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The prognosis and management of inactive HBV carriers

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Advisory Board/Speaker Bureau for

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Outline of the presentation

- Diagnosis
- Natural history
- Management and follow-up
- Immunosuppression


OLE

Diagnosis of inactive carriers - EASL 2012

1) The ‘‘inactive HBV carrier state’’ is characterized by very low or undetectable serum HBV DNA levels, normal serum aminotransferases and anti-HBe seropositivity.

2) A minimum follow-up of 1 year with alanine aminotransferase (ALT) levels at least every 3–4 months and serum HBV DNA levels is required before classifying a patient as inactive HBV carrier.

3) ALT levels should remain persistently within the normal range according to traditional cut-off values (approximately 40 IU/ml) [14] and HBV DNA should be <2000 IU/ml.

4) Some inactive carriers, however, may have HBV DNA levels between 2,000 and 20,000 IU/ml

Invernizzi F, Viganò M, Grossi G, Lampertico P, Liver Int 2016; 36 (Suppl. S1): 100–104

Diagnosis of inactive carriers - EASL 2012

1) The ‘‘inactive HBV carrier state’’ is characterized by very low or undetectable serum HBV DNA levels and normal serum aminotransferases.

2) A minimum follow-up of 1 year with alanine aminotransferase

Diagnosis of inactive carriers is similar in AASLD 2015 and APASL 2015 guidelines

[14] and HBV DNA should be <2000 IU/ml.

4) Some inactive carriers, however, may have HBV DNA levels between 2,000 and 20,000 IU/ml

Invernizzi F, Viganò M, Grossi G, Lampertico P, Liver Int 2016; 36 (Suppl. S1): 100–104

Baseline diagnostic work-up in inactive carriers

- History and physical examination
- Family history of liver disease, HCC
- Laboratory tests
- Test for HBV replication, qHBsAg
- Tests for coinfections
- Abdominal ultrasound
- Fibroscan
- (Liver biopsy not indicated)

Normal ALT levels and HBV-DNA >2,000-<20,000 IU/ml

Follow-up and indications for liver biopsy in HBeAg-negative chronic hepatitis B virus infection with persistently normal ALT: A systematic review

George V. Papatheodoridis[1,*], Spilios Manolakopoulos[1], Yun-Fan Liaw[2], Anna Lok[3]

[1]*2nd Department of Internal Medicine, Athens University Medical School, "Hippokration" General Hospital of Athens, Greece;* [2]*Liver Research Unit, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taipei, Taiwan;* [3]*Division of Gastroenterology and Hepatology, University of Michigan Health System, Ann Arbor, MI, USA*

1) A systematic review of all the available histological data on HBeAg-negative patients with persistently normal ALT (PNALT) to determine the prevalence of significant liver disease and its associating factors.

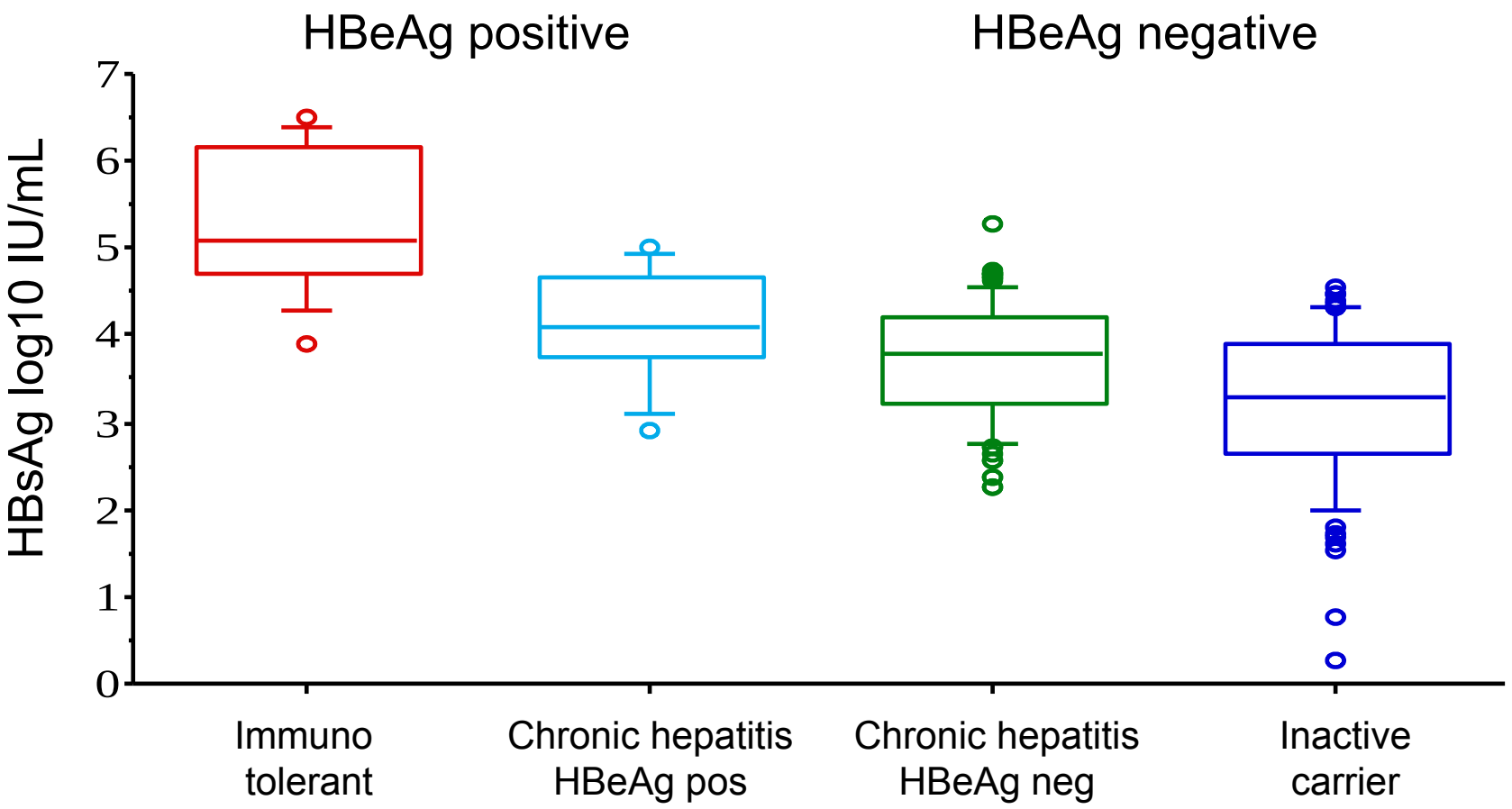
2) 4 studies with 246 patients had good or acceptable definitions of PNALT (≥3 ALT determinations during 6–12 months)

3) The prevalence of mild inflammatory activity and moderate fibrosis was 1.4% and 1% among those with HBV DNA levels <2000 IU/ml and 7% and 10% among patients with HBV DNA levels between 2000 and 20,000 IU/ml.

GV Papatheodoridis, S Manolakopoulos, YF Liaw, A Lok, J Hepatol 2012

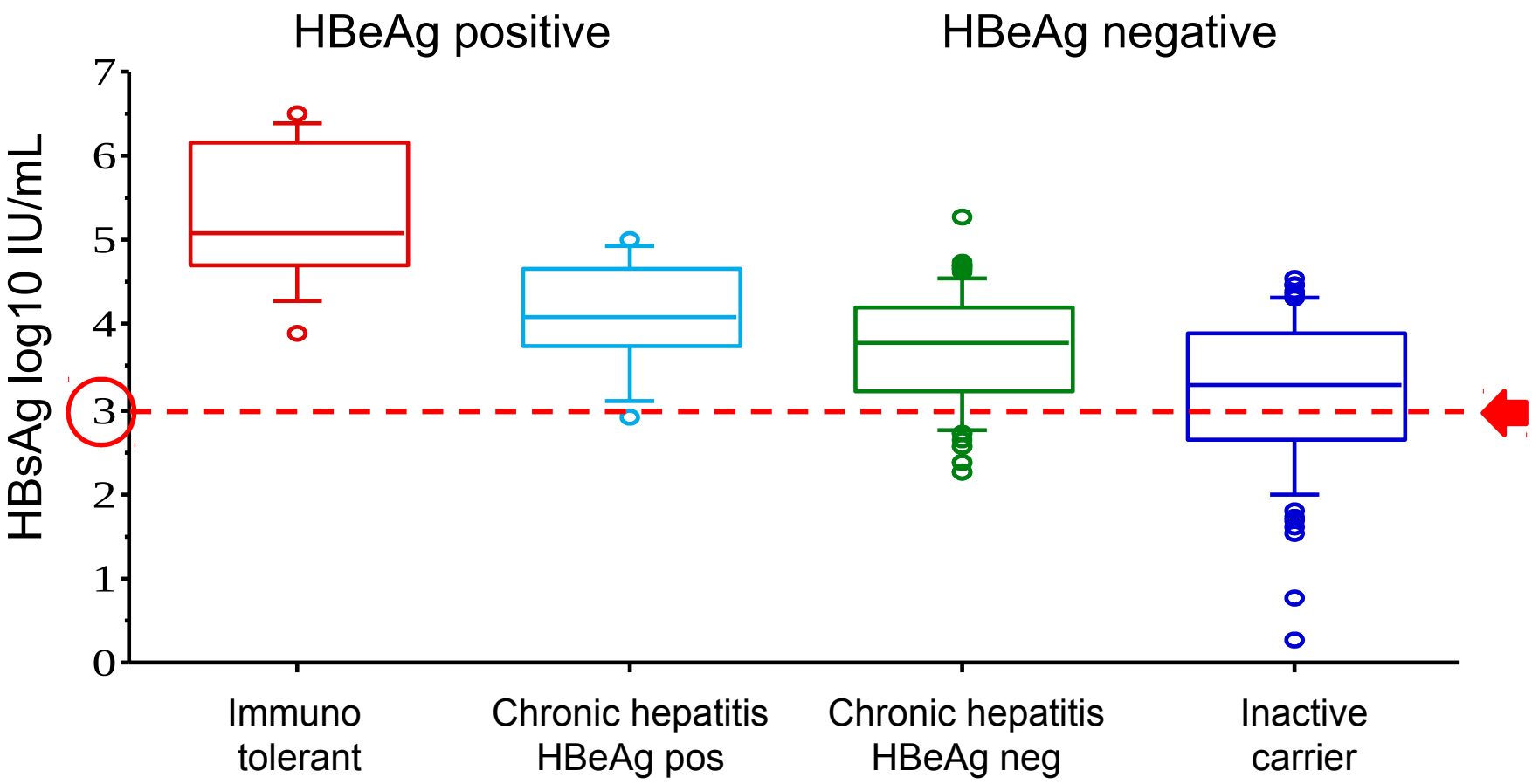
HBsAg levels

qHBsAg in the natural history of HBV infection



Nguyen T. et al. J Hepatol 2010;52;508; Jaroszewicz. et al. J Hepatol 2010;52;514; Chan et al Hepatology 2010;52:1232; Martinot-Peignoux et al. Hepatology 2010;52:992A

qHBsAg in the natural history of HBV infection



Nguyen T. et al. J Hepatol 2010;52;508; Jaroszewicz. et al. J Hepatol 2010;52;514; Chan et al Hepatology 2010;52:1232; Martinot-Peignoux et al. Hepatology 2010;52:992A

Identification of inactive infection using HBsAg and HBV DNA levels

Analysis of HBV genotype D patients

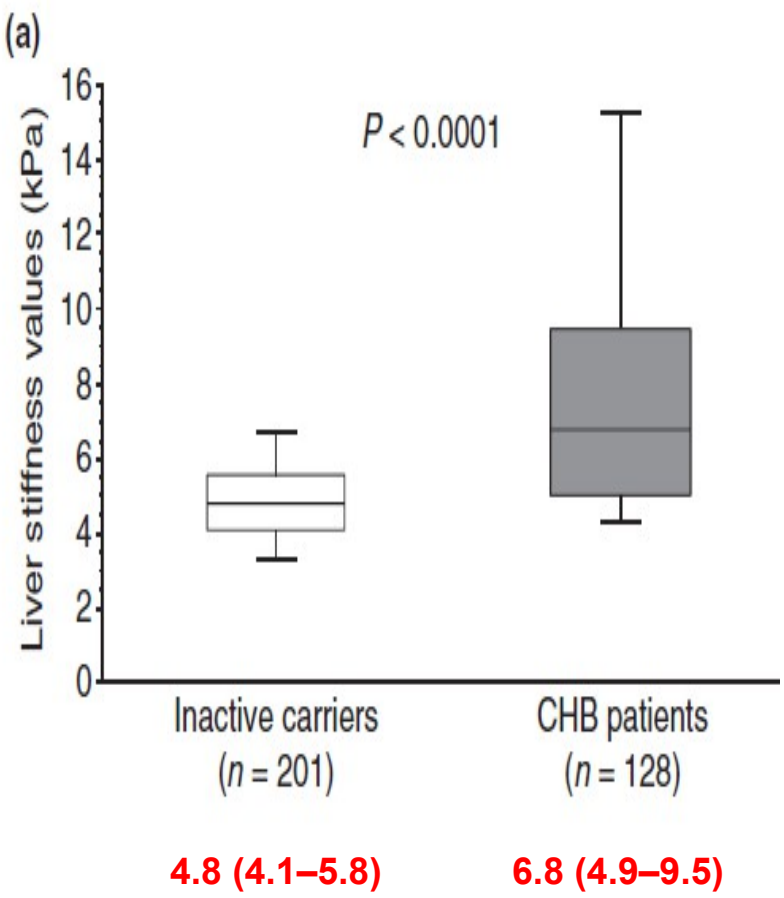
Prediction of:	Inactive infection
HBsAg levels HBV DNA levels	<1000 IU/mL plus <2000 IU/mL
Population	209
Sensitivity (%)	91.1
Specificity (%)	95.4
PPV (%)	87.9
NPV (%)	96.7
Diagnostic accuracy (%)	94.5

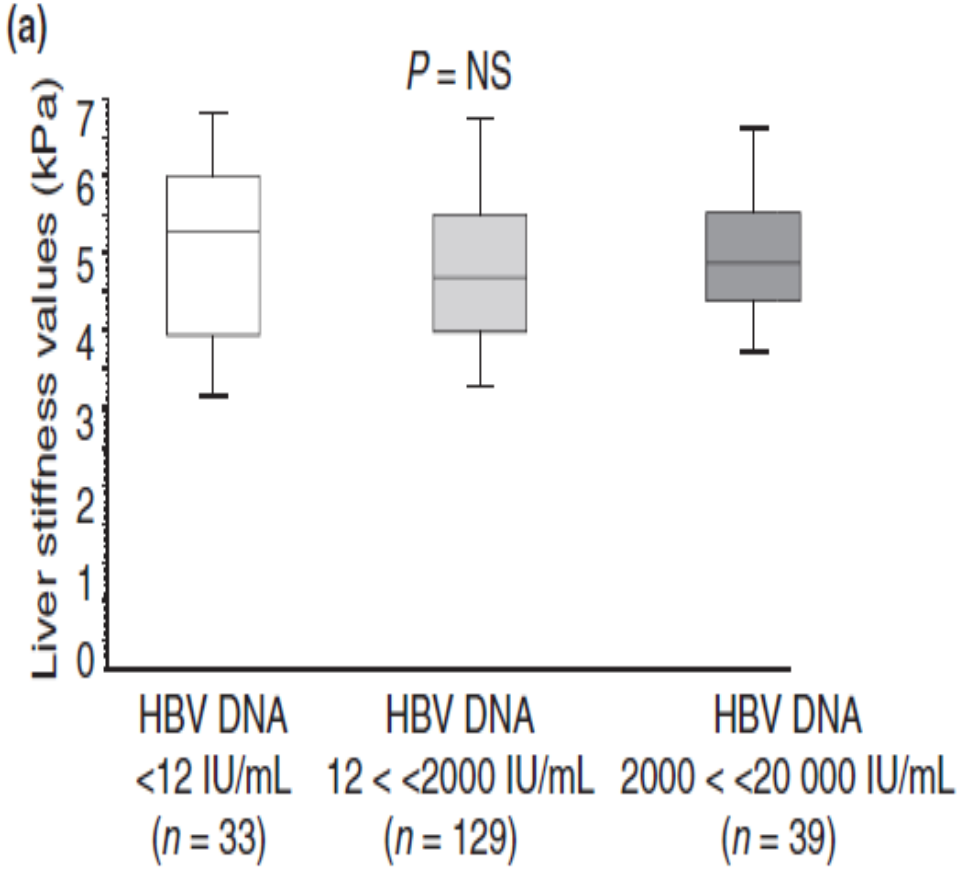
This provides comparable information to 1-year of monthly monitoring

Brunetto M et al. Gastroenterology 2010

Fibroscan

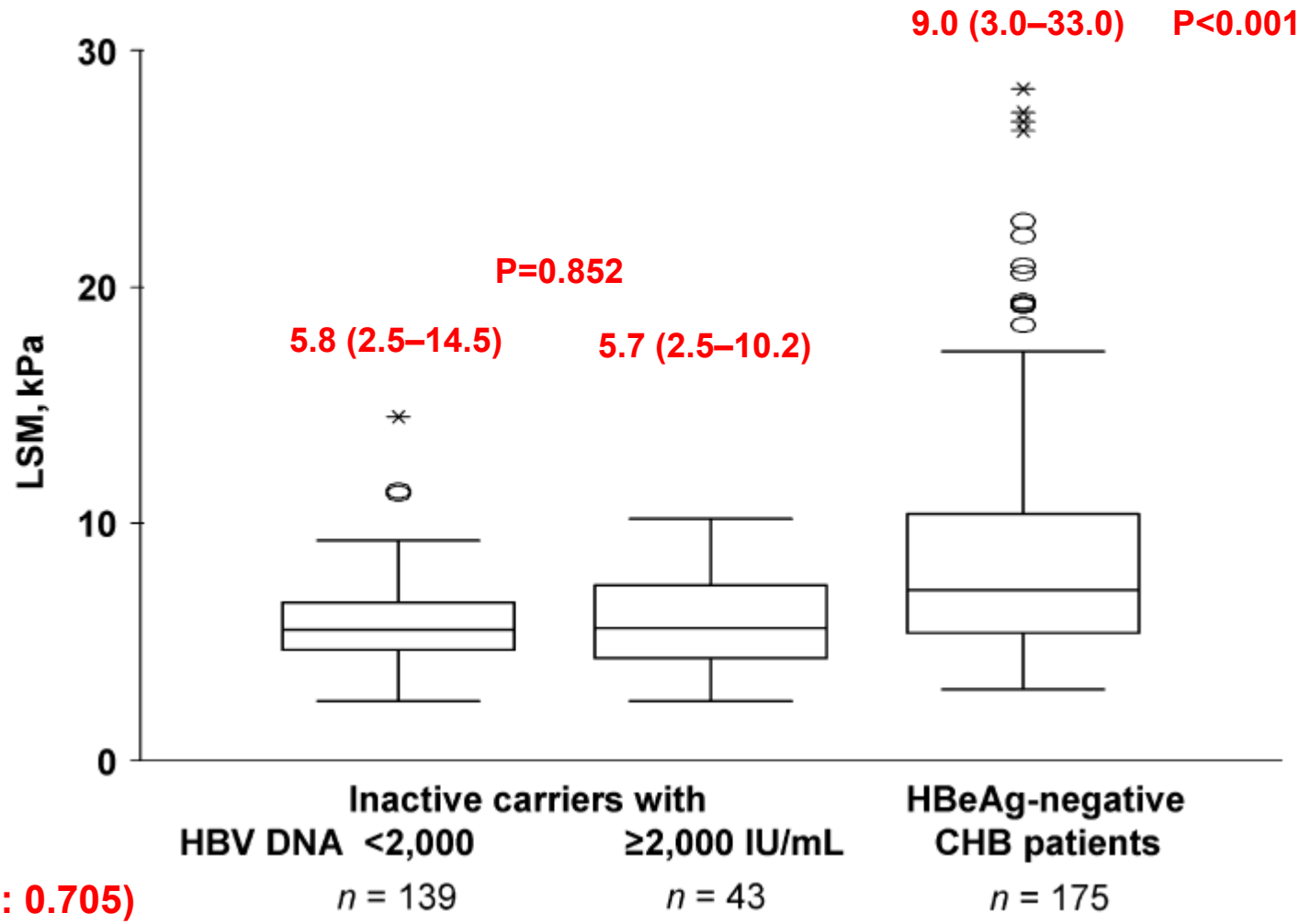
TE and biomarkers for liver fibrosis assessment and follow-up of inactive hepatitis B carriers





Castera L et al, APT 2011

Transient elastography for liver fibrosis assessment and follow-up of inactive hepatitis B carriers



(AUROC: 0.705)

Papatheodorids GV et al, JVH 2014

Natural history of inactive carriers in the long-term follow-up cohort studies

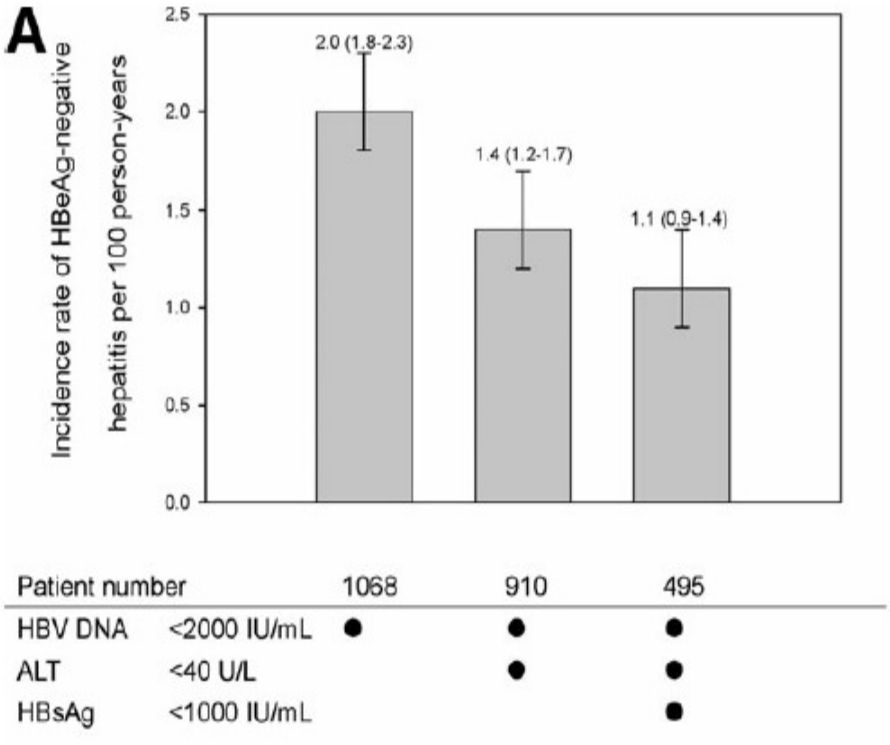
Author (ref)	Year	Country	Num. of Pts	Male (%)	Age (yrs)	Follow-up (years)	HBsAg loss (%)	HBV reactivation (%)	HCC (%)
De Franchis (ref 8)	1993	Italy	68	81%	31	10.8	15%	4.4%	0
Villeneuve (ref 23)	1994	Canada	200	81%	29	16	0.7% per year	0.5%	0
Martinot-Peignoux (ref 11)	2002	France	38	54%	34	3.2	3.5%	2.6%	NA
Hsu (ref 24)	2002	Taiwan	189	79%	32	8.2	4.8%	NA	1.6%
Manno (ref 9)	2004	Italy	296	78%	36	30	32%	2.1%	0.7%
Fattovich (ref 25)	2008	Italy	40	63%	30	23	45%	0%	5%
Habersetzer (ref 26)	2015	France	109	NA	NA	6	10%	NA	NA

Invernizzi F, Viganò M, Grossi G, Lampertico P, Liver Int. 2016; 36 (Suppl. S1): 100–104

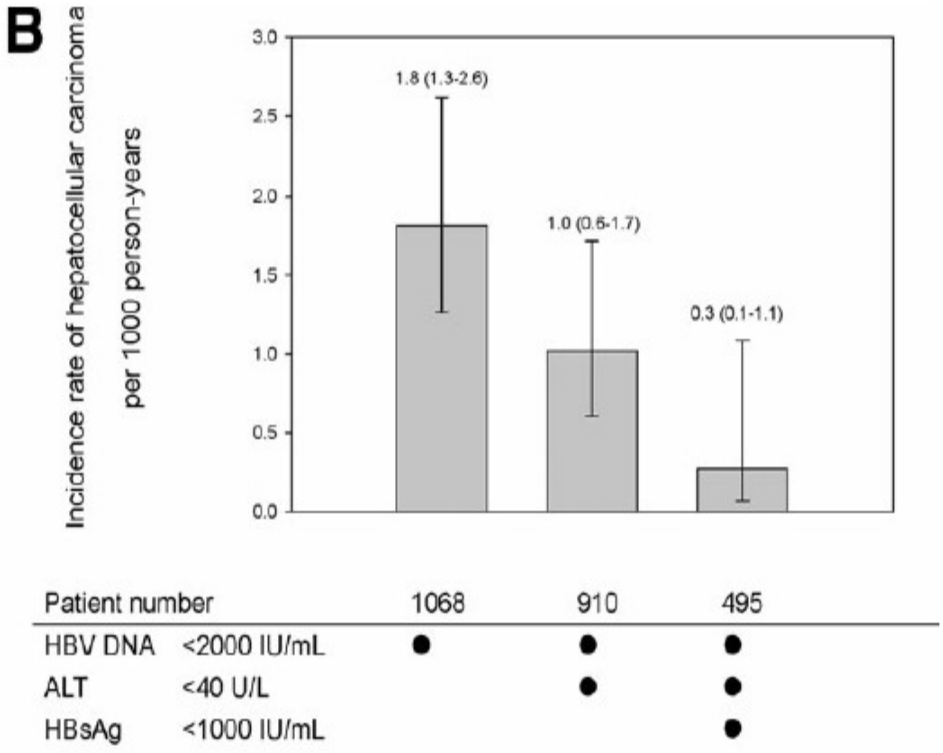
Disease progression in HBeAg-ve patients with HBV DNA <2000 IU/mL – A study from Taiwan

Baseline: 1,068 HBeAg-negative, HBV-DNA <2,000 IU/mL, 15% ALT >ULN, GT B and C.
Followed for a mean of 13.0 years

HBeAg-ve CHB/100 py

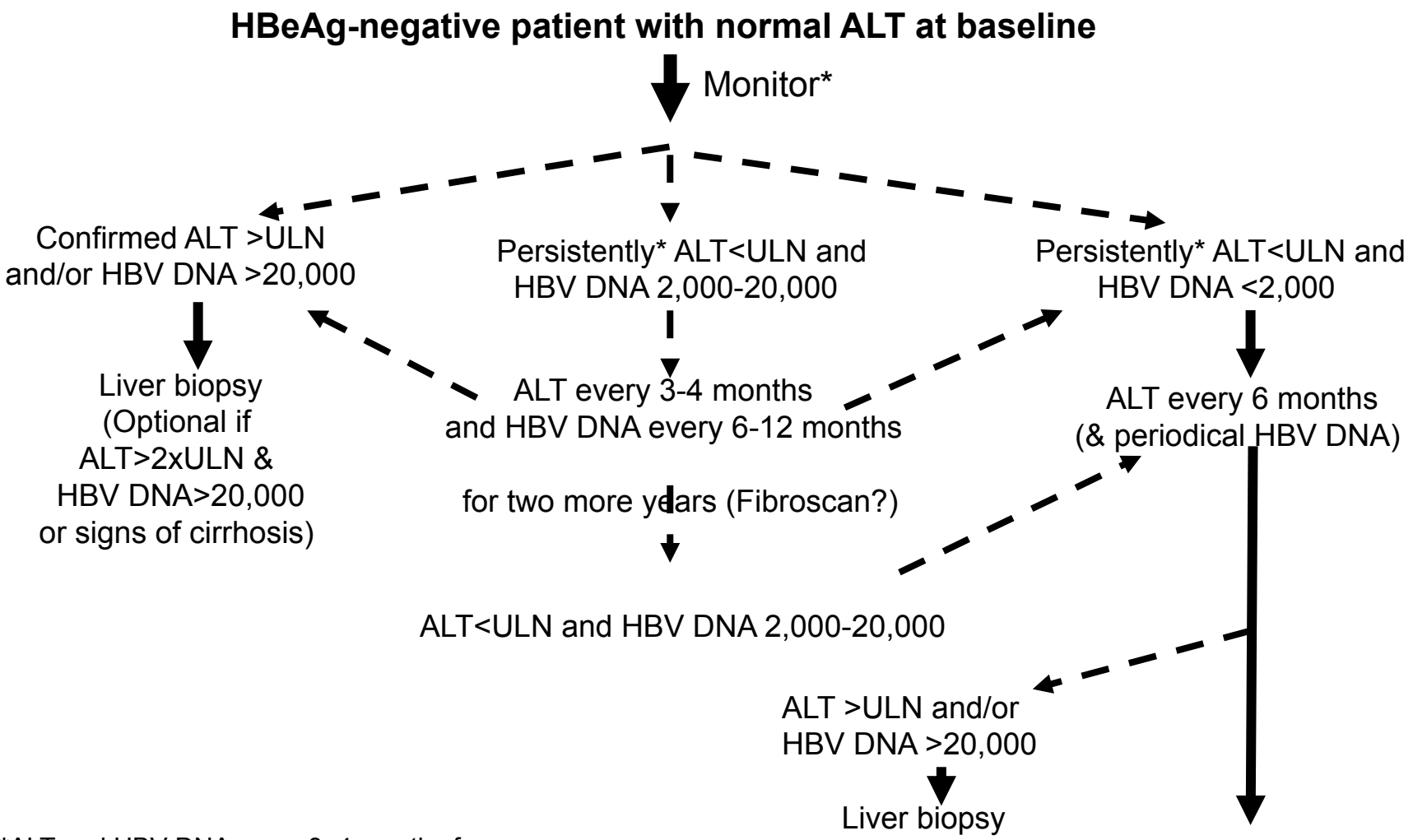


HCC/1000 py



Tseng TC et al. Hepatology 2013;57:441-50

Management of HBeAg-negative carriers with normal ALT



*ALT and HBV DNA every 3–4 months for one year

Papatheodoridis, Manolakopoulos, Liaw, Lok. J Hepatol 2012

Recommendations for HCC surveillance in HBV

AASLD 2011	APASL 2010	EASL-EORTC 2012
• Cirrhosis • Asian males over age 40 • Asian females over age 50 • Family history of HCC • African/ North American blacks	• Cirrhosis	• Cirrhosis • Non-cirrhotic HBV carriers with active hepatitis • Family history of HCC

Surveillance: 6-month US for AASLD and EASL (+ AFP for APASL)

[1] Bruix J, Sherman M, AASLD: Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020-1022. [2] Omata M, et al. APASL. Hepatol Int 2010;4:439-474. [3] EASL-EORTC. Clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908-943.

Immunosuppresson

Risk of HBV reactivation in immunosuppressed patients

Disease	HBsAg positive	HBsAg negative Anti-HBc positive
Bone marrow or stem cell transplantation	32–50%	up to 50%
Anti-CD20 monoclonal antibodies (rituximab)	50%	18%
Solid organ transplantation	50–90%	0.9–5%
Systemic cancer chemotherapy	39-41%	3%
TNF-alfa antagonists	39%	5%

Risk of reactivation based upon:
underlying extrahepatic disease, immunosuppressive regimen and HBV profile

Hwang end Lok et al., Nat Rev Gastroenterol 2013

HBV reactivation in immunocompromised patients

HBsAg+ (overt)

DNA+++ Anti-HBe+ qHBsAg+/++ Chronic

HBsAg- (OBI)

DNA+++ HBeAg+ qHBsAg +++ 50% Recovery

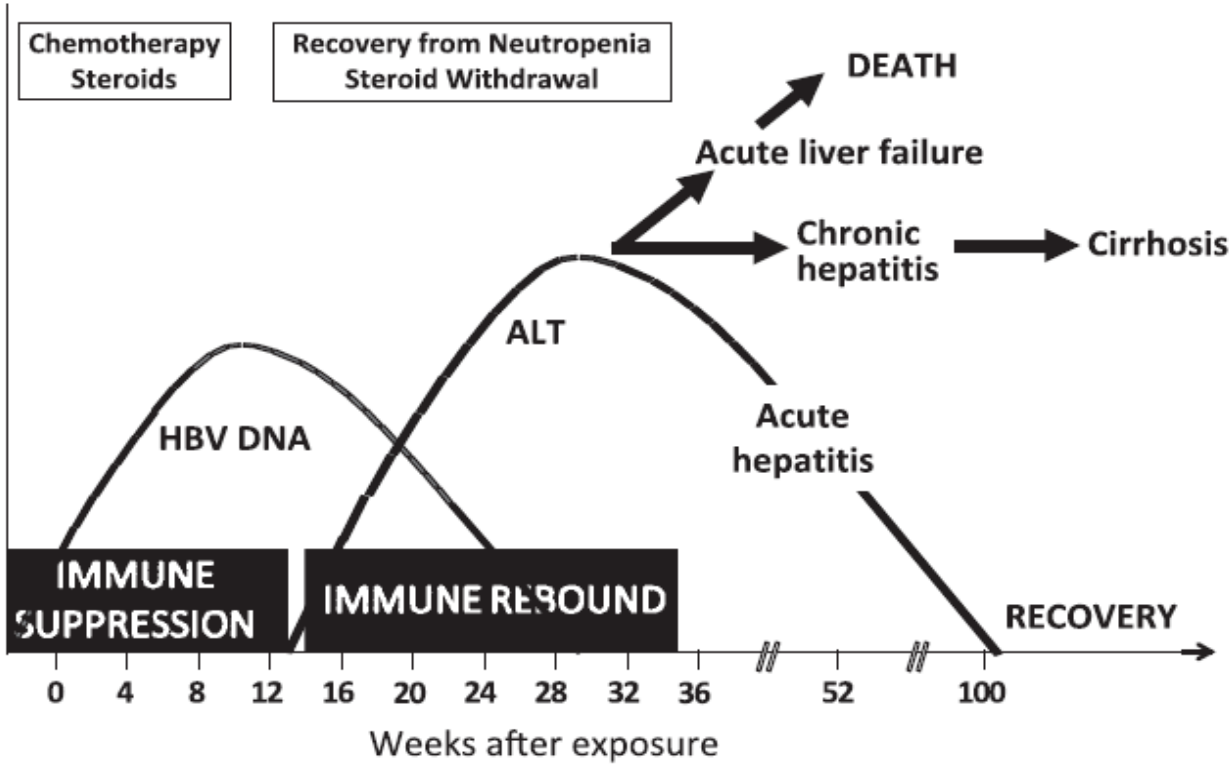
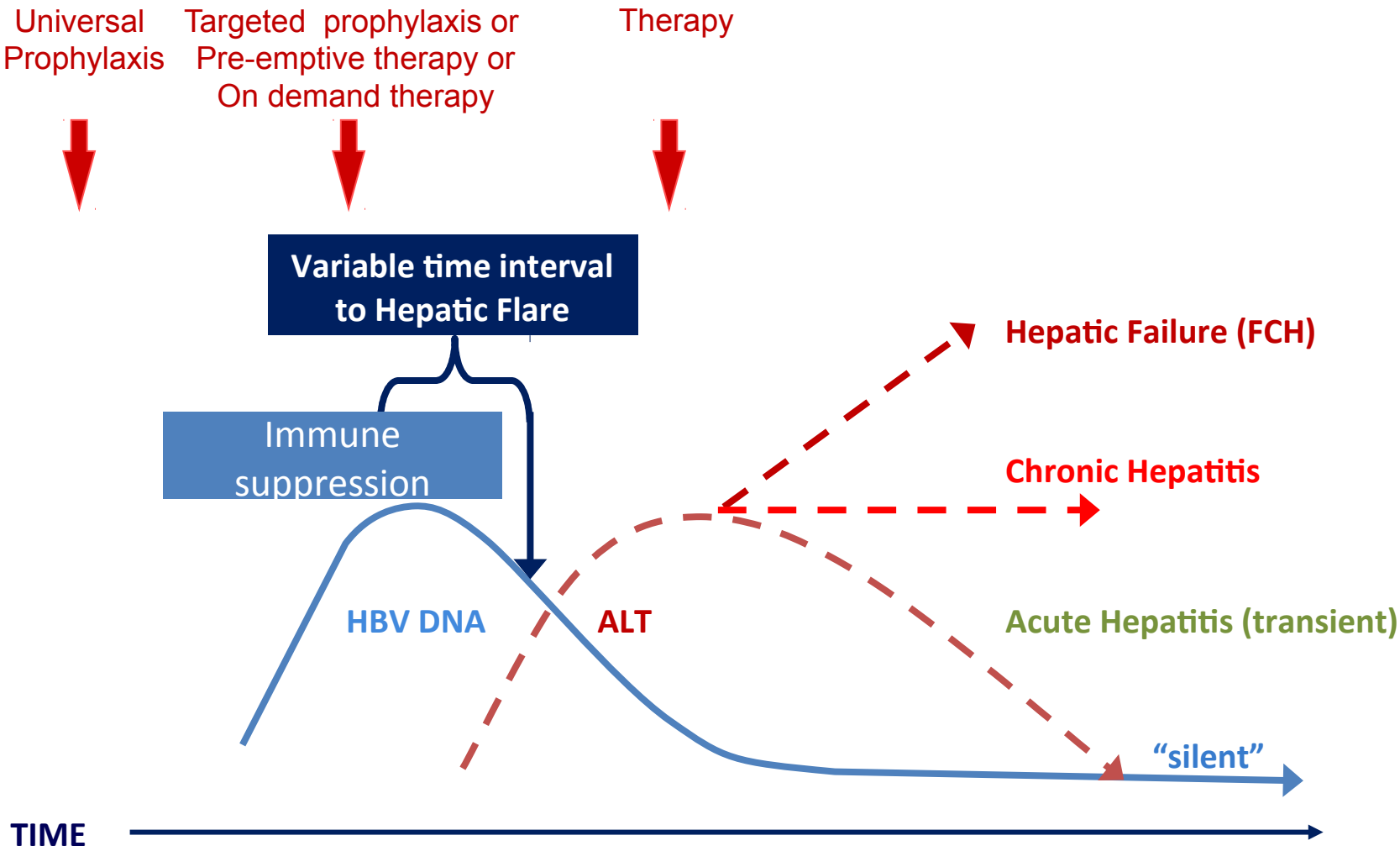


Figure 4 Typical course of hepatitis B virus (HBV) reactivation under chemotherapy. HBV DNA becomes detectable during immunosuppression which is followed by an increase in alanine aminotransferase (ALT) after withdrawal of the compound in part due to a rebound of the immune response, especially a recovery from neutropenia. Acute hepatitis can either lead to chronic hepatitis or acute liver failure and death but also to chronic hepatitis leading to liver cirrhosis. (Published previously (Xunrong *et al*, 2001).[58]

Prevention/management of HBV reactivation



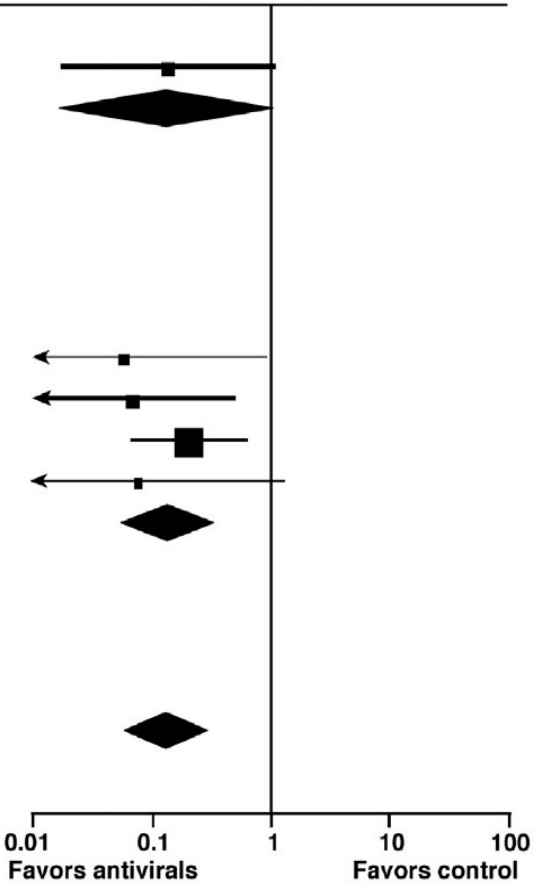
FCH = fibrosing cholestatic hepatitis

Adapted from Lau GKK, et al. Crit Rev Oncol Hematol 1999;31:71-76

Antiviral agents vs no prophylaxis in HBsAg positive patients – A meta-analysis

1. HBV Reactivation

Study or subgroup	Antivirals Events	Antivirals Total	Control Events	Control Total	Weight	Risk ratio M-H, random, 95% CI
1.1.1 entecavir						
Huang 2013	1	41	7	39	15.4%	0.14 [0.02, 1.05]
Subtotal (95% CI)		41		39	15.4%	0.14 [0.02, 1.05]
Total events	1		7			
Heterogeneity: not applicable						
Test for overall effect: Z = 1.91 (*P* = .06)						
1.1.2 lamivudine						
Lau 2003	0	15	8	15	8.4%	0.06 [0.00, 0.94]
Jang 2006	1	36	15	37	16.6%	0.07 [0.01, 0.49]
Hsu 2008	3	26	14	25	51.5%	0.21 [0.07, 0.63]
Long 2011	0	21	6	21	8.1%	0.08 [0.00, 1.28]
Subtotal (95% CI)		98		98	84.6%	0.13 [0.06, 0.32]
Total events	4		43			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.65$; df = 3 (*P* = .65); $I^2 = 0\%$						
Test for overall effect: Z = 4.54 (*P* < .00001)						
Total (95% CI)		139		137	100.0%	0.13 [0.06, 0.30]
Total events	5		50			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.63$; df = 4 (*P* = .80); $I^2 = 0\%$						
Test for overall effect: Z = 4.91 (*P* < .00001)						
Test for subgroup differences: $Chi^2 = 0.00$; df = 1 (*P* = .99); $I^2 = 0\%$						



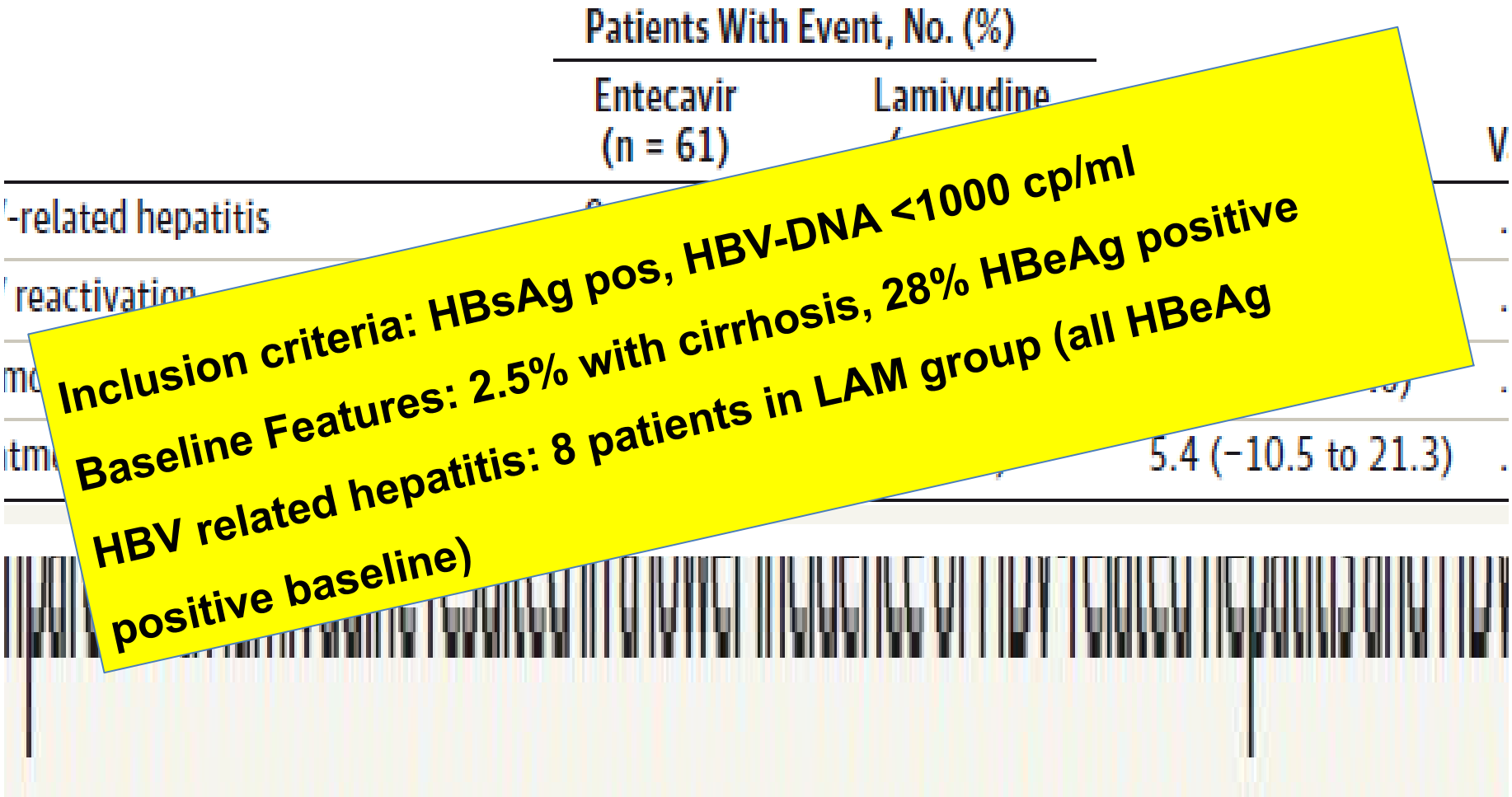
Perrillo R et al, Gastroenterology 2015;148:221–244

Reactivation Among Patients With Untreated Diffuse Larg
B-Cell Lymphoma Receiving R-CHOP Chemotherapy

	Patients With Event, No. (%)			
	Entecavir (n = 61)	Lamivudine (n = 60)	Difference (95% CI), %	V
-related hepatitis	0	8 (13.3)	13.3 (4.7 to 21.9)	.
reactivation	4 (6.6)	18 (30.0)	23.4 (10.2 to 36.6)	.
motherapy disruption	1 (1.6)	11 (18.3)	16.7 (6.4 to 27.0)	.
tment-related adverse events	15 (24.6)	18 (30.0)	5.4 (−10.5 to 21.3)	.

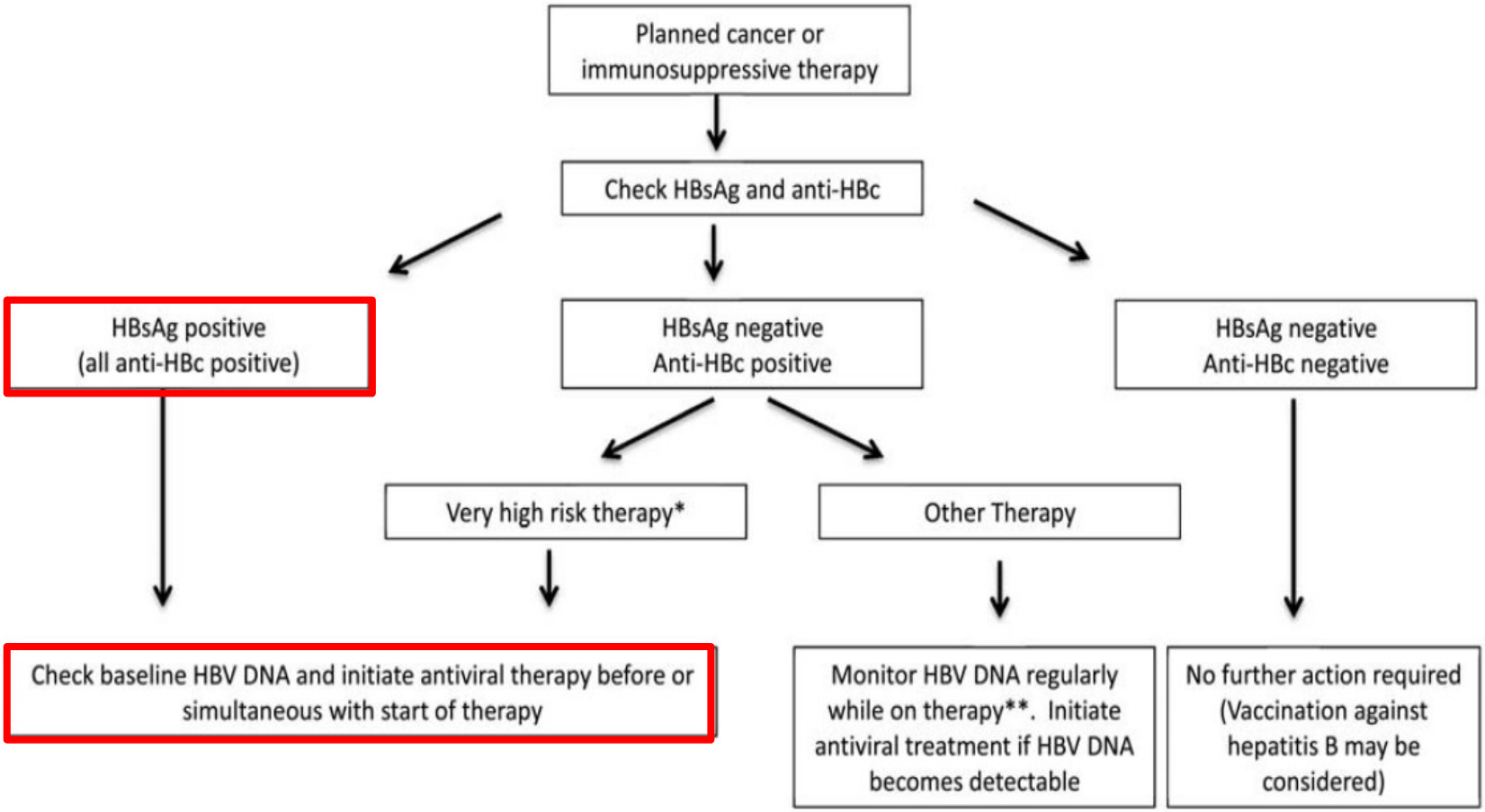
Huang et al., JAMA 2014

Reactivation Among Patients With Untreated Diffuse Larg
B-Cell Lymphoma Receiving R-CHOP Chemotherapy



Huang et al., JAMA 2014

Recommended AGA algorithm for HBV testing and treatment in patients undergoing immunosuppressive therapy.



Very high risk therapies include the use of anti-CD20 or Hematopoietic Stem Cell Transplantation (see Table 3)

***Frequency of monitoring between monthly and every 3 months*

Di Bisceglie AM et al, Hepatology 2015;61:703-711

HBsAg positive carriers and immunosuppression
EASL 2014 Special HBV Conference

1) Screening for HBV should be carried out before immunosuppressive therapy begins.

2) For active carriers (HBV DNA >2000 IU/ml, ALT >ULN, HBeAg positive or negative) should be treated (ETV or TDF).

3) For inactive carriers of HBV (HBV DNA <2000 IU/ml, ALT <ULN, anti-HBe positive) universal prophylaxis with NUC should be administered regardless of the immunosuppressive regimen. LAM is recommended only in patients with low (<2000 IU/ml) HBV DNA levels who are to undertake a short (<12 months) duration of immunosuppression. ETV or TDF is the recommended prophylaxis in other patients.

4) For HBsAg negative, anti-HBc positive carriers…….

Lampertico P, Maini M, Papatheodoridis G, J Hepatol 2015

Management of Inactive carriers
Summary: what do we know

1) Most of the HBV carriers are inactive carriers

2) Diagnosis and follow-up of inactive carriers have been established by international guidelines (similar criteria)

3) Minimum criteria: PNALT, HBV-DNA <2,000 IU/ml for at least 12 months (check for fibrosis, qHBsAg, <20,000 IU/ml)

4) Favorable prognosis, long-term monitoring (no treatment)

5) During immunosuppression, high risk of reactivation, universal prophylaxis with NUC is mandatory.

6) Prophylaxis with LAM or ETV/TDF according to immunosuppression regimen, baseline viremia, compliance and so on…..during immunosuppression and 12-18 months thereafter

Management of Inactive carriers
Challenges in 2016

1) Is life-long monitoring necessary?

2) How do we monitor over time ? (DNA, ALT, qHBsAg ?)

3) HCC surveillance ? (when ? how ? for whom ?)

4) Immunosuppression:
   - low risk of reactivation, no need of prophylaxis ?
   - LAM vs ETV/TDF ?
   - How long should the consolidation time be?
   - How many ICs will become active carrers after CHT ?

Acknowledgments

- Mauro Viganò
- Vito Di Marco, Teresa Santantonio, Maurizia Brunetto
- George Papatheodoridis

Backup slides

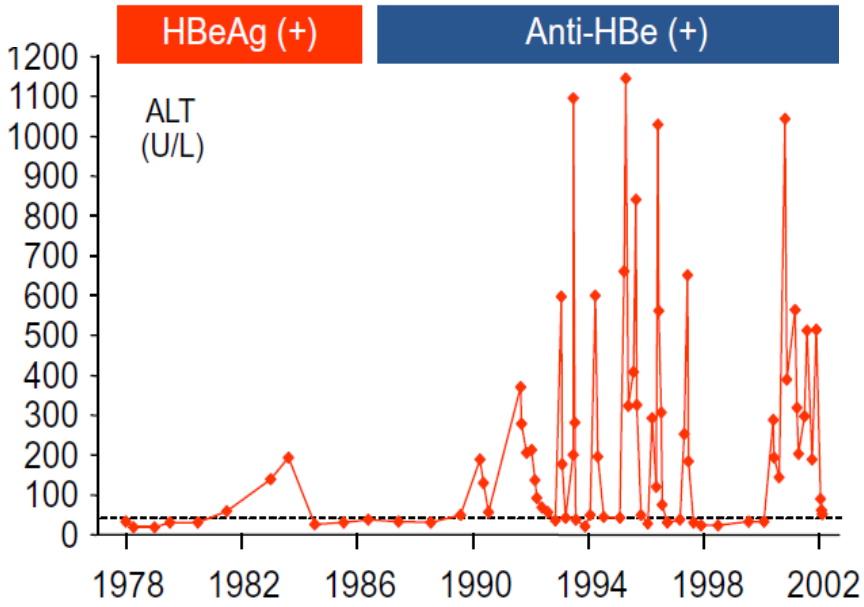
HBsAg positive carriers and immunosuppression
APASL 2015 guidelines

1) All candidates for chemotherapy and immunosuppressive therapy should be screened for HBsAg and anti-HBc prior to initiation of treatment (A1).
2) Prophylactic anti-viral therapy should be given to HBsAg(+) cancer patients who receive cytotoxic or immunosuppressive therapy, both during therapy (regardless ofHBV DNA levels) and for 12 months after cessation of therapy to reduce the incidence and severity of HBV reactivation (A1).
3) Prophylactic anti-viral therapy is recommended for HBsAg (+) patients who received immunosuppressive agents for auto-immune and rheumatic diseases. However, the duration may be long-term, and its cost-effectiveness is not yet established.

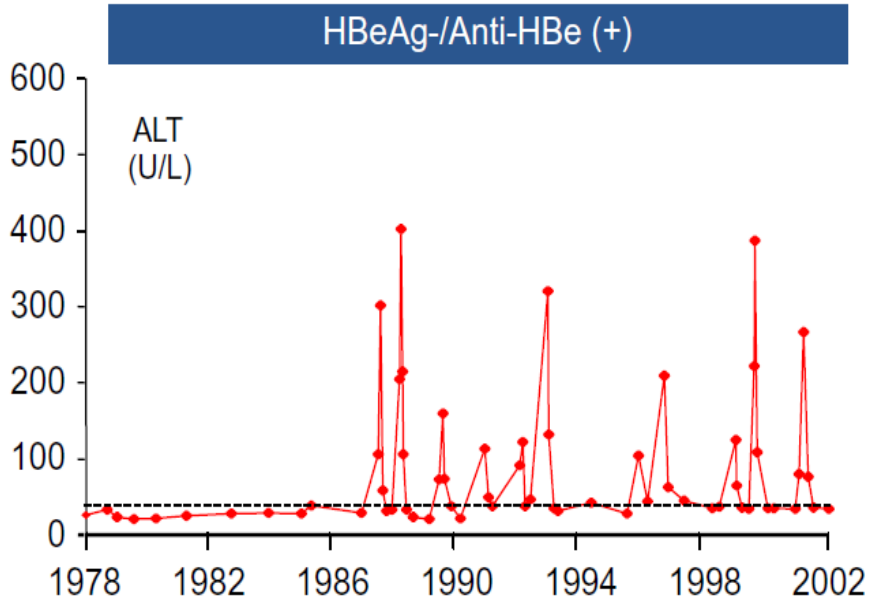
Sarin SK et al, Hepatol Int 2015

Natural history of HBeAg negative carriers in Euro-Mediterranean countries

Case 1



Case 2



These are not inactive carriers !!

Hadziyannis S et al. J Hepatol 2011

Baseline HBV status assessment

	HBsAg-positive		HBsAg-negative
HBsAg levels	High (>1000)	Low (<1000)	negative
HBeAg	Pos or Neg	Neg	Neg
Anti-HBe	Neg or Pos	Pos	Neg or Pos
Anti-HBc	Pos	Pos	Pos
HBV DNA UI/mL (serum)	**>2,000**	**<2,000°°**	Neg*
HBV DNA UI/mL (liver)	Pos	Pos	Pos
ALT	Increased (Persistently or Intermittently)	Normal (Persistently)	Normal (Persistently)
Chronic hepatitis^^	>90%	<90%	No^
HBV status	**Active carrier**	**Inactive carrier**	**Anti-HBcore**

° anti-HBe pos. ; °° in 1/3 of cases 2.000-20.000 UI; * >90% of “true” OBI;

^ in the absence of other causes of liver disease a history of previous hepatitis B; ^^HAI >4

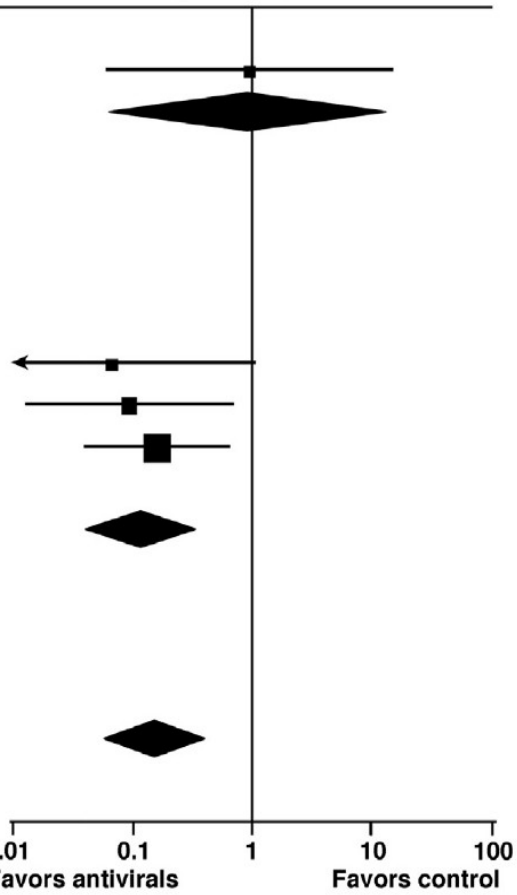
Do not forget Fibroscan and ultrasound !!

Marzano A et al., DLD 2007 (2011)

Antiviral agents vs no prophylaxis in HBsAg positive patients – A meta-analysis

1.2 HBV Hepatits flare

Study or subgroup	Antivirals Events	Antivirals Total	Control Events	Control Total	Weight	Risk ratio M-H, random, 95% CI
1.2.1 entecavir						
Huang 2013	1	41	1	39	13.0%	0.95 [0.06, 14.69]
Subtotal (95% CI)		41		39	13.0%	0.95 [0.06, 14.69]
Total events	1		1			
Heterogeneity: not applicable						
Test for overall effect: Z = 0.04 (*P* = .97)						
1.2.2 lamivudine						
Lau 2003	0	15	7	15	12.6%	0.07 [0.00, 1.07]
Jang 2006	1	36	11	37	24.4%	0.09 [0.01, 0.69]
Hsu 2008	2	26	12	25	50.1%	0.16 [0.04, 0.65]
Long 2011	0	21	0	21		Not estimable
Subtotal (95% CI)		98		98	87.0%	0.12 [0.04, 0.35]
Total events	3		30			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.41$; df = 2 (*P* = .81); $I^2 = 0\%$						
Test for overall effect: Z = 3.91 (*P* < .00001)						
Total (95% CI)		139		137	100.0%	0.16 [0.06, 0.42]
Total events	4		31			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.35$; df = 3 (*P* = .50); $I^2 = 0\%$						
Test for overall effect: Z = 3.66 (*P* = .0002)						
Test for subgroup differences: $Chi^2 = 1.89$; df = 1 (*P* = .17); $I^2 = 47.2\%$						



Perrillo R et al, Gastroenterology 2015;148:221–244