® 2016

Hepatitis B Virus Reactivation and Prophylaxis During Solid Tumor Chemotherapy: A Systematic Review and Meta-analysis.

- Reactivation in chronic HBV without prophylaxis ranged from 4% to 68% (median, 25%)
  - Prophylaxis reduced the risk for
    - HBV reactivation (OR, 0.12 [95% CI, 0.06 to 0.22])
    - HBV-related hepatitis (OR, 0.18 [CI, 0.10 to 0.32])
    - Chemotherapy interruption (OR, 0.10 [CI, 0.04 to 0.27]).
- Patients with resolved HBV infection, none received HBV prophylaxis and reactivation risk ranged from 0.3% to 9.0%.



Odds ratio for HBV reactivation with and without antiviral prophylaxis in patients with chronic HBV infection.

Moderate to very high risk

- We recommend that antiviral therapy be administered concurrently or prior to initiating immunosuppressive therapy
- Aantiviral therapy started after the onset of reactivation may not prevent a flare

Moderate to very high risk

- For most patients, we initiate antiviral treatment for HBV and immunosuppressive therapy concurrently
- For patients with a high baseline serum HBV DNA level (eg, >4 $\log_{10}$ iu/ml), we prefer to delay immunosuppressive therapy until the HBV DNA level is suppressed to <3 $\log_{10}$international units/mL.

Low risk or very low risk

- We suggest monitoring patients
- We obtain HBV DNA and liver chemistries while immunosuppressive therapy is being administered, and for six months after treatment is discontinued.
  - For patients with a **detectable** HBV DNA at baseline, we perform laboratory monitoring monthly.
  - For patients with an **undetectable** HBV DNA at baseline, we perform laboratory monitoring every three months.
- We initiate antiviral treatment in patients with evidence of HBV reactivation

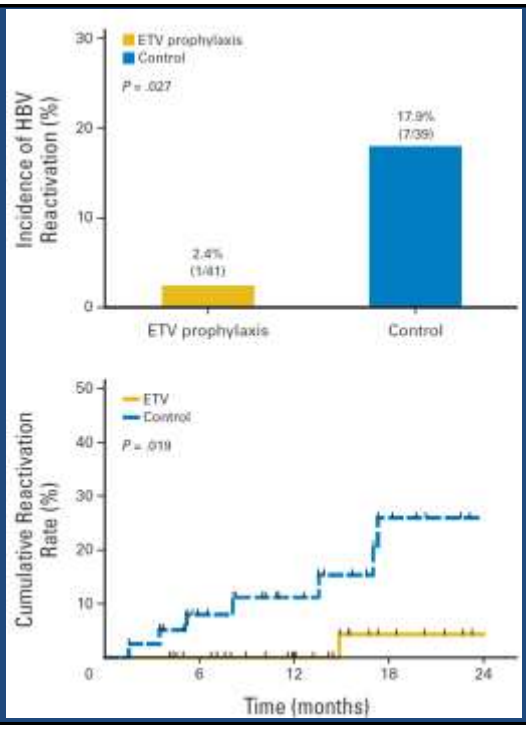
Which agents to use

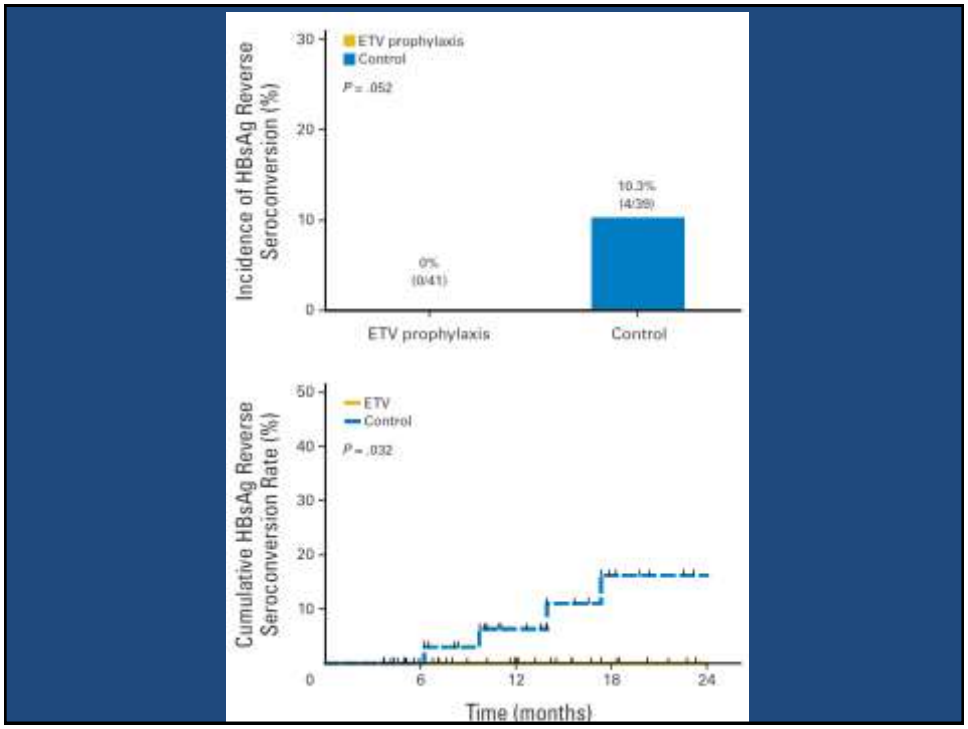
- We suggest tenofovir or entecavir as preventive therapy

Randomized Controlled Trial of Entecavir Prophylaxis for Rituximab-Associated Hepatitis B Virus Reactivation in Patients With Lymphoma and Resolved Hepatitis B

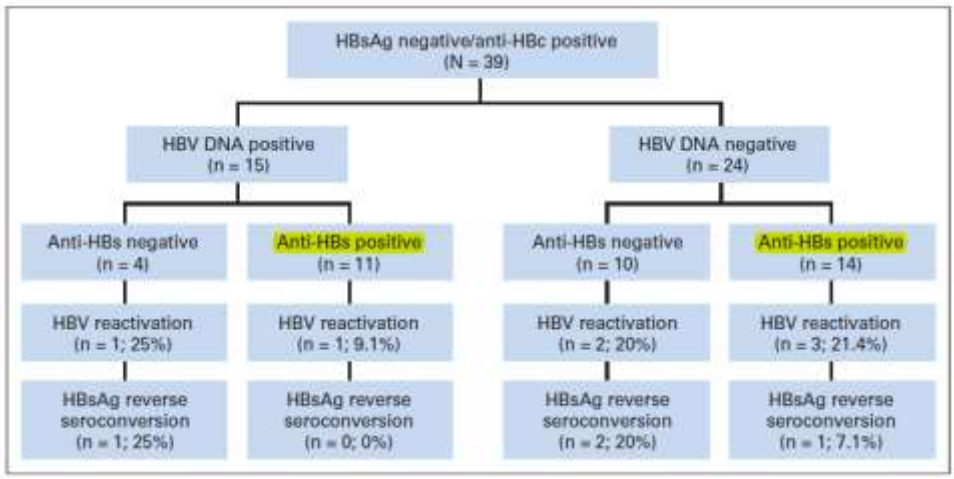
- 80 patients with lymphoma and resolved hepatitis B were randomly assigned to
  - Prophylactic entecavir (ETV) before chemotherapy to 3 months after completing chemotherapy (n 41)
  - Therapeutic ETV at the time of HBV reactivation and HBsAg reverse seroconversion since chemotherapy (n 39)

Yi-Hsiang Huang,et al. J Clin Oncol 31:2765-2772. 2013 by American Society of Clinical Oncology





Randomized Controlled Trial of Entecavir Prophylaxis for Rituximab-Associated Hepatitis B Virus Reactivation in Patients With Lymphoma and Resolved Hepatitis B



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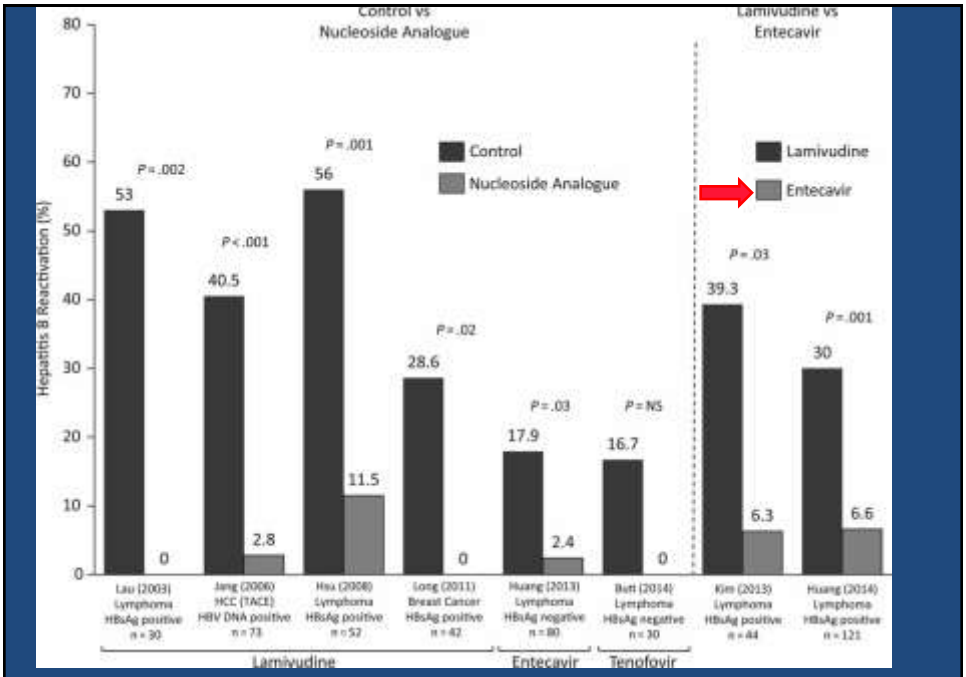


Clinical Infectious Diseases 2016:62 (Suppl 4) • Gonzalez and Perrillo

Entecavir vs Lamivudine for Prevention of Hepatitis B Virus Reactivation Among Patients With Untreated Diffuse Large B-Cell Lymphoma Receiving R-CHOP ChemotherapyA Randomized Clinical Trial *JAMA.* 2014

Table 3. Efficacy Comparison of the Lamivudine and Entecavir Groups

Outcome	No. (%) of Patients		Difference Between Groups, % (95% CI)	Odds Ratio (95% CI)	*P* Value
	Entecavir (n = 61)	Lamivudine (n = 60)			
Incidence of hepatitis	5 (8.2)	14 (23.3)	15.1 (2.4-27.8)	0.29 (0.10-0.88)	.02[a]
Severity of hepatitis[b]					
Grade 1	2 (3.3)	3 (5.0)			
Grade 2	0	4 (6.7)			.58[c]
Grade 3	3 (4.9)	5 (8.3)			
Grade 4	0	2 (3.3)			
HBV reactivation	4 (6.6)	18 (30.0)	23.4 (10.2-36.6)	0.16 (0.05-0.52)	.001[a]
HBV-related hepatitis	0	8 (13.3)	13.3 (4.7-21.9)	0.05 (0.003-0.89)	.003[c]
Delayed hepatitis B	0	5 (8.3)	8.3 (1.3-15.3)		.03[c]
Chemotherapy disruption	1 (1.6)	11 (18.3)	16.7 (6.4-27.0)	0.07 (0.01-0.60)	.002[a]
Premature termination	0	1 (1.7)			
Delay ≥7 d	1 (1.6)	10 (16.7)			

Entecavir vs Lamivudine for Prevention of Hepatitis B Virus Reactivation Among Patients With Untreated Diffuse Large B-Cell Lymphoma Receiving R-CHOP ChemotherapyA Randomized Clinical Trial

JAMA. 2014

Table 4. Analysis of Factors Associated With HBV Reactivation

	Total Sample Size	No. of Events	Type of Analysis: Bivariable OR (95%CI)	Bivariable P Value[b]	Multivariable[a] OR (95%CI)	Multivariable P Value[c]
Antiviral prophylaxis						
Lamivudine	60	18	6.11 (1.93-19.37)	.001	6.46 (1.87-22.29)	.004
Entecavir	61	4				
Sex						
Male	68	16	2.41 (0.87-6.67)	.08	2.62 (0.80-8.55)	.11
Female	53	6				
Age, y						
≤40	54	8	0.66 (0.25-1.71)	.39		
>40	67	14				
Ann Arbor stage						
I-II	47	4	3.46 (1.09-10.96)	.03	3.59 (1.01-12.77)	.049
III-IV	74	18				
International Prognostic Index						
0-2	105	18	1.61 (0.47-5.57)	.68		
3-5	16	4				
Hepatitis B e antigen status						
Seropositive	34	7	1.24 (0.46-3.38)	.67		
Seronegative	87	15				
Hepatic cirrhosis						
Yes	3	2				

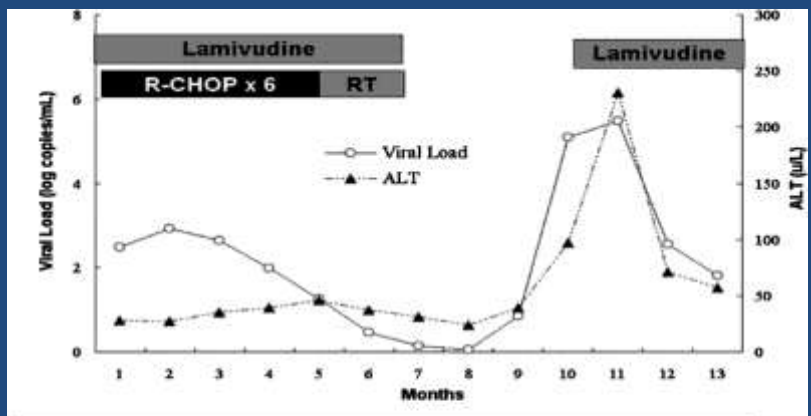
Duration of therapy

- The duration of therapy for treatment and prevention depends upon the
  - type of immunosuppressive therapy
  - patient's baseline HBV DNA level
  - degree of underlying liver disease.
    - at least 6 months after withdrawal of immunosuppression (with the exception of anti-CD20 therapy)
    - at least 12 months after stopping anti-CD20 agents

Duration of therapy

- Antiviral therapy may need to be continued long-term for certain HBsAg-positive patients (eg, those with a baseline HBV DNA >2000 international units/mL or evidence of cirrhosis)

Delayed HBV reactivation after premature cessation of preemptive lamivudine in a lymphoma patient receiving six courses rituximab (R) and CHOP

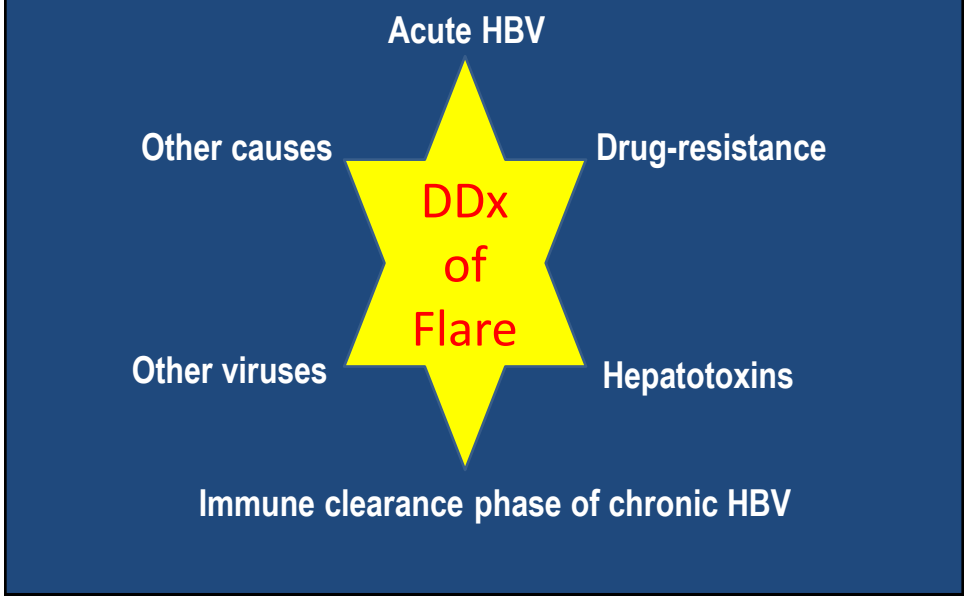


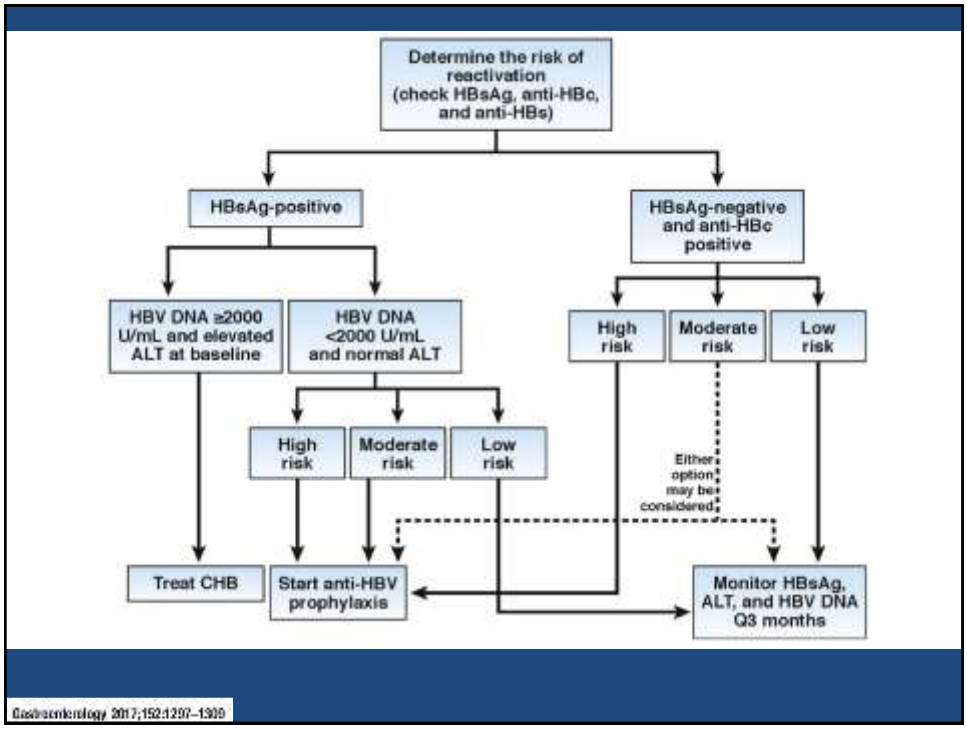
Month	1	2	3	4	5	6	7	8	9	10	11	12	13
ALC (cumm)	2184	1863	1912	2246	1371	1625	1344	1120	1040	956	1367	1455	1890
CD20 (%)	20	19	4.8	0.7	0	0	0	0	0	0	2	10	15
HBeAg	-									-			-
Anti-HBe Ab	+									+			+

Daniel Shouval, **Immunosuppression and HBV Reactivation** Semin Liver Dis 2013; 33(02):

HBV FLARE

- A rise in transaminases with an ALT that is at least 3 to 5 times the baseline value +/- clinical signs and symptoms of hepatitis.
- Flares can occur at various times during the course of immunosuppressive therapy.
  - while the patient is receiving immunosuppressive therapy
  - after withdrawal of therapy (glucocorticoids, TNF-alpha inhibitors)
- Among patients receiving chemotherapy, flares often occur during the gaps between cycles, most often after the first two to three cycles .




Determine the risk of reactivation (check HBsAg, anti-HBc, and anti-HBs)
HBsAg-positive
HBsAg-negative and anti-HBc positive
HBV DNA ≥2000 U/mL and elevated ALT at baseline
HBV DNA <2000 U/mL and normal ALT
High risk
Moderate risk
Low risk
High risk
Moderate risk
Low risk
Either option may be considered
Treat CHB
Start anti-HBV prophylaxis
Monitor HBsAg, ALT, and HBV DNA Q3 months
Gastroenterology 2017;152:1297–1309