Le riattivazioni di HBV nei pazienti in terapia immunosoppressiva: update

Piero Colombatto - Barbara Coco

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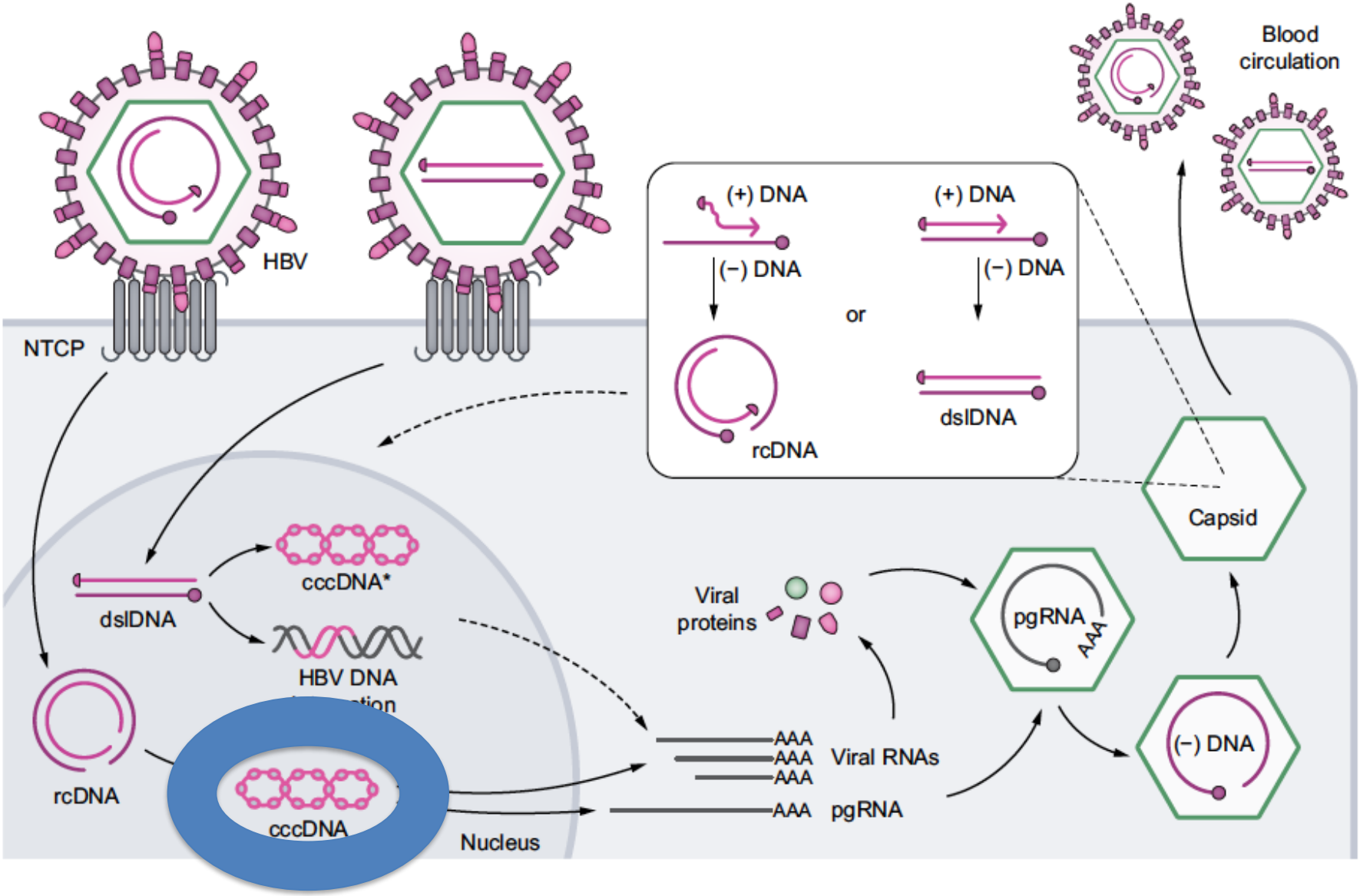
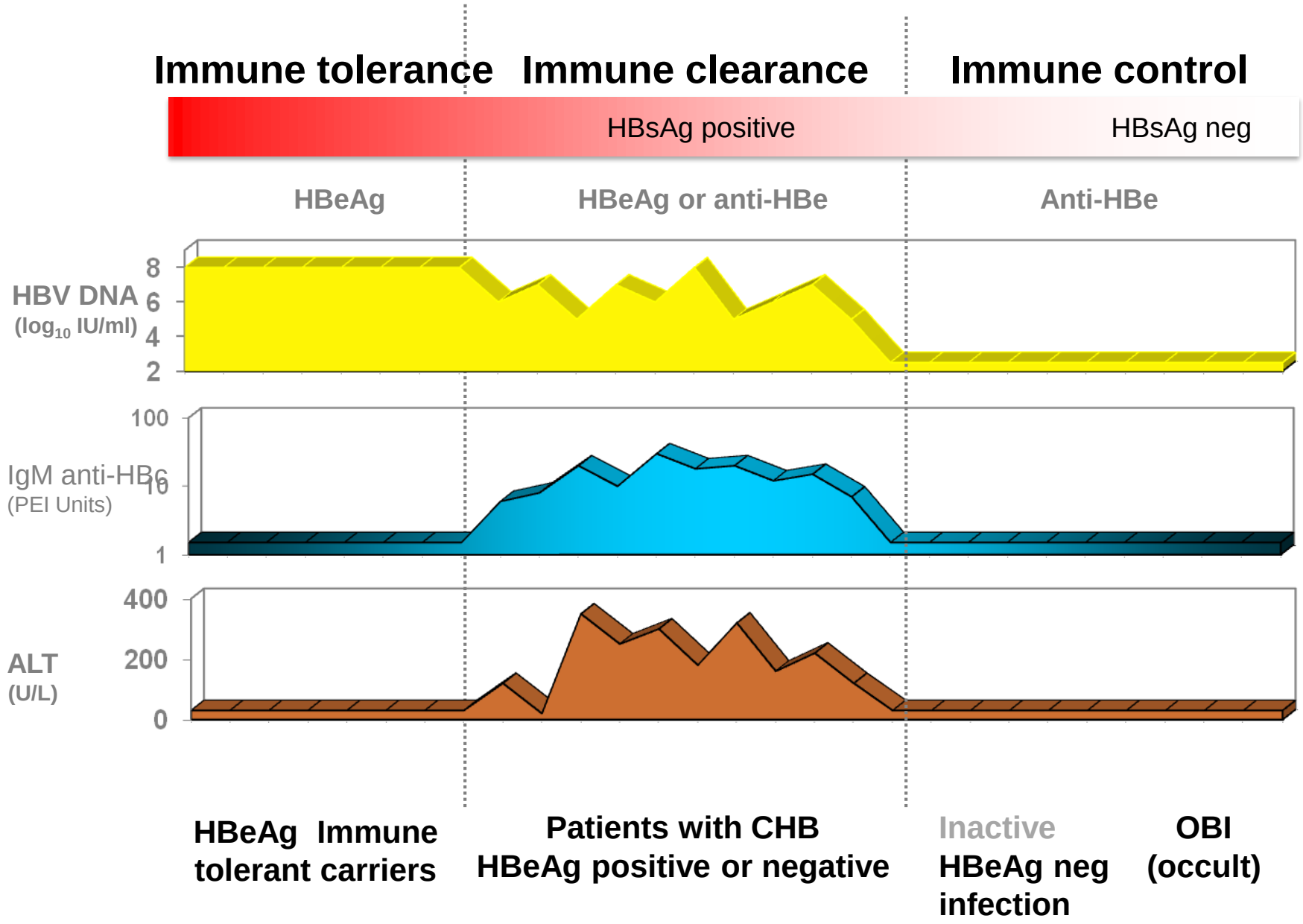
Centro Riferimento Regionale *"Diagnosi e trattamento delle epatopatie croniche e del tumore di fegato"*

HBV life cycle

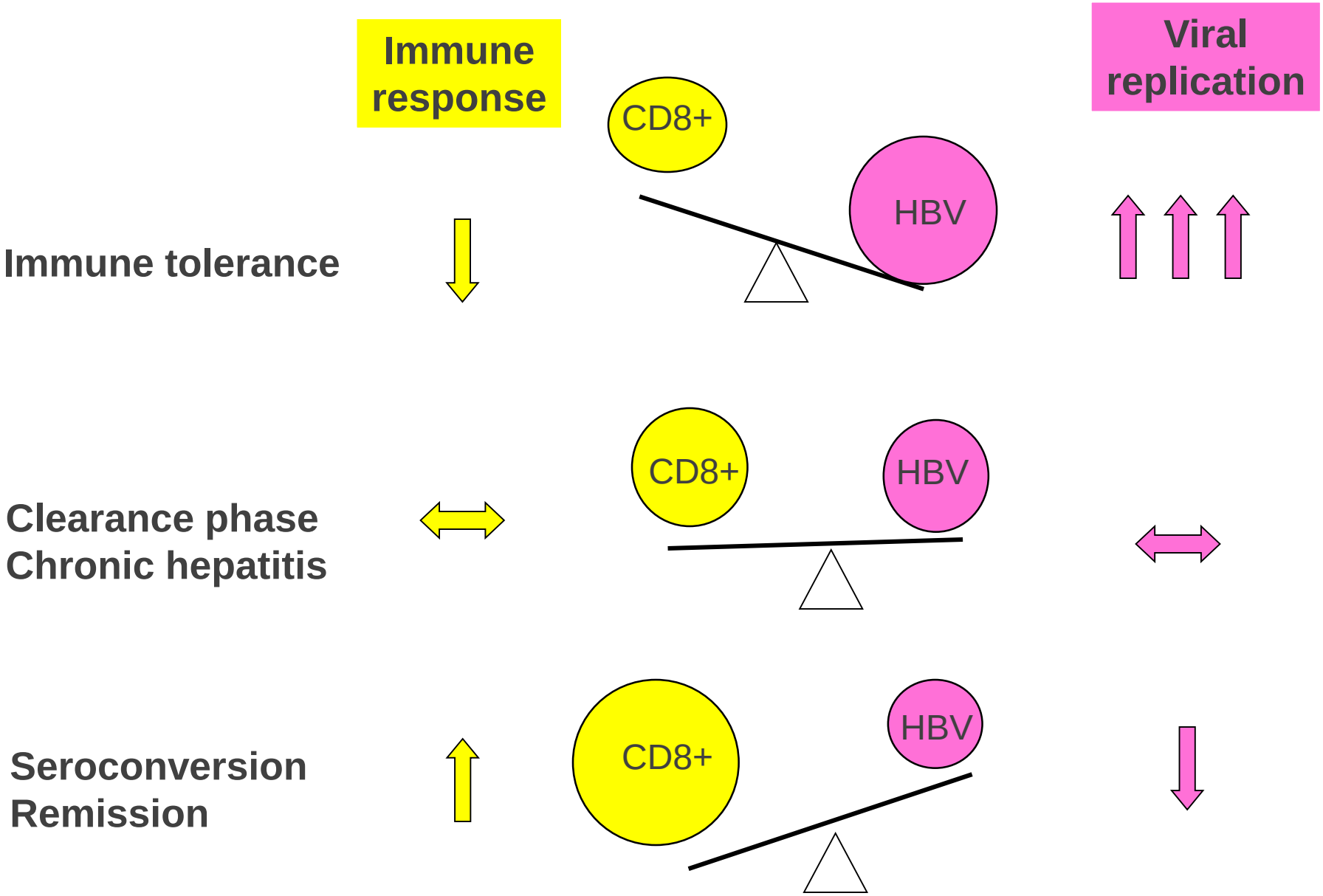


Zoulim et al. J Hep 2024

Natural history of Chronic Hepatitis B Virus Infection

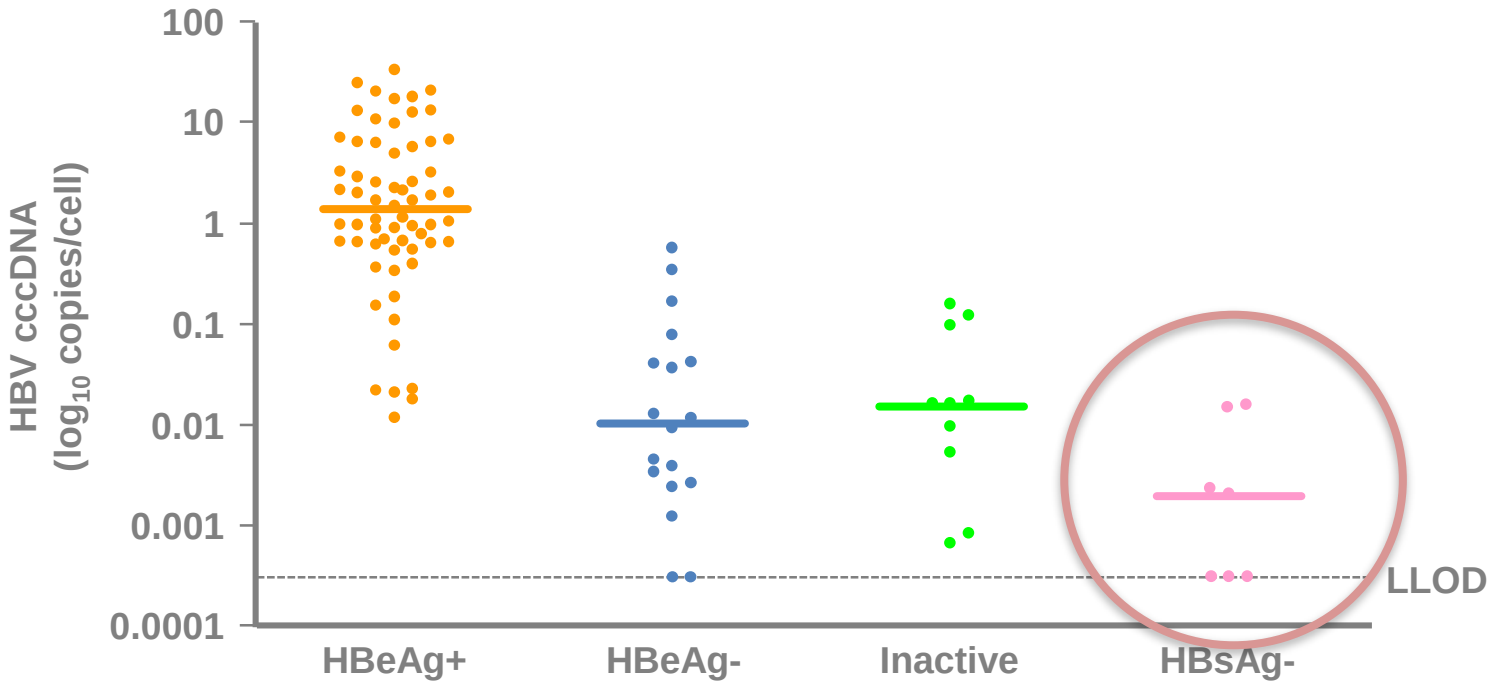


Immunopathology of Chronic HBV Infection

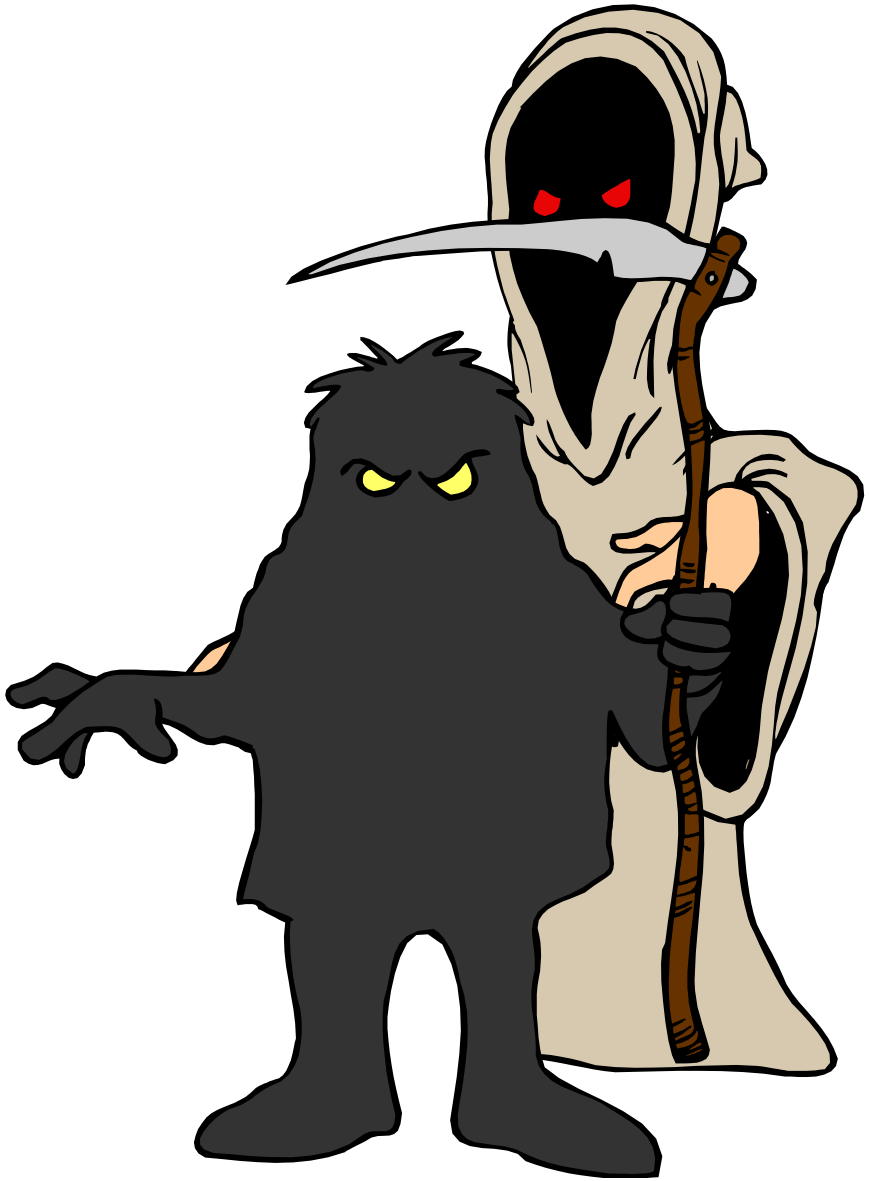


Guidotti, Science 1999; Guo, J. Virol 2000; Kakimi J Exp Med 2000; Zhu J Virol 2001

Persistence of cccDNA during the natural history of chronic hepatitis B



Werle-Lapostolle et al. Gastroenterology 2004

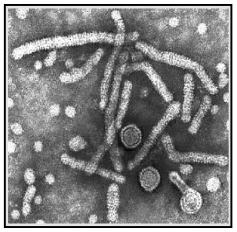


Occult HBV infection:

detection of HBV-DNA in the *serum* or *liver tissue* of HBsAg negative patients, both anti-HBc positive or negative

Torbenson M. et al, Lancet Infectious Diseases 2002

Serum



HBV-DNA

Virions

replication

HBsAg

Virions + defective particles
(exceeding virions by a factor of 10^2-10^5)

replication

cccDNA/integrants
trascriptional
activity

Serum HBV-DNA decline:
reduction of replication

Serum HBsAg decline:
reduction of cccDNA amount
and/or cccDNA/integrants
transcription/mRNAs translation

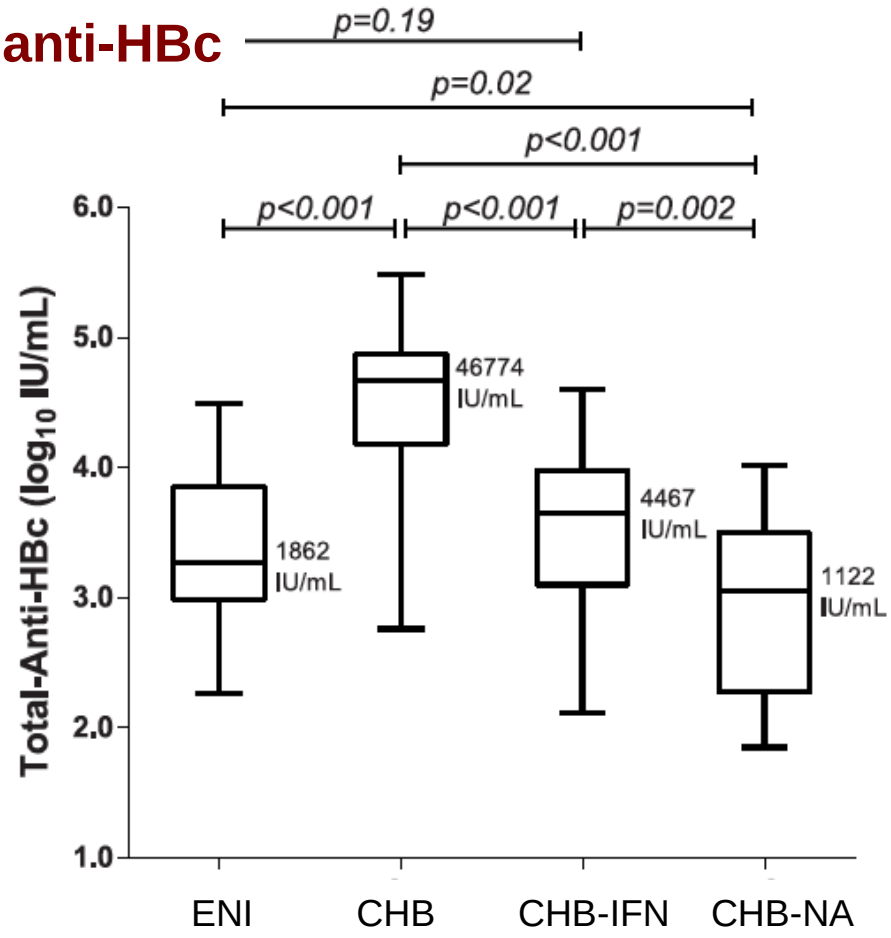
Brunetto et al, J Hepatol 2010

PLOS ONE

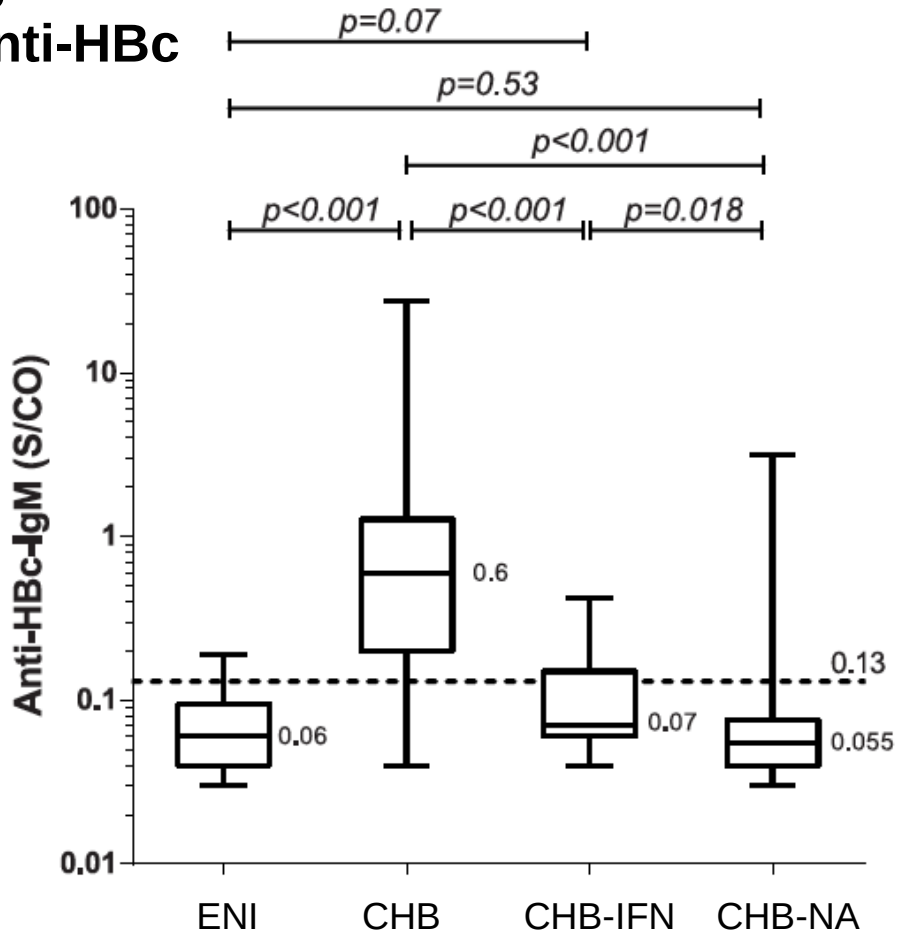
Total Hepatitis B Core Antigen Antibody, a Quantitative Non-Invasive Marker of Hepatitis B Virus Induced Liver Disease

Quan Yuan[1☯], Liu-Wei Song[1☯], Daniela Cavallone[2], Francesco Moriconi[2], Beatrice Cherubini[2], Piero Colombatto[2], Filippo Oliveri[2], Barbara Agata Coco[2], Gabriele Ricco[2], Ferruccio Bonino[3], James Wai Kuo Shih[1], Ning-Shao Xia[1‡], Maurizia Rossana Brunetto[2‡*]

Total anti-HBc



IgM anti-HBc



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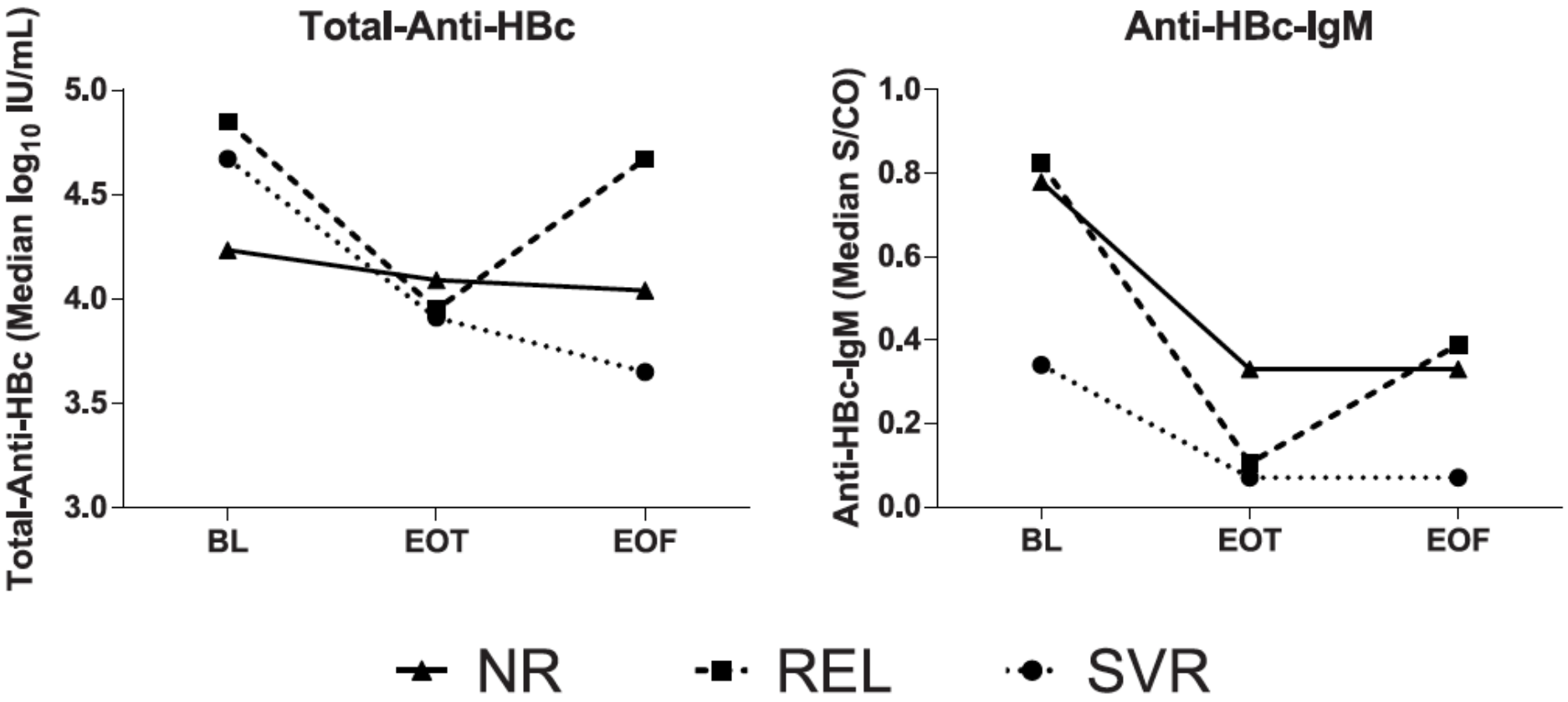
Total anti-HBc

IgM anti-HBc



HBV carrier (occult or overt)

Decreased immune recognition of HBV-infected hepatocytes

Chemotherapy immunosuppression

Increased HBV replication

Direct stimulation by specific drugs (steroids)

serum HBV DNA
intrahepatic HBcAg
number of productively HBV-infected hepatocytes

Restored T-cell functionupon immunosuppression withdrawal

Rebound immune recognition of HBV-infected hepatocytes

Adapted from Lalazar G et al. Br J Hematol 2007

A I S F

ASSOCIAZIONE ITALIANA PER LO STUDIO DEL FEGATO

Riconosciuta con D.M. del 7.5.1998, G.U. del 20.6.1998
Iscritta nell'Elenco di cui all'art. 1, comma 353, della Legge 23.12.2005 n. 266, D.P.C.M. 15.4.2011
Iscritta nell'Elenco di cui all'art. 14, comma 1, del D.L. 14.3.2005, n. 35, convertito nella Legge 14.5.2005 n. 80, D.P.C.M. 15.4.2011

PUBLIC AFFAIRS AWARDS
ECCELLENZA 2011
SOCIETA' ASSOCIAZIONI SCIENTIFICHE

GESTIONE CLINICA DELLA EPATITE B NEGLI IMMUNOCOMPROMESSI: AGGIORNAMENTO ITALIANO 2017

DEFINITION of HBV REACTIVATION

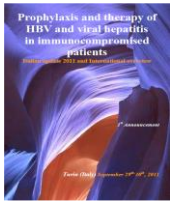
Anti-HBc + → **Seroreversion (SR)**: re-emergence of HBsAg

HBeAg Neg. Infection
→ **Viral Breakthrough (BKT)**: increase of viremia > 1 Log,
→ **Clinical event:** transition to CHB (BKT with ALT elevation)

CHB → **Clinical event:** BKT with ALT elevation / progression of liver damage

Marzano et al. DLD 2017

Risk stratification for HBV reactivation



Disease	Drugs	Prophylaxis
BMT	HIGH: Rituximab - HSCT	HBsAg+ or anti-HBc+
SOTs	combined therapy: TNFa-inhibitors, Other biological DMARDs	HBsAg+
HIV	MEDIUM: Leflunomide, Methotrexate, Cyclophosfamide, Combination therapies, Medium/high-dose prednisone (>7.5 mg/die)	
Rheum	LOW: Calcineurin inhibitors, Azathioprine, 6-mercaptopurine	
IBD	NULL: Low-dose prednisone (<7.5 mg/die), Sulfasalazine, Hydroxychlorochine	

RISK: >10% (HIGH) → <10% (MEDIUM) → <1% (LOW) → 0 (NULL)

Incidence of HBV Reactivation in Cancer HBsAg Positive Patients undergoing Chemotherapy

No. of studies	Cancer type	Chemotherapy regimens	No. HBsAg + patients	HBV reactivation %
5	Various solid cancer	Systemic chemotherapy	429	**20 – 37%**
2	Breast cancer	Systemic chemotherapy	50	**19 - 41%**
3	HCC	Systemic chemotherapy TACE	218	**25 - 36%**
4	Lymphoma	Systemic chemotherapy	117	**38 - 48 %**

W. Yeo and P.J. Johnson, Hepatology 2006

Incidence of HBV reactivation in HBsAg neg/anti-HBc pos patients with lymphoma undergoing cytotoxic chemotherapy

	Chemotherapy with Rituxmab		Chemotherapy without Rituxmab	
	Treated Patients	Rate of HBV Reactivation	Treated patients	Rate of HBV reactivation
E. Angelucci, Haematologica '08	74	**2 (2.7%)**	245	**2 (0.8%)**
Yeo W, J Clin Oncol. 2009	21	**5 (23.8%)**	25	**0**
Ji D, Eur J Haematol. '10	43	**1 (2.3%)**	45	**0**
Matsue K, Cancer. 2010	56	**5 (8.9%)**		
Niitsu N, J Clin Oncol. 2010	51	**6 (12%)**		
Koo YX Cancer, 2010	46	**1 (2.1%)**		

Risk of HBV reactivation in HBsAg neg/anti-HBc pos patients with Hemopoietic Stem Cell Transplantation (HSCT)

Authors	Patients with HSCT	Rate of HBV reactivation
Viganò et al. Bone Marrow Transplant. 2010	50	**6 (12%)**
Ramos CA et al. Biol Blood Marrow Transplant. 2010	76	**9 (11.7%)**
Ceneli O et al. World J Gastroenterol. 2010	35	**2 (5.7%)**
Hammond SP et al Biol Blood Marrow Transplant. 2009	61	**12 (19.7%)**
Matsue K et al Eur J Haematol. 2009	21	**6 (28.5%)**

EASL | JOURNAL OF HEPATOLOGY

- All candidates for chemotherapy and immunosuppressive therapy should be tested for HBV markers prior to immunosuppression (Evidence level I, grade of recommendation 1).
- All HBsAg-positive patients should receive ETV or TDF or TAF as treatment or prophylaxis (Evidence level II-2, grade of recommendation 1).
- HBsAg-negative, anti-HBc positive subjects should receive anti-HBV prophylaxis if they are at high risk of HBV reactivation (Evidence level II-2, grade of recommendation 1).

= If viremic, they should be treated similarly to HBsAg-positive patients.

→ These subjects can be **tested for serum HBV DNA** before immunosuppressio

↓ **HBV DNA not detected**

The risk of HBV reactivation can be classified as: **high (>10%), moderate (1–10%)** or **low (<1%).**

Risk: >10% <10%

Prophylaxis should **continue for at least 12 months (18 for rituximab-based regimens) after** cessation of **the immunosuppressive treatment** and discontinued only if the underlying disease is under remission

Liver function tests and **HBV DNA should be tested every 3 to 6 months** during prophylaxis **and <u>for at least 12 months after NA withdrawal</u>**

Prophylaxis with ETV or TDF or TAF (even LAM)

Surveillance and early (preemptive) treatment

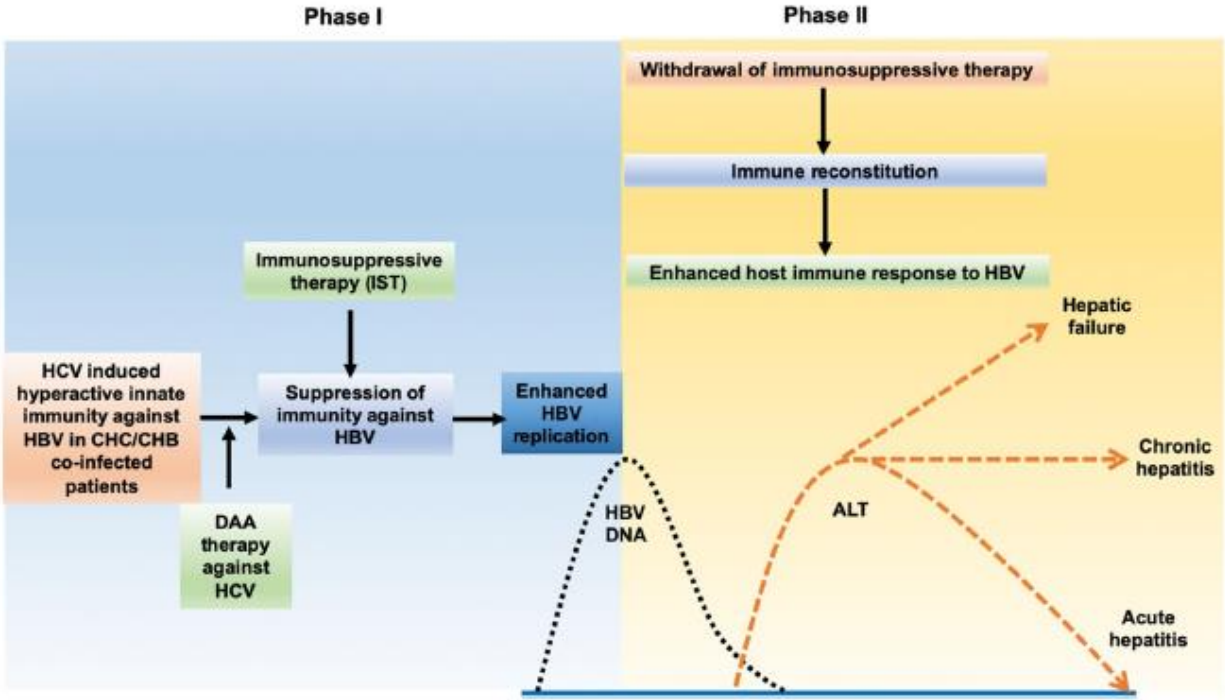
For selected clinical settings: poor compliance, long term, new drugs, concomitant conditions...etc

APASL Guidelines

Table 4 Risk stratification of HBV reactivation among HBsAg-positive patients and HBsAg-negative/anti-HBc-positive patients

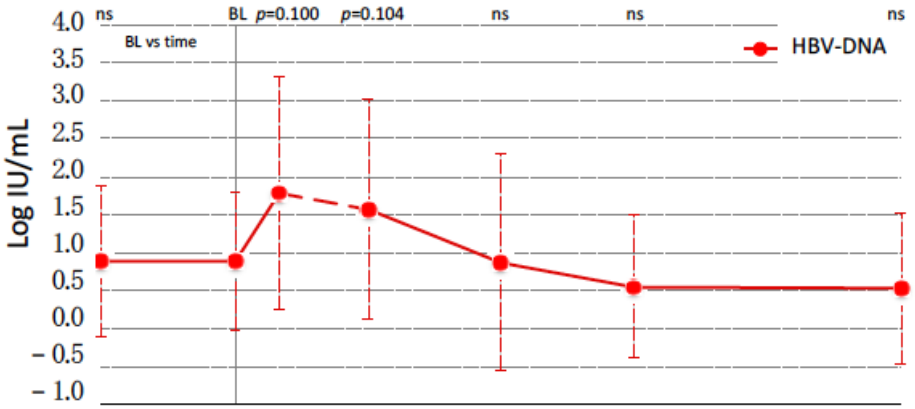
Risk level	HBV serology	
	HBsAg(+)	HBsAg(-)/anti-HBc(+)
High (> 10%)	Anti-CD20 monoclonal antibodies: Rituximab, Ofatumumab, Obinutuzumab Steroid (high dose) ≥ 20 mg/day for ≥ 4 weeks Anti-TNF agents with higher potency: Adalimumab, Infliximab, Golimumab, Certolizumab Anthracyclines Hematopoietic stem cell transplantation (both allogeneic and autologous) DAA for HBV/HCV coinfection (high risk in meta-analysis and prospective study), except non-cirrhotics with HBsAg < 10 IU/ml Immune Checkpoint inhibitors (moderate to high risk): Anti-PD-1: nivolumab, pembrolizumab Anti-PD-L1: atezolizumab Anti-CTLA-4: ipilimumab Tyrosine kinase inhibitors (moderate-to-high): Imatinib, Nilotinib, Dasatinib, Erlotinib, Gefitinib, Osimertinib, Afatinib	Anti-CD20 monoclonal antibodies: Rituximab, Ofatumumab, Obinutuzumab Allogeneic hematopoietic stem cell transplantation
Moderate (1–10%)	Cytotoxic chemotherapy (except anthracyclines) Anti-TNF agents with lower potency: Etanercept Steroid (median dose): 10–20 mg/day for ≥ 4 weeks Proteasome inhibitor: Bortezomib Ustekinumab	Anthracyclines Autologous hematopoietic stem cell transplantation Anti-TNF agents with higher potency: Adalimumab, Infliximab, Golimumab, Certolizumab Proteasome inhibitor: Bortezomib Ustekinumab
Low (< 1%)	Methotrexate Azathioprine Steroid (low dose < 10 mg/day) DAA for HBV/HCV coinfection for non-cirrhotic patients with HBsAg < 10 IU/ml	Cytotoxic chemotherapy (except anthracyclines) Steroid (high dose) ≥ 20 mg/day Anti-TNF agents with lower potency: Etanercept Tyrosine kinase inhibitors Imatinib, Nilotinib, Dasatinib DAA for HCV
Uncertain (More studies needed, no prophylaxis recommendation until further evidence)	Abatacept Tocilizumab Ibrutinib Alemtuzumab Natalizumab Ocrelizumab Ibritumomab	Immune Checkpoint inhibitors Anti-PD-1: nivolumab, pembrolizumab Anti-PD-L1: atezolizumab Anti-CTLA-4: ipilimumab

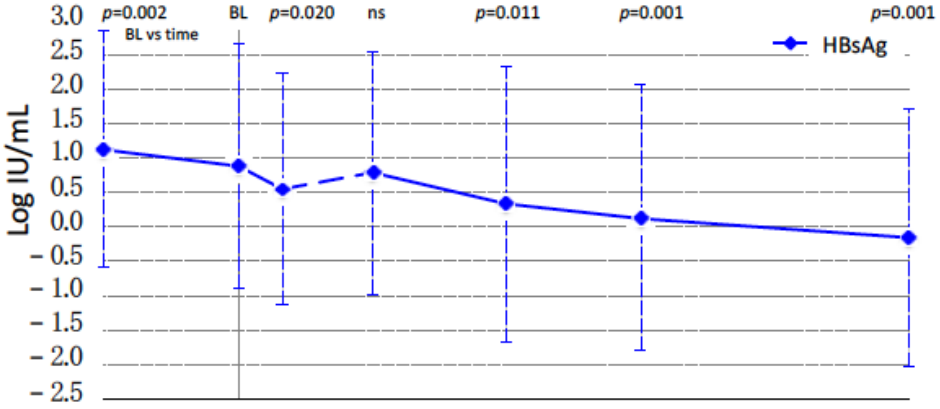
HBV riactivation during/after DAAs treatment in HBV-HCV co-infected patients



Article

Different Kinetics of HBV-DNA and HBsAg in HCV Coinfected Patients during DAAs Therapy





Colombatto et al. JCM 2022

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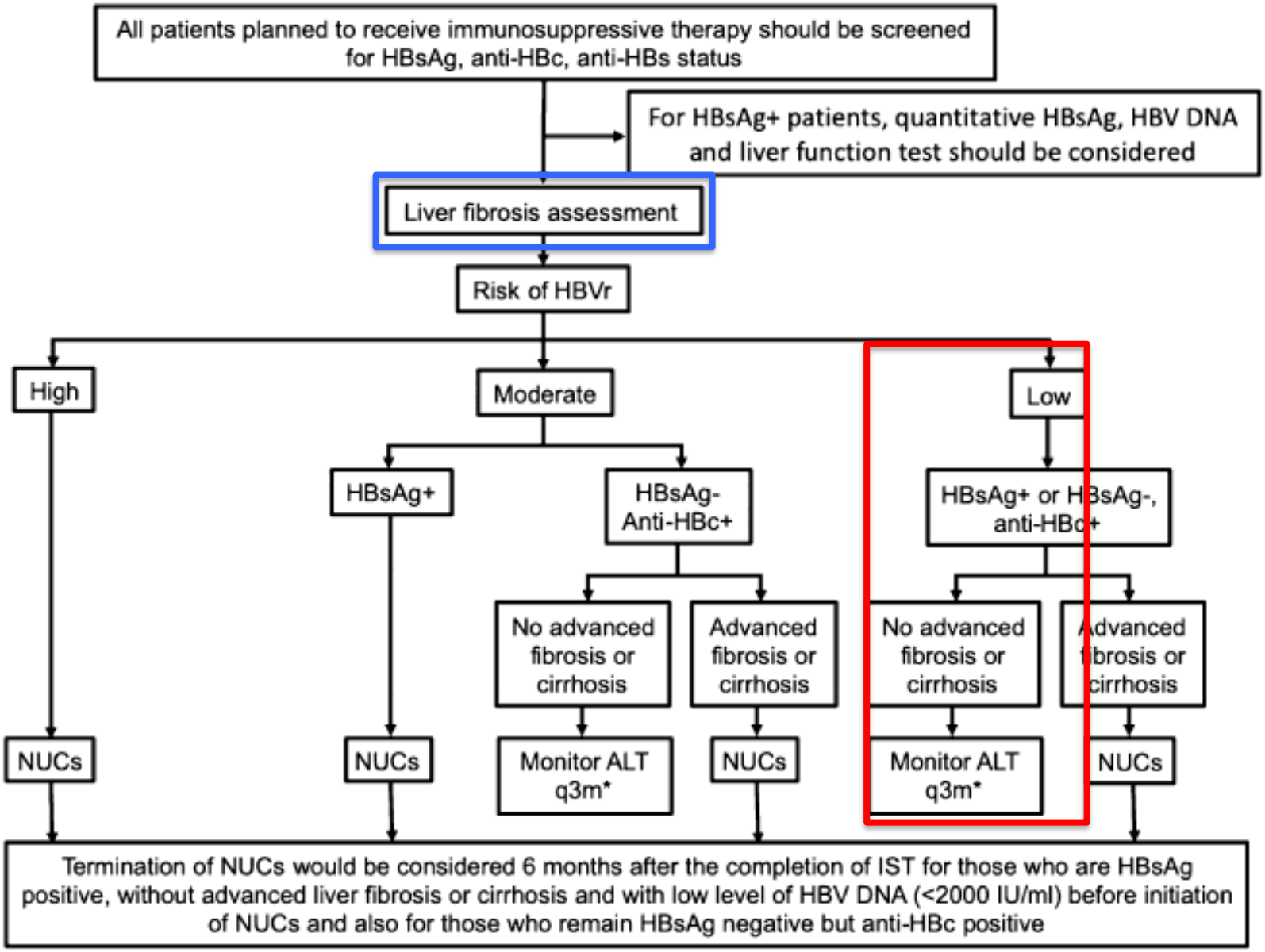

BC Cancer Protocol Summary for Hepatitis B Virus Reactivation Prophylaxis

TESTS:

- **Baseline***:
  - HBsAg, HBsAb, HBcoreAb
  - Patients with HBsAg positive and/or HBcoreAb positive also require a baseline HBV DNA (HBV viral load)
  - Results do not have to be available to proceed with first treatment, but results must be checked before proceeding with cycle 2 of cancer treatment

    ** Baseline serology (particularly HBsAb) should be repeated if patient relapses, and/or needs additional lines of antineoplastic systemic therapy and the patient is not on prophylaxis*
- **Every 3 months:**
  - Patients with HBsAg positive and HBcoreAb positive or negative: HBV DNA (HBV viral load) and ALT during cancer treatment and at least 12 months after stopping antiviral for HBV prophylaxis
  - Patients with HBsAg negative and HBcoreAb positive: HBV DNA (HBV viral load) and ALT during cancer treatment and for at least 12 months after stopping antiviral for HBV prophylaxis

Drug	Dose	BC Cancer Administration Guideline
entecavir	0.5 mg daily*	PO
or		
tenofovir	300 mg daily*	PO

*See Appendix for indication and duration of HBV prophylaxis

Appendix: Risk of hepatitis B reactivation with immunosuppressive therapy

Risk of HBV reactivation*	Cancer Treatment*	Serology	Antiviral for HBV prophylaxis	Prophylaxis duration *after end of cancer treatment*	Monitoring including *after prophylaxis discontinued*
Very high	B-cell depleting therapy (e.g., riTUXimab, obinutuzumab, polatuzumab, BTK inhibitors, CAR T-cell therapy, plasma cell antibodies (eg. CD38 daratumumab, isatuximab), bi-specific anti-B-cell/plasma cell antibodies, alemtuzumab)	HBsAg+ **OR** HBcAb+	entecavir†	18 months	Monitor HBV DNA (HBV viral load) and ALT q3months and for at least 12 months after stopping antivirals
High	Autologous or allogeneic stem cell transplant	HBsAg+ **OR** HBcAb+	entecavir†	12 months after completion of all immunosuppressive therapy	
	High-dose corticosteroids‡, anthracyclines	HBsAg+	entecavir†	6 months§	
Moderate 1%-10%	Tyrosine kinase inhibitors	HBsAg+	entecavir†	6 months§	
	Moderate-dose corticosteroids‡	HBsAg+	entecavir†	6 months§	
	Other highly or moderately immunosuppressive LY/MY/LK protocols*	HBsAg+	entecavir†	6 months§	
	Tyrosine kinase inhibitors High or Moderate -dose corticosteroids‡ Anthracyclines Other highly or moderately immunosuppressive LY/MY/LK protocols*	HBsAg- and HBcAb+	If anti-HBs titres >100 U/L: No prophylaxis		
			If anti-HBs titres ≤100 U/L: entecavir†	6 months§	
Low < 1%	Other low immunosuppressive LY/MY/LK protocols*	HBsAg+ **OR** HBsAg- and HBcAb+	No prophylaxis		

* LY/MY/LK are lymphoid, plasma cell, or myeloid malignancy treatment protocols. They are designated as low, moderately, or highly immunosuppressive within the protocols. Refer to specific protocol for designation.

† Entecavir is preferred but tenofovir is an acceptable alternative. Tenofovir may cause renal toxicity. Both agents require dose adjustment in patients with pre-existing renal dysfunction. Patients currently on lamivudine do not need to switch therapy; however consider a switch to entecavir or tenofovir at the next Special Authority Renewal.

‡ High-dose = predniSONE equivalent ≥ 20 mg/d for ≥ 4 weeks[3] Moderate-dose = predniSONE equivalent 10 - 20 mg/d for ≥ 4 weeks[3]

§ Longer duration would require exceptional coverage review and description of patient specific factors requiring extended prophylaxis, including specific treatment regimen for the underlying malignancy and the most recent hepatitis serology report.

Infect Dis Ther (2024) 13:1607–1620
https://doi.org/10.1007/s40121-024-00997-0

ORIGINAL RESEARCH

Implementation of Guideline-Based HBV Reactivation Management in Patients with Chronic HBV Infections of HBsAg or Resolved HBV Infection Undergoing Immunosuppressive Therapy

Yasuhito Tanaka · Daisuke Nakamoto · Yi Piao · Hajime Mizutani · Ryozo Wakabayashi · Yoshiyuki Saito · Kyung min Kwon · Harriet Dickinson

Table 2 Number and proportion of patients who received appropriate management to prevent HBV reactivation

	Overall		Hepatitis B reactivation risk classification							
			High risk		Intermediate risk		Low risk		Risk uncertain	
Overall	6242		641		555		4965		81	
Patients who received appropriate management	1273	20.4%	276	43.1%	223	40.2%	741	14.9%	33	40.7%
Patients who did not receive appropriate management	4855	77.8%	358	55.9%	325	58.6%	4,125	83.1%	47	58.0%
Patients who were censored	114	1.8%	7	1.1%	7	1.3%	99	2.0%	1	1.2%

HBV exposed patients and immuno-suppressive treatment

CONCLUSIONS

An appropriate management requires:

1. characterization of HBV infection phase

2. the definition of the individual risk of HBV reactivation according to the phase of infection, the underlying diseases and the type of immuno-suppressive treatment

3. the identification of the most appropriate antiviral treatment to prevent HBV reactivation

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INNOVATIVE MODEL OF
IMPC
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