3ο Εκπαιδευτικό Σεμινάριο «Λοιμώξεις σε ανοσοκατεσταλμένους ασθενείς» Ναύπακτος 31-Ιανουαρίου- 2 Φεβρουαρίου 2020

Προφύλαξη για HBV επανενεργοποίηση

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Ναύπακτος 1 Φεβρουαρίου 2020

Disclosures

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Επανενεργοποίηση HBV λοίμωξης - Ορισμοί

- Επανεμφάνιση ή αύξηση του DNA του ιού HBV στον ορό ασθενών με προηγηθείσα ή χρόνια HBV λοίμωξη
- Ανοσοκατεσταλμένα άτομα, ανοσοκατασταλτικές θεραπείες
- Επιπολασμός: 2% στην Ευρώπη, > 10% στην Αν. Ασία

Wang B et al. Haematologica 2019; 104(3): 435- 443

Χρόνια HBV λοίμωξη- Ορισμός

- Η παραμονή του HBsAg στον ορό με την παρουσία ποικίλων επιπέδων του HBV DNA
- EASL 2017: διακρίνει τους ασθενείς ανάλογα με την παρουσία HbeAg

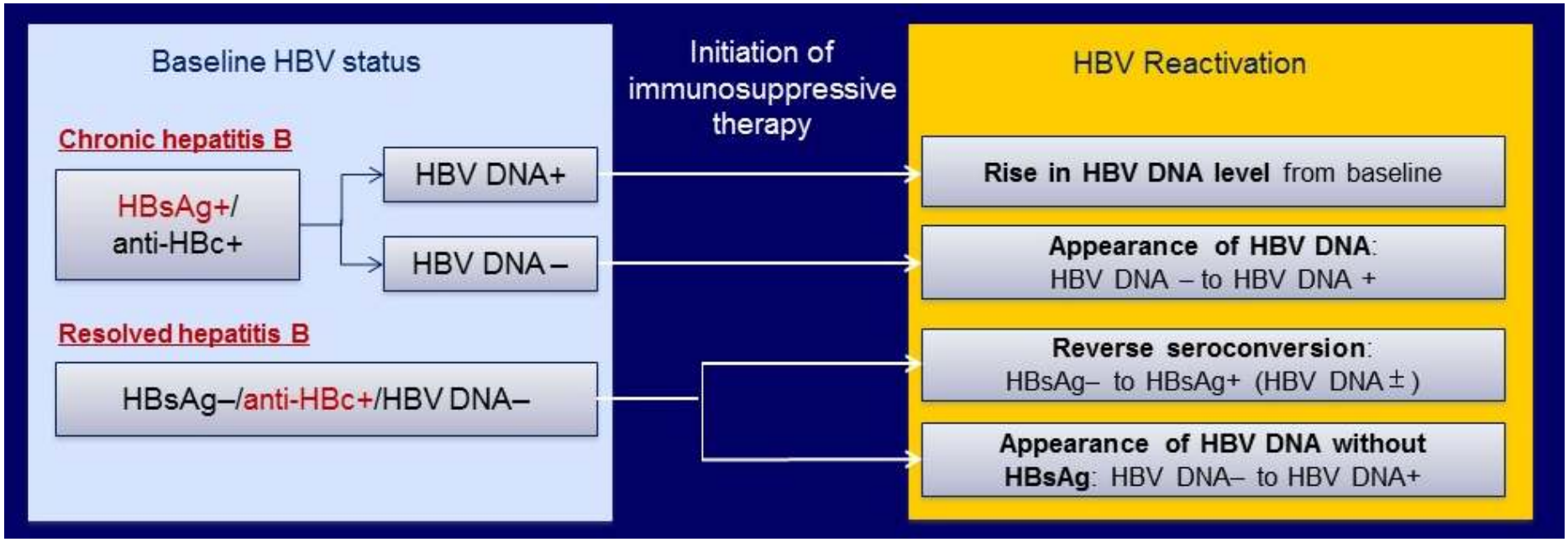
Table 1. Up-dated nomenclature for natural history phases of chronic hepatitis B virus (HBV) infection, adapted from the 2017 EASL Clinical Practice Guidelines.

	HBeAg positive		HBeAg negative	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	$>10^7$ IU/mL	$10^4 – 10^7$ IU/mL	<2000 IU/mL*	>2000 IU/mL
ALT	Normal	Elevated	Normal	Elevated**
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe
Old terminology	Immune tolerant	Immune reactive	Inactive carrier	HBeAg negative chronic hepatitis

EASL: European Association for the Study of the Liver; HBeAg: hepatitis B e antigen; ALT: alanine transaminase. *Can be 2000-20000 IU/mL in some patients without signs of chronic hepatitis. **Either persistently or intermittently.

Wang B et al. Haematologica 2019; 104(3): 435- 443

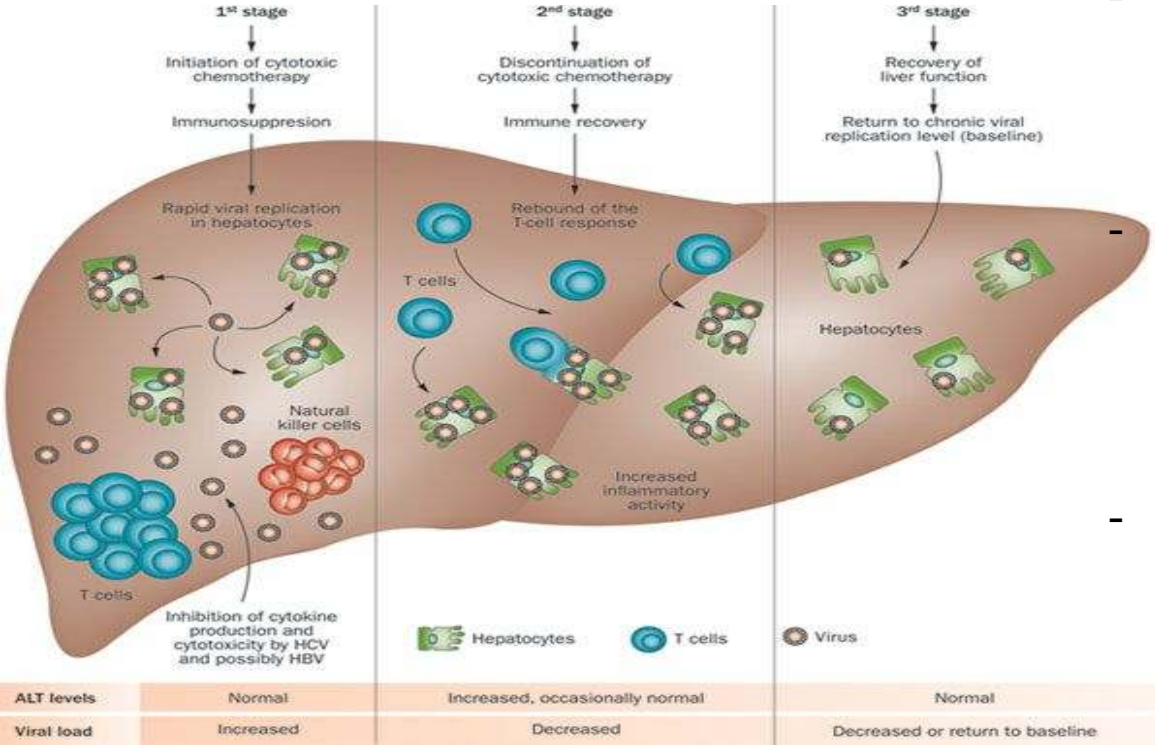
Επανενεργοποίηση HBV λοίμωξης - Ορισμοί



Reactivation-related hepatitis: increase in ALT or AST ≥3 x baseline)

Hoofnagle et al. Hepatology; 2011
Hwang et al. Nat Rev Gastroenterol Hepatol; 2014

Παθογένεια



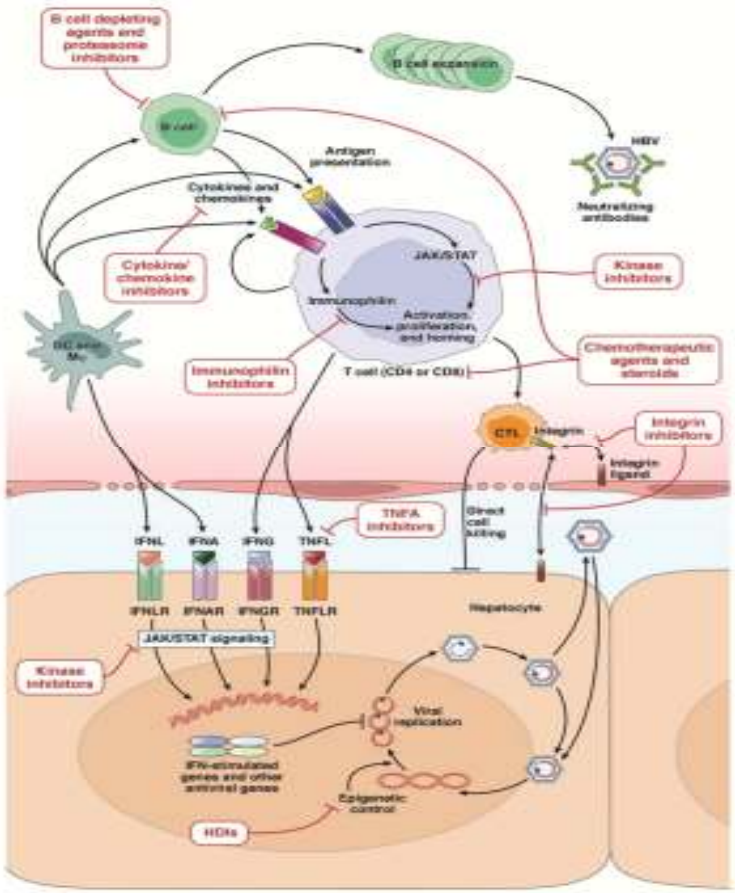
- Reactivation typically starts with an increase in viral replication caused by chemotherapy-induced immune suppression **(stage 1)**
- After chemotherapy is discontinued, the function of the immune system is restored, and hepatocytes infected with HBV are destroyed **(stage 2)**.
- In the recovery stage, clinical hepatitis (indicated by an increase in ALT levels) resolves and markers of HBV infections return to baseline levels **(stage 3).**

Torres et al. Nat Rev Clin Oncol; 2012

Παθογένεια

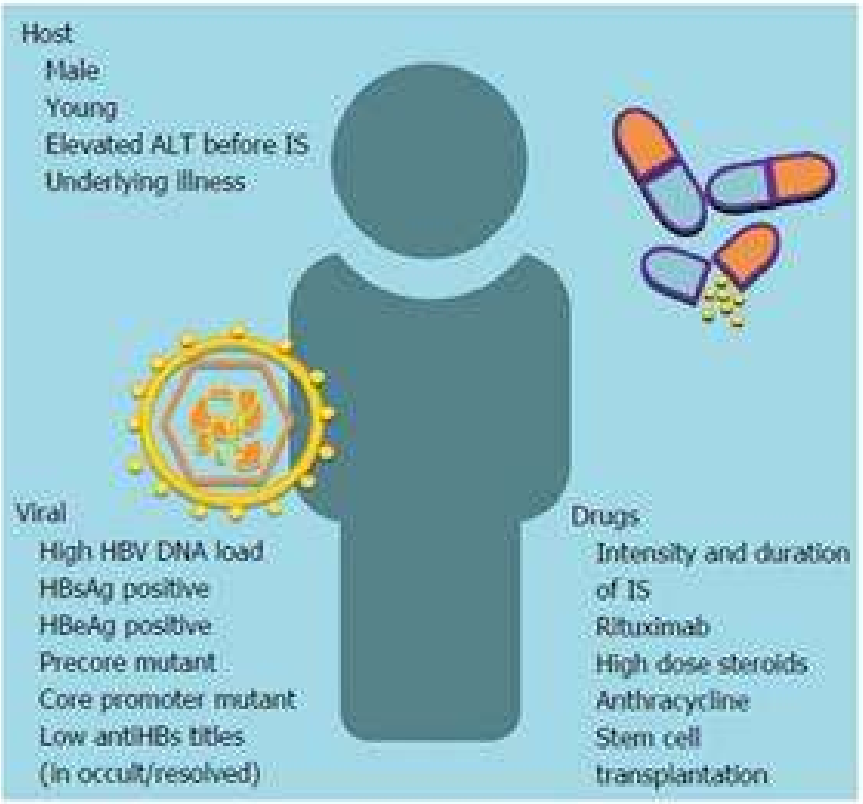
HBV replication and propagation is controlled by various innate and adaptive immune mechanisms.

- The epigenetic regulation of HBV transcription can be altered by the HDIs.
- The innate immune control mechanisms such as IFNA and TNF-like molecules (TNFL) and their signaling pathways can be blocked by various immunosuppressive therapies such as TNFA and kinase inhibitors.
- The adaptive immunity controlling HBV including antigen-presenting cells (dendritic cells and macrophages), T and B cells can be inhibited by various immunosuppressive therapies targeting at different steps of immune response.



Loomba et al. Gastroenterology; 2017

Risk factors of HBV reactivation



Wang et al. Haematologica; 2019
Bessone F et al. World J Hepatol; 2016

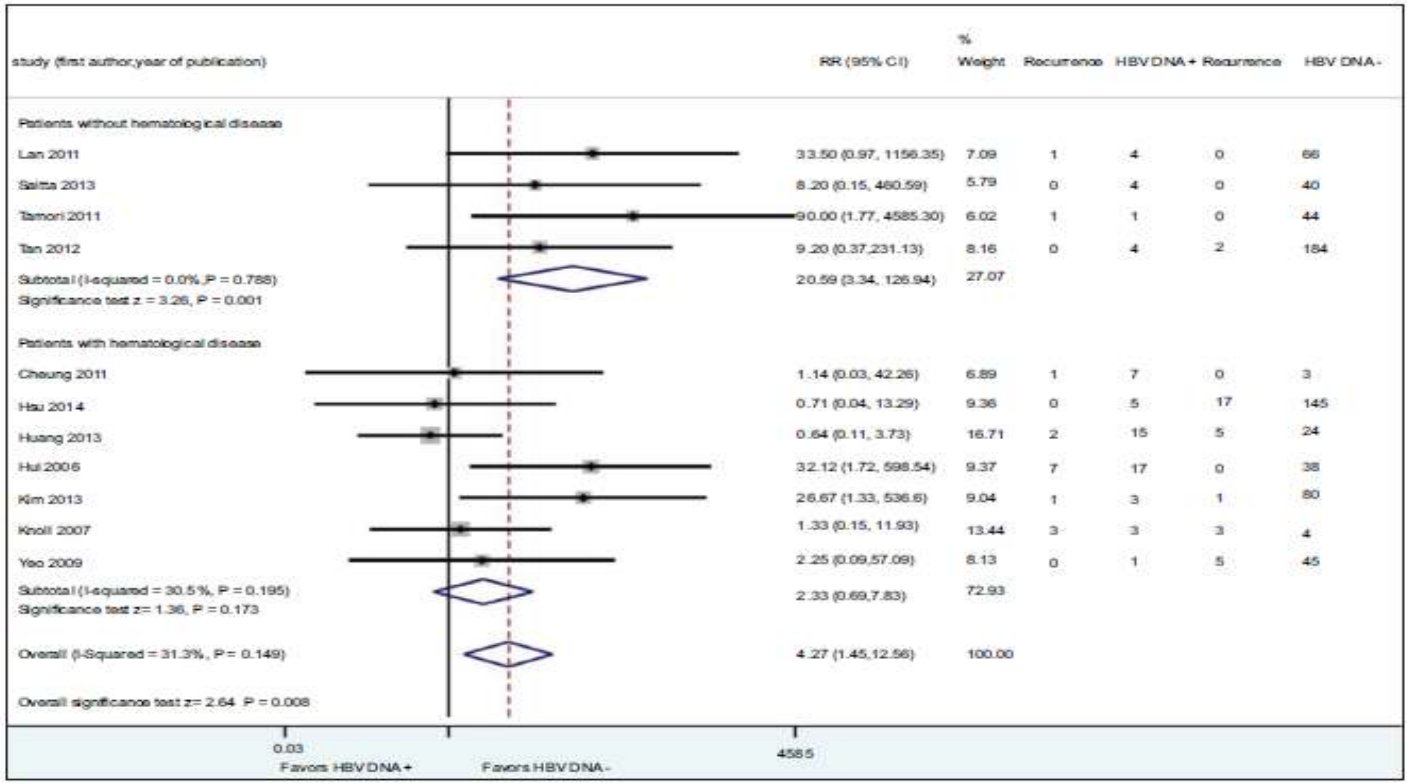
Risk factors- Host

- Male sex
- Older age
- Presence of cirrhosis
- Type of underling disease needing immunosuppression

Risk factors- Virus

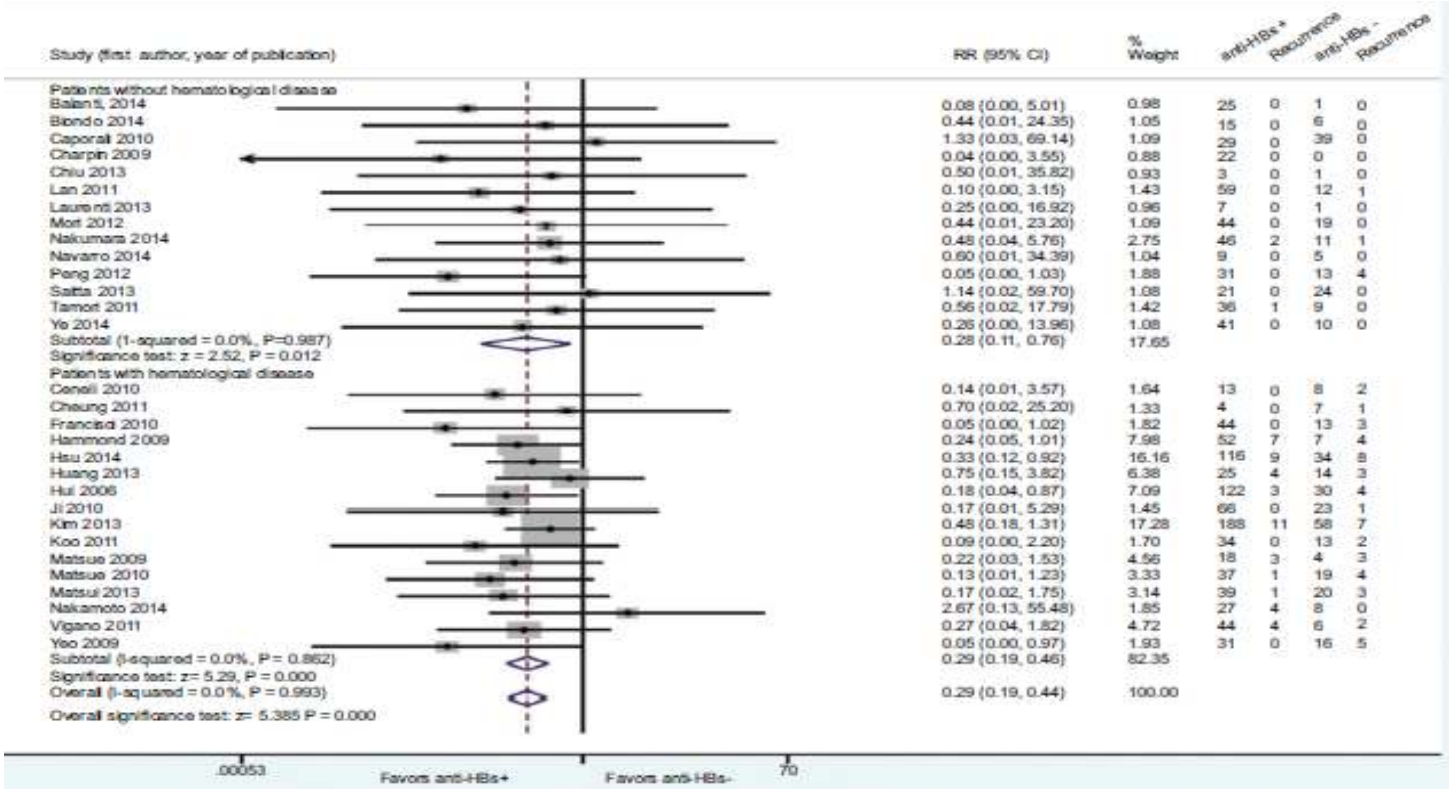
- High baseline HBV DNA
- Absence of anti-HBs
- HBeAg positivity
- Chronic hepatitis B
- Co-infection with HCV, HDV or HIV

Risk factors- HBV DNA



Cholongitas E et al. Ann Gastroenterol; 2018

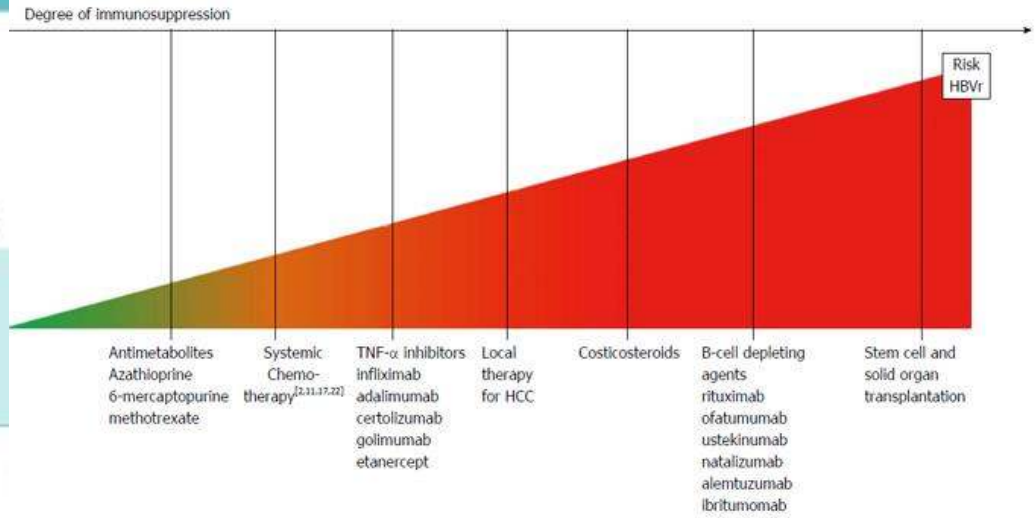
Risk factors- Anti-HBs



Cholongitas E et al. Ann Gastroenterol; 2018

Risk factors- Drugs

Risk group	Treatment regimen
High risk (>10%)	B-cell-depleting anti-CD20-directed monoclonal antibodies (e.g. rituximab) HSCT +/- diagnosis of GvHD Systemic cancer chemotherapy - anthracycline derivatives (e.g. doxorubicin)
Moderate risk (1-10%)	Tyrosine kinase inhibitors (e.g. imatinib, ibrutinib) Corticosteroids ≥20mg prednisolone, ≥4 weeks
Low risk (<1%)	Traditional immunosuppressive monotherapy (e.g. azathioprine, methotrexate) Corticosteroids ≤4 weeks



Wang et al. Haematologica; 2019
Bessone F et al. World J Hepatol; 2016

Risk factors- Drugs

Risk Group	HBVr Drug Risk Estimates *HBsAg positive or anti-HBc positive*	Potential Disorders for Treatment
High risk group > 10%	**B cell depleting agents such as rituximab and ofatumumab** o HBsAg pos/anti-HBc pos: 30-60% (A) o HBsAg neg/anti-HBc pos: >10% (A)	Lymphoma/leukemia, rheumatoid arthritis, idiopathic thrombocytopenic purpura, cryoglobulinemia
	Anthracycline derivatives such as doxorubin and epirubicin o HBsAg pos/anti-HBc pos: 15-30% (A)	Breast, ovarian, uterine, and lung cancers; lymphoma and leukemias; transarterial chemoembolization
	Corticosteroids for ≥ 4 weeks o HBsAg pos/anti-HBc pos: >10% (B) (mod./high dose*)	Inflammatory bowel disease, vasculitis, sarcoidosis, autoimmune disorders

Perrillo et al. Gastroenterology; 2015

Risk factors- Drugs

Moderate risk group **1% to 10%**	**TNF alpha inhibitors**: such as etanercept, adalimumab, certolizumab, infliximab o HBsAg pos/anti-HBc pos: 1-10% (B) o HBsAg neg/anti-HBc pos: 1% (C)	Inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis
	Other cytokine inhibitors and integrin inhibitors: abatacept, ustekinimab, natalizumab, vedolizumab o HBsAg pos/anti-HBc pos: 1-10% (C) o HBsAg neg/anti-HBc pos: 1% (C)	Plaque psoriasis, inflammatory bowel disease
	Tyrosine kinase inhibitors: imatinib, nilotinib o HBsAg pos/anti-HBc pos: 1-10% (B) o HBsAg neg/anti-HBc pos: 1% (C)	Chronic myelogenous leukemia, gastrointestinal stromal tumors
	Corticosteroids for ≥ 4 weeks o HBsAg pos/anti-HBc pos: 1-10% (C) (low dose*) o HBsAg neg/anti-HBc pos: 1-10% (C) (mod./high dose*)	Inflammatory bowel disease, vasculitis, sarcoidosis, autoimmune disorders
	Anthracycline derivatives such as doxorubin and epirubicin o HBsAg neg/anti-HBc pos: 1-10% (C)	Breast, ovarian, uterine, and lung cancers; lymphoma and leukemias; transarterial chemoembolization

Perrillo et al. Gastroenterology; 2015

Risk factors- Drugs

Low risk group **< 1%**	**Traditional immunosuppressive agents**: azathioprine, 6-mercaptopurine, methotrexate o HBsAg pos/anti-HBc pos: < 1% (A) o HBsAg neg/anti-HBc pos: << 1% (A)	Inflammatory bowel disease, psoriasis, sarcoidosis, autoimmune liver disease, arthritis
	Intraarticular corticosteroids o HBsAg pos/anti-HBc pos: << 1% (A) o HBsAg neg/anti-HBc pos: << 1% (A)	Arthritis
	Corticosteroids for ≤ 1 week o HBsAg pos/anti-HBc pos: < 1% (B) o HBsAg neg/anti-HBc pos: << 1% (A)	Asthma, contact dermatitis
	Corticosteroids for ≥ 4 weeks o HBsAg neg/anti-HBc pos: <1% (B) (low dose*)	Inflammatory bowel disease, vasculitis, sarcoidosis, autoimmune disorders

Confidence in evidence: (A) High confidence that the estimate lies within group risk boundaries
(B) Moderate confidence that the estimate lies within group risk boundaries
(C) Little or no confidence that the estimate lies within group risk boundaries

* Glucocorticoids: prednisone (or equivalent): low dose: < 10 mg; moderate dose: 10 to 20 mg; high dose: > 20 mg

Perrillo et al. Gastroenterology; 2015

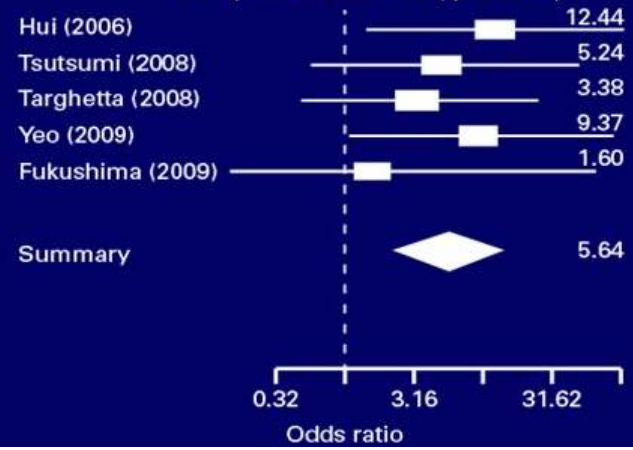
HBV reactivation after Rituximab

Meta-analysis of 183 case reports
between 1997-2009
(27+156 case reports + series)

	Overall
Median doses of Rituximab before HBV-R*	6 (range 3-10)
Median time from last dose to HBV-R*	3 months (range 0-12)
HBV-R* occurred ≥6 months after last dose	29%
HBV-related hepatitis**	45%
Fulminant liver failure†	55%
HBV-related Death‡	48%

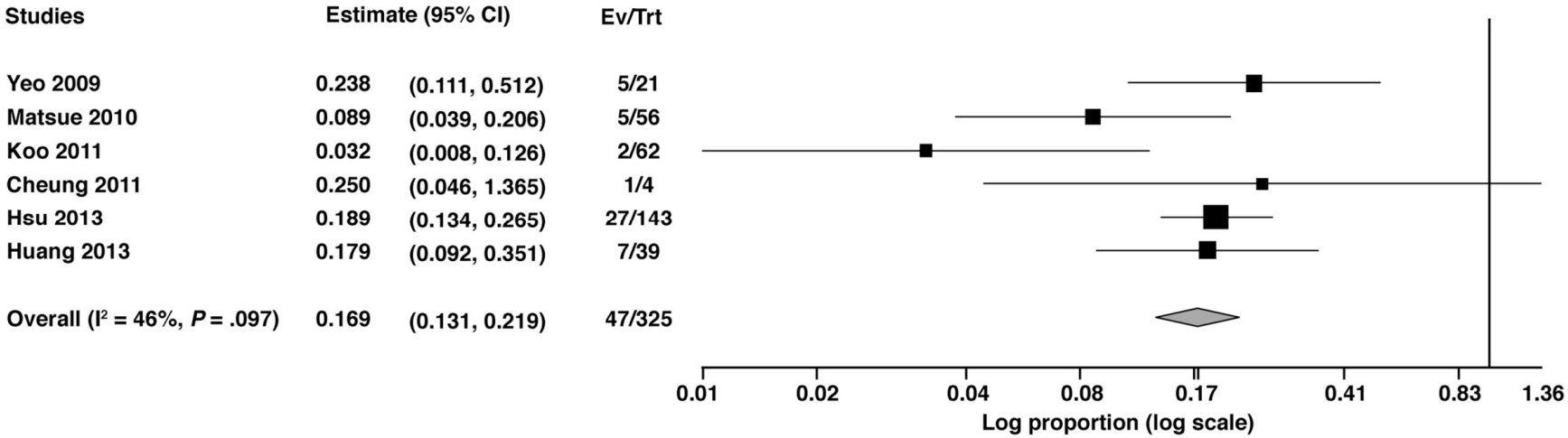
• Nearly one-third of HBV reactivation occurred >6 months after last rituximab dose: long half-life of rituximab →'***Delayed' HBV reactivation and sustained β-cell suppression***

Meta-analysis of 5 case series
(including the control group)
Cumulative incidence of HBV-R: 8.2% vs. 0.6% (Rituximab vs. No rituximab, p<0.0001)
Odds Ratio from the pooled effect of rituximab-based therapy: 5.64 (95% CI 2.18-14.54, p=0.0003)



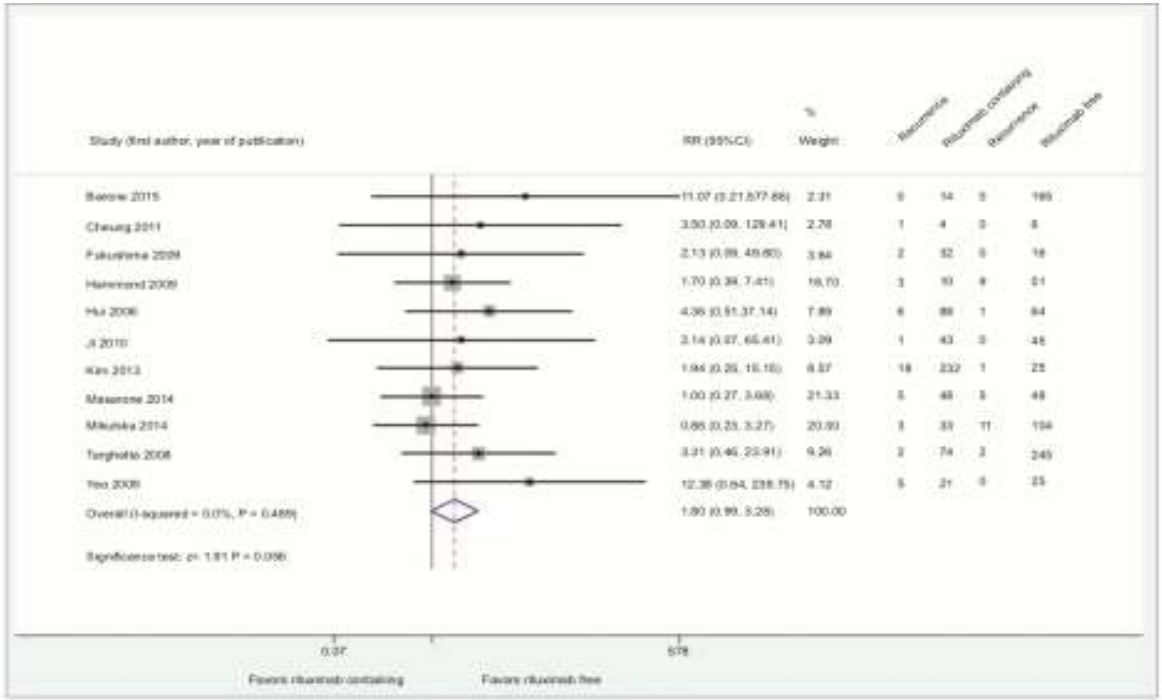
Evens et al. Ann Oncol; 2011

Pooled baseline risk estimate without prophylaxis of HBVr with rituximab in pts who have recovered from hepatitis B infection (HBsAg-negative, anti-HBc-positive).



Perrillo et al. Gastroenterology; 2015

Rates of HBV reactivation between HBsAg-neg, anti-HBc-pos pts treated with and without rituximab-containing regimens

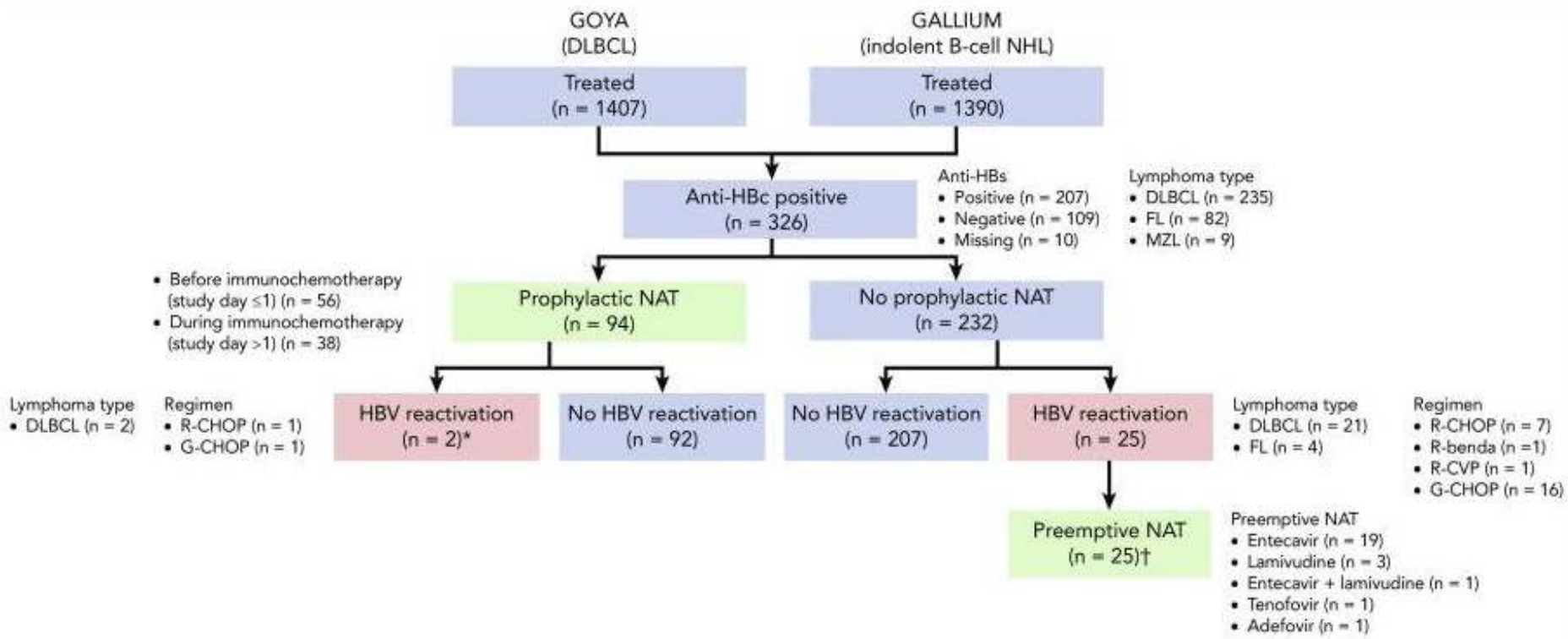


Rituximab-containing (**6.6%** vs. **19.8%**; RR 0.32, 95%CI 0.15-0.69, P=0.003)

Rituximab-free regimens (**3.3% vs. 9.2%;** RR 0.36, 95%CI 0.14-0.96, P=0.042)

Cholongitas E et al. Ann Gastroenterol; 2018

Risk of HBV reactivation in HBV- pts with anti-CD20 mAbs



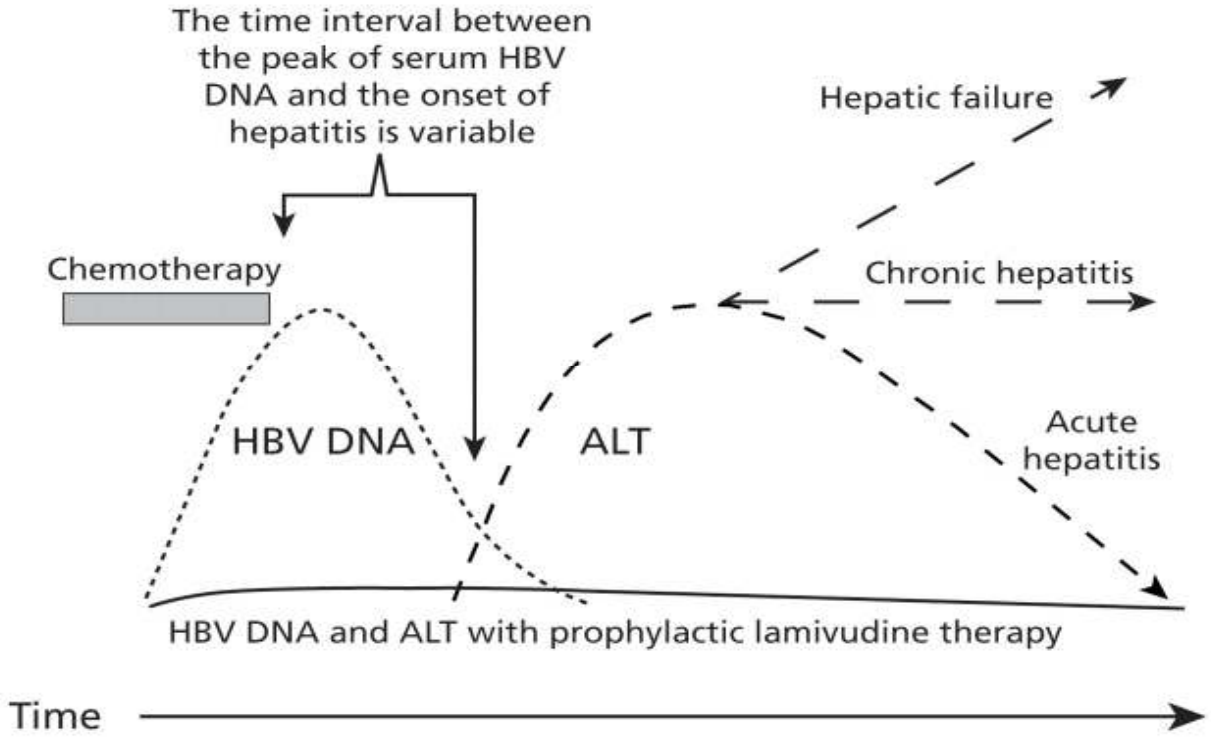
Kusumoto et al. Blood; 2019

HBV reactivation & allo-HSCT

- Καλά αναγνωρισμένη επιπλοκή:
  - 40% στα 2 έτη για ασθενείς με παρελθούσα λοίμωξη
  - 70-86% στα 5 έτη για HBsAg+ λήπτες
- Παράγοντες κινδύνου:
  - ηλικία (> 50 έτη)
  - ανιχνεύσιμο HBV DNA πριν την μεταμόσχευση
  - GvHD (79.5% vs 21% σε 85 anti-HBc ασθενείς)
- HBV status του δότη

Seto WK, et al. Hepatology 2017
Jun CH, et al Hepatol Int 2017

Κλινική πορεία



Mortality:
30% untreated vs. 12% treated
Lamivudine 17% vs. 3.5% entecavir

Keam et al. J Natl Compr Canc Netw; 2011

Ορισμός

Definitions Fulminant Hepatic Failure

A. biochemical evidence of acute liver injury (usually <8 wk duration)

– no evidence of chronic liver disease; and

B. hepatic-based coagulopathy defined as :

1. prothrombin time (PT) >15 sec or
2. international normalized ratio (INR) >1.5
3. not corrected by vitamin K in the

A. presence of clinical hepatic encephalopathy,

OR

or

- biochemical ;acute liver injury (usually <8 wk)
- no evidence of chronic liver disease; and

1) PT >20 sec

or

2) INR >2

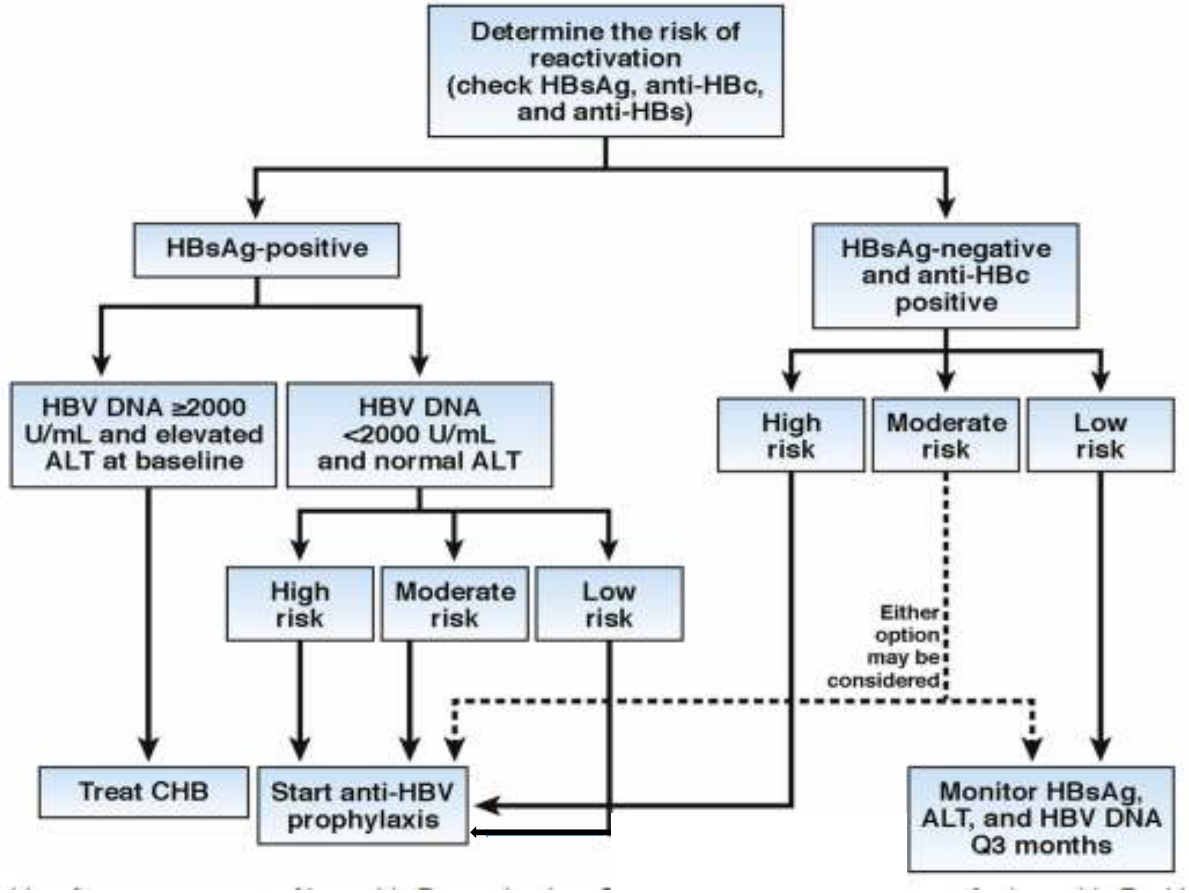
regardless of the presence of clinical hepatic encephalopathy.

Singh et al. Cleve Clin J Med; 2016

HBV reactivation- Treatment

- Prophylactic
  - Antiviral treatment to all patients considered at moderate or high risk prior to commencing immunosuppression
- Pre-emptive therapy
  - Regular monitoring of ALT, HBsAg and HBV DNA during treatment, with antiviral therapy started when HBV DNA and/or ALT levels rise
- Prophylactic treatment is more effective in preventing reactivation
  - 11.5% vs 56% in HBsAg + patients
  - 4.3% vs 23.9% in anti-HBc + patients

Κατευθυντήριες οδηγίες



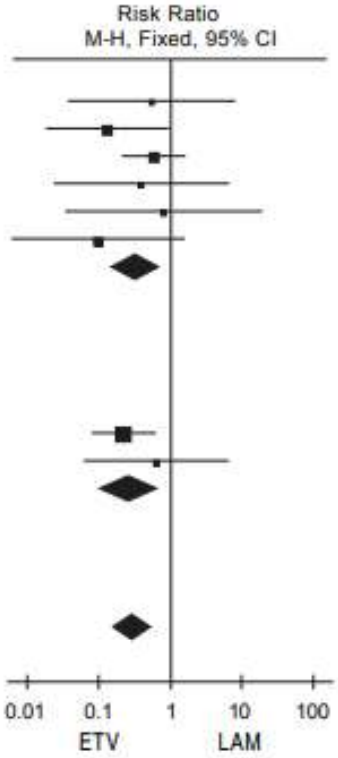
Έναρξη:
2-4 εβδομάδες πριν την έναρξη της θεραπείας

Διάρκεια προφύλαξης
> 6 μήνες μετά το τέλος της θεραπείας
> 12 μήνες στην περίπτωση του Rituximab

Loomba et al. Gastroenterology; 2017 τροποποιημένο

Entecavir vs Lamivudine

Study or subgroup	ETV Events	ETV Total	LAM Events	LAM Total	Weight	Risk Ratio M-H, Fixed, 95% CI
a) Restrospective cohort studies						
Chen, 2013	1	26	1	14	2.6%	0.54 [0.04, 7.97]
Huang, 2011	1	30	14	54	19.7%	0.13 [0.02, 0.93]
Li, 2011	4	34	18	89	19.6%	0.58 [0.21, 1.60]
Ryu, 2012	0	5	3	15	3.8%	0.38 [0.02, 6.33]
Ueda, 2013	0	26	1	63	1.8%	0.79 [0.03, 18.79]
Xia, 2013	0	21	9	39	13.3%	0.10 [0.01, 1.57]
Subtotal (95% CI)		**142**		**274**	**60.7%**	**0.32 [0.15, 0.67]**
Total events	6		46			
Heterogeneity: χ^2 = 3.35, df = 5 (P = 0.65); I^2 = 0%						
Test for overall effect: Z = 3.01 (P = 0.003)						
b) RCTs						
Huang, 2013	4	61	18	60	35.8%	0.22 [0.08, 0.61]
Lan, 2012	1	25	2	31	3.5%	0.62 [0.06, 6.45]
Subtotal (95% CI)		**86**		**91**	**39.3%**	**0.25[0.10, 0.64]**
Total events	5		20			
Heterogeneity: χ^2 = 0.64, df = 1 (P = 0.42); I^2 = 0%						
Test for overall effect: Z = 2.90 (P = 0.004)						
Total (95%CI)		**228**		**365**	**100.0%**	**0.29 [0.17, 0.52]**
Total events	11		66			
Heterogeneity: χ^2 =4.36, df = 7 (P = 0.74); I^2 = 0%						
Test for overall effect: Z = 4.15 (P = 0.0001)						
Test for subgroup differences: χ^2 = 0.14, df = 1 (P = 0.71); I^2= 0%						



Yang et al. Ann Hepatol; 2016

Επιλογή θεραπείας

HBV reactivation

88%. 90%

Telbivudine	0.99 (0.07, 13.63)	0.22 (0.01, 4.08)	0.15 (0.01, 1.95)	0.04 (0.00, 0.53)	0.01 (0.00, 0.25)
1.01 (0.07, 14.80)	**Control**	0.22 (0.05, 0.86)	0.15 (0.08, 0.25)	0.04 (0.01, 0.10)	0.01 (0.00, 0.09)
4.51 (0.25, 96.37)	4.58 (1.16, 19.51)	**Adefovir**	0.67 (0.16, 2.83)	0.16 (0.03, 0.82)	0.03 (0.00, 0.52)
6.86 (0.51, 103.28)	6.72 (3.93, 12.94)	1.49 (0.35, 6.16)	**Lamivudine**	0.24 (0.10, 0.60)	0.04 (0.00, 0.59)
27.86 (1.88, 486.97)	28.01 (10.50, 74.96)	6.17 (1.22, 28.81)	4.09 (1.68, 9.77)	**Entecavir**	0.16 (0.00, 2.62)
171.78 (3.96, 12826.89)	173.06 (11.26, 5702.10)	37.59 (1.93, 1494.05)	25.35 (1.71, 791.85)	6.22 (0.38, 212.23)	**Tenofovir**

HBV-related hepatitis

100%

Control	0.10 (0.05, 0.20)	0.01 (0.00, 0.06)
9.54 (5.08, 19.79)	**Lamivudine**	0.10 (0.01, 0.52)
96.33 (16.60, 999.68)	9.78 (1.92, 93.05)	**Entecavir**

HBV-related death

61%

Control	0.23 (0.01, 2.57)	0.33 (0.16, 0.72)	0.12 (0.01, 0.71)
4.31 (0.39, 166.36)	**Adefovir**	1.41 (0.13, 56.74)	0.52 (0.02, 30.09)
3.00 (1.38, 6.39)	0.71 (0.02, 7.86)	**Lamivudine**	0.37 (0.03, 2.06)
8.17 (1.42, 91.32)	1.92 (0.03, 53.01)	2.71 (0.48, 31.00)	**Entecavir**

Zhang et al. Expert Rev Anti Infect Ther; 2017

Key points

- All patients undergoing immunosuppressive drug therapy and interventions such as HSCT should be screened for HBV infection prior to initiation of therapy, including testing for HBsAg, HBV DNA, anti-HBc antibody and anti-HBs antibody.
- Patients with serological evidence of past or active HBV infection should be assessed by an appropriate specialist hepatitis service.
- All HBsAg-positive patients should be considered high-risk for reactivation and require antiviral treatment prior to immunosuppressive therapy with a third-generation nucleoside/nucleotide analog.
- Anti-HBc positive patients receiving an immunosuppressive drug regimen considered to be high-risk for causing reactivation (e.g. anti-CD20 monoclonal antibodies) should be offered prophylactic antiviral treatment.
- The risk of HBV reactivation may be protracted and monitoring and/or antiviral treatment may be required for up to 1 year after the immunosuppressive treatment has been completed.

Wang B, et al Haematologica 2019

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ΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ
ATTIKON