MÁSTER EN HEPATOLOGÍA

ORGANIZA:

UAM UNIVERSIDAD AUTONOMA DE MADRID

Universidad de Alcalá

Asignatura: Hepatitis Virales

Hepatitis B: reactivación

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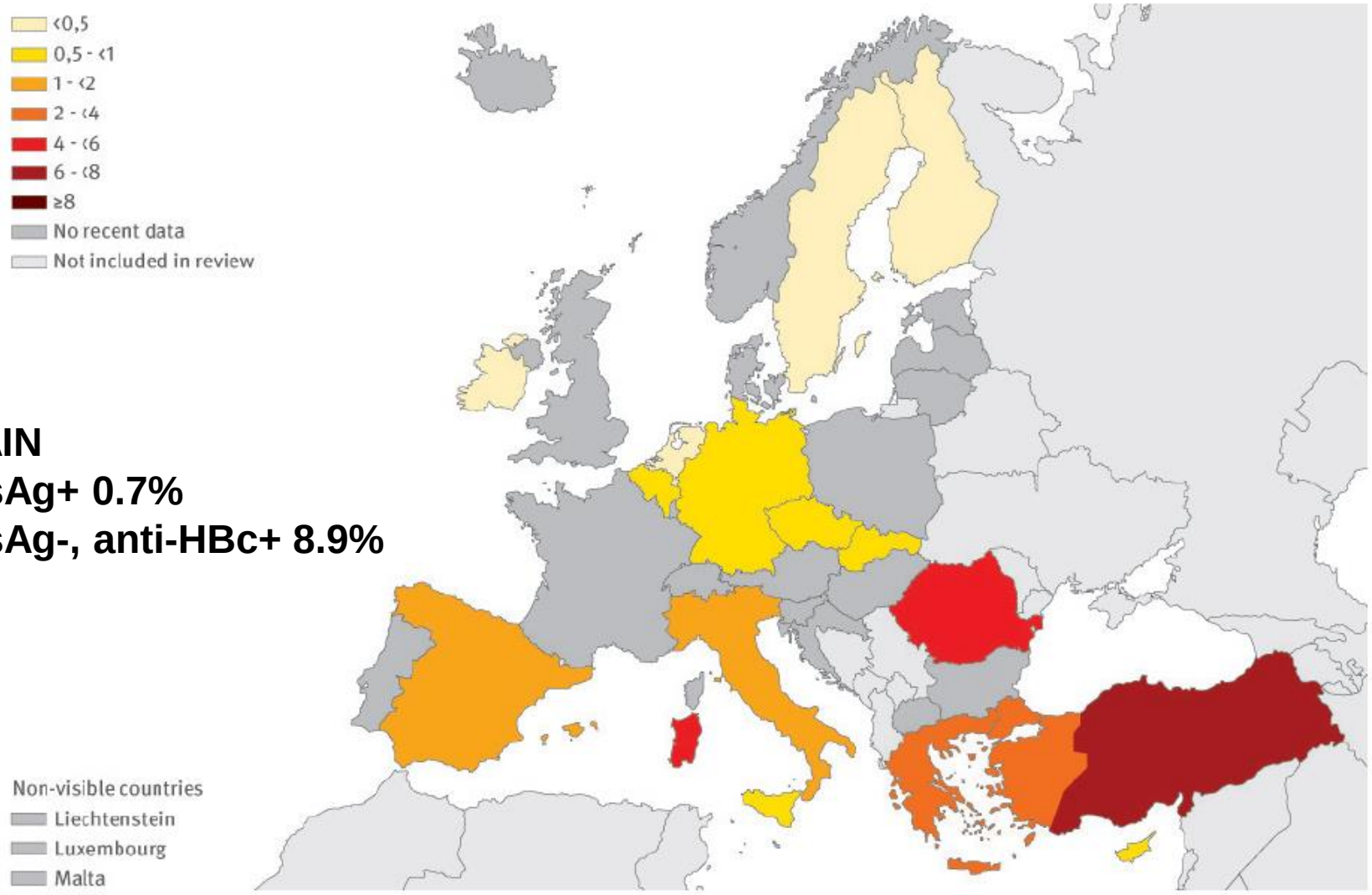
HBV infection in Europe

- Hepatitis B prevalence in the general population: HBsAg based



SPAIN
HBsAg+ 0.7%
HBsAg-, anti-HBc+ 8.9%

Technical report. Hepatitis B and C in the EU neighbourhood: prevalence, burden of disease and screening policies. European Centre for Disease Prevention and Control. September 2010 (available at www.ecdc.europa.eu); Salleras. Vaccine 2007

REACTIVATION

- Definition of reactivation
- Clinical Course
- Risk factors
- Prophylaxis and Treatments
- Conclusions

REACTIVATION

- [x] Definition of reactivation
- [ ] Clínical Course
- [ ] Risk factors
- [ ] Prophylaxis and Treatments
- [ ] Conclusions

Definition

- Reappearance or increase in viral replication

  (↑ **DNA-VHB ≥1 log_{10}**)

- Often with increase in ALT

  (↑**ALT >3xLSN o >3xVB**)

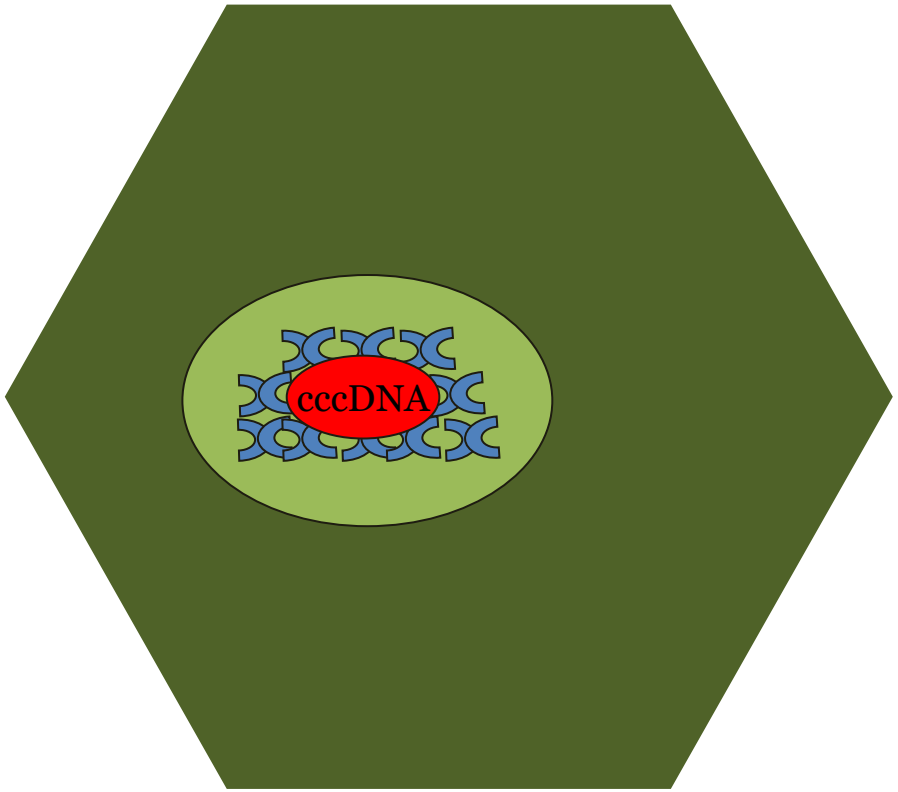
- In patient with past history of HepatitsB :

  1) **Chronic Carrier :** HBsAg (+)

  2) **Resolved Hepatitis B :** antiHBc (+) y/o antiHBs (+)

Yeo ert al, Hepatology 2006
Lalazar et al, Br J Haematol 2007
Barclay et al, J Clin Virol 2008
Hoofnagle JH, Hepatology 2009

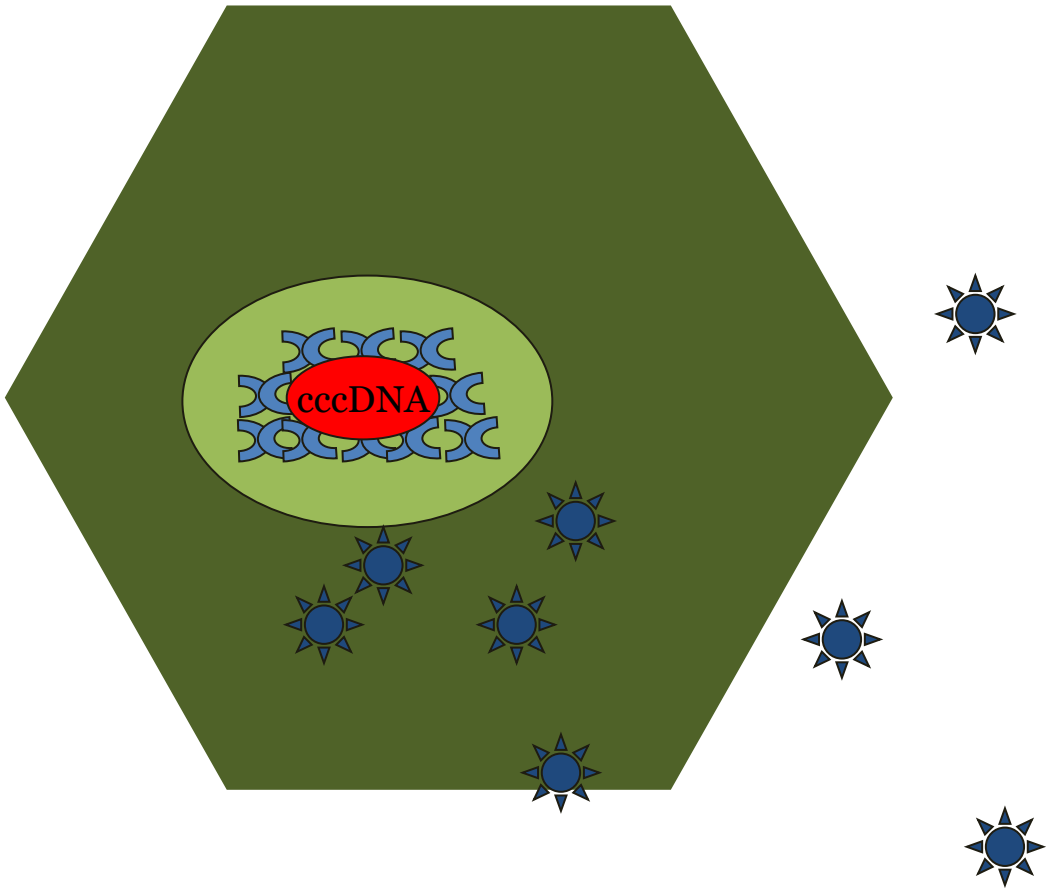
Immune control



- Immune control—not clearance
- “Resolved HBV” a misnomer—still HBV DNA in liver

Werle-Lapostolle B, et al. Gastroenterology. 2004;126:1750-1758.

Immune control



- Immune control—not clearance
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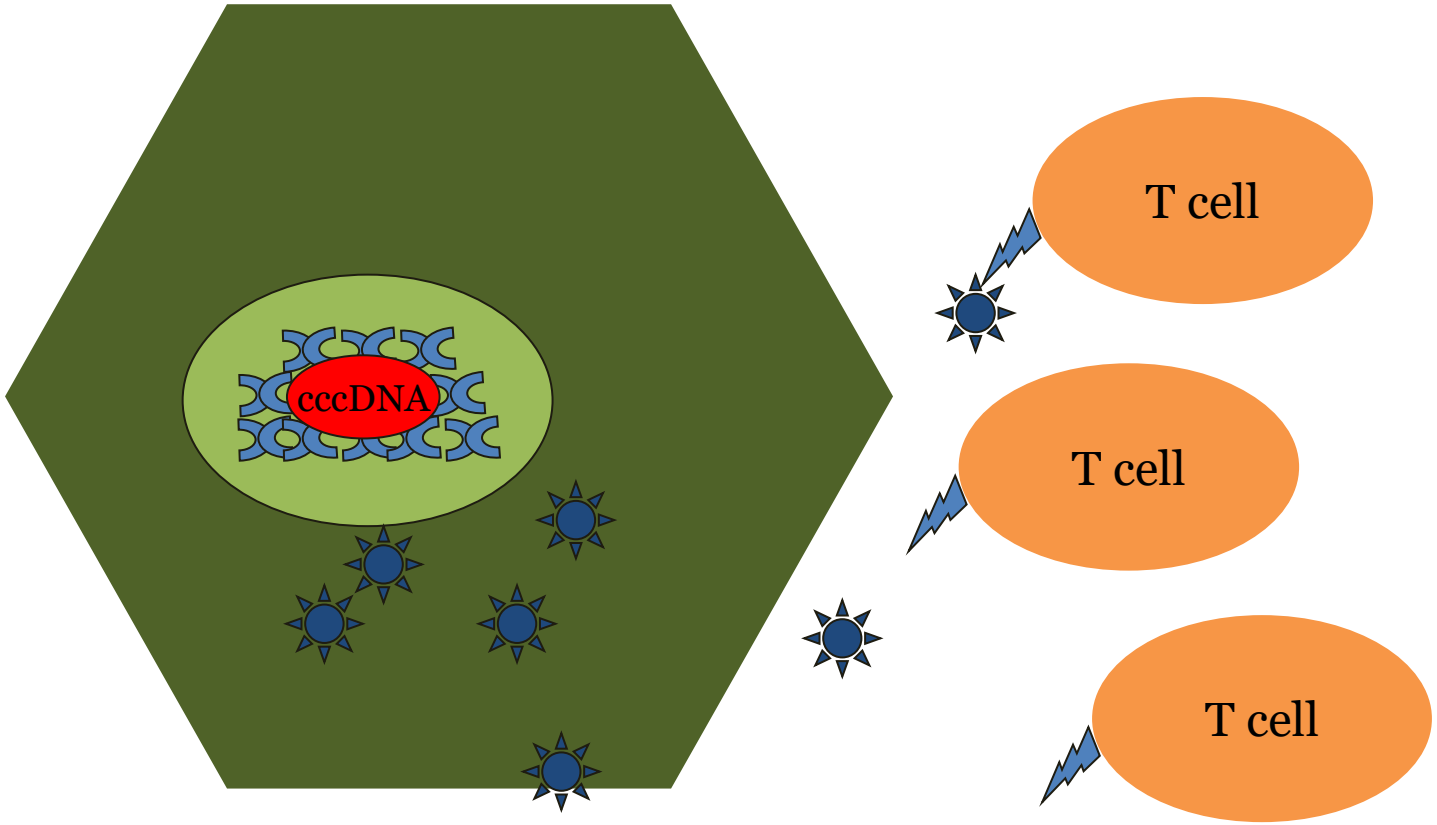
Werle-Lapostolle B, et al. Gastroenterology. 2004;126:1750-1758.

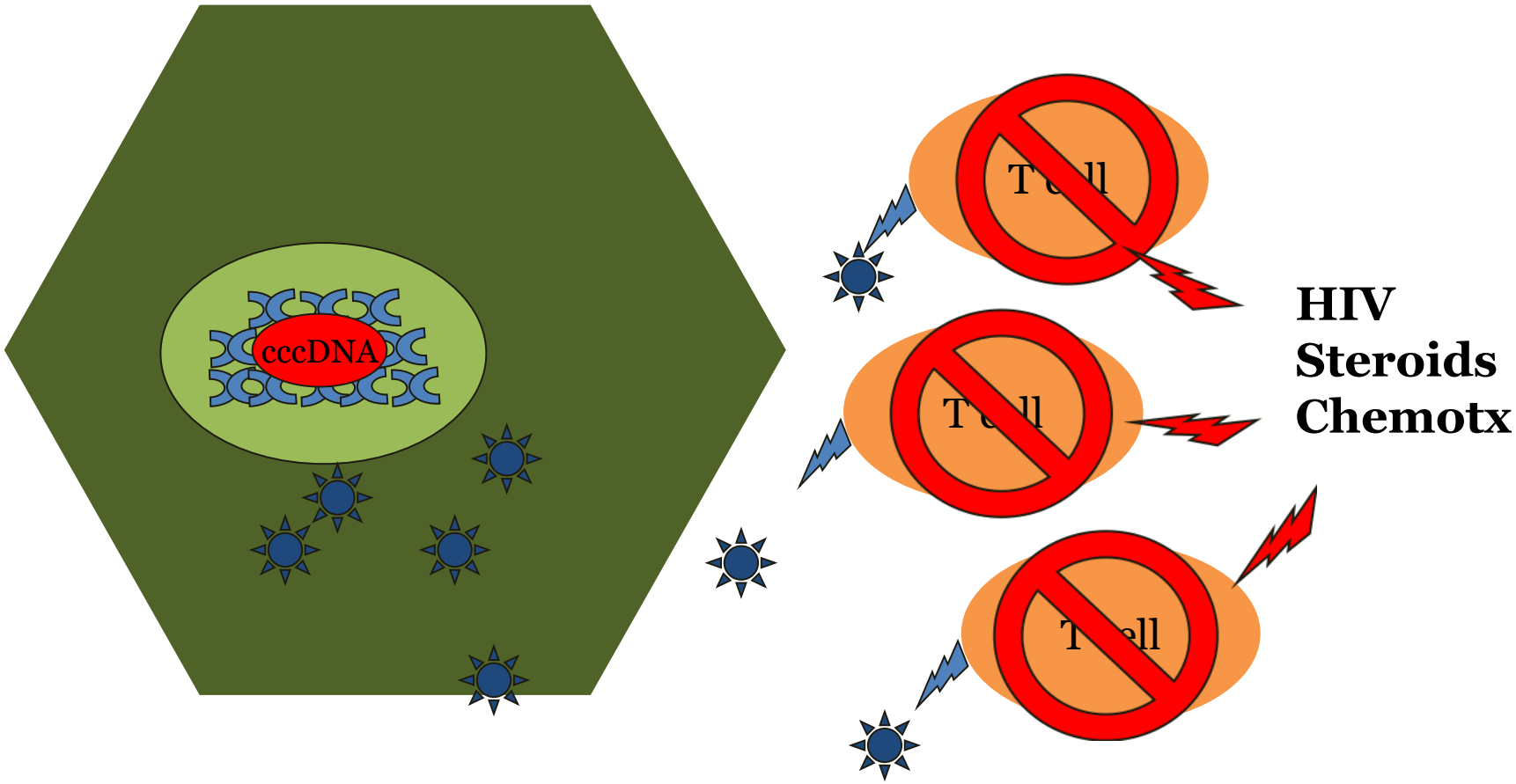
La Hepatitis B no se cura



- Control inmune y NO CURACION
- En los casos resueltos queda DNA en el hepatocito

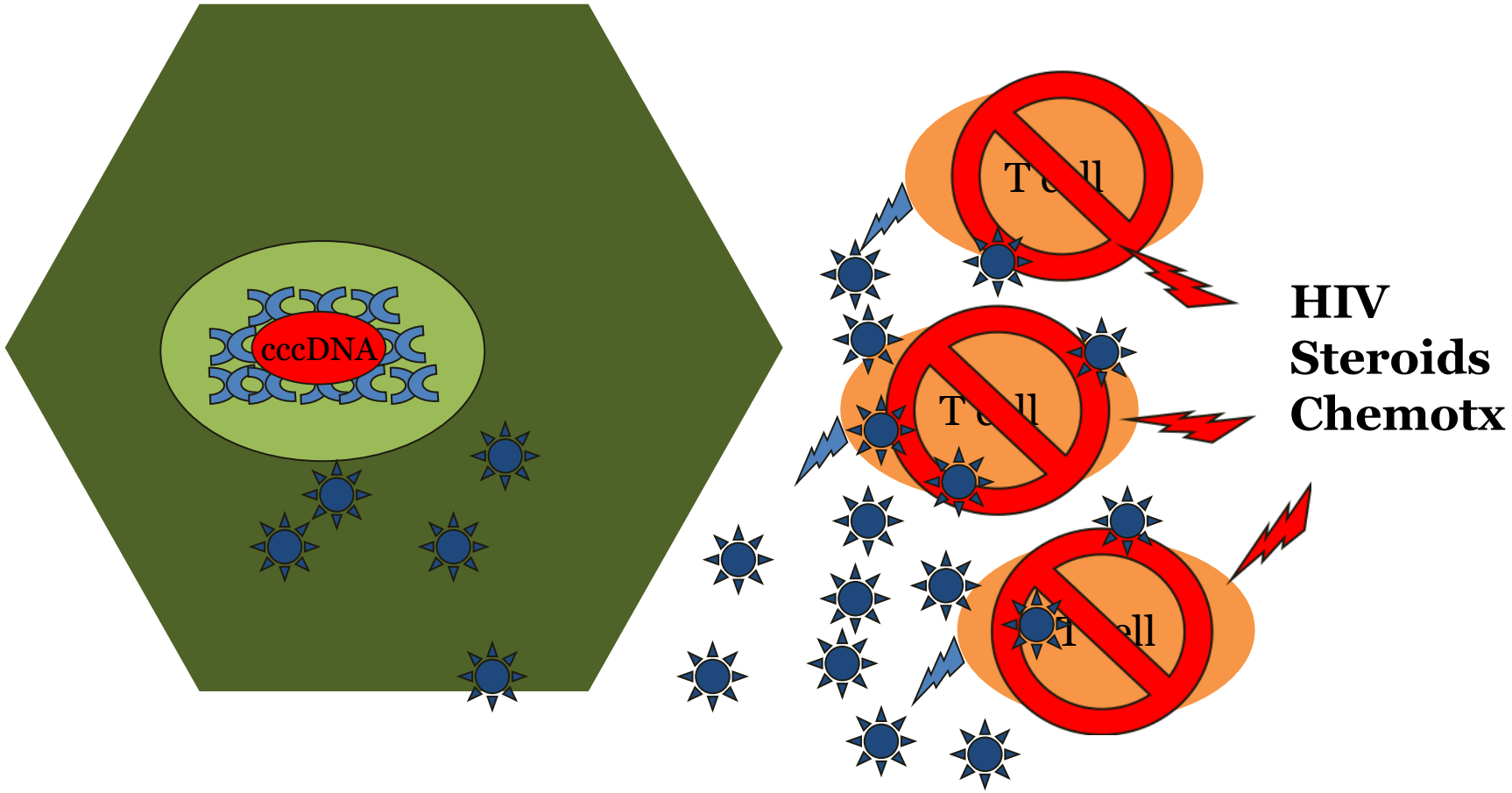
Werle-Lapostolle B, et al. Gastroenterology. 2004;126:1750-1758.

Immune control



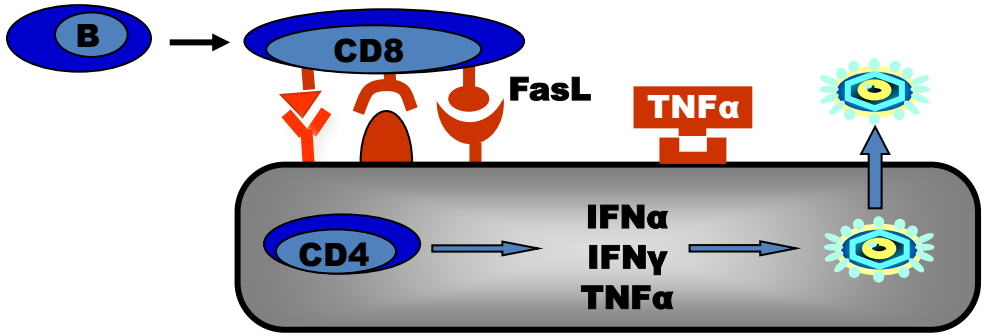
Werle-Lapostolle B, et al. Gastroenterology. 2004;126:1750-1758.

Immune control



Werle-Lapostolle B, et al. Gastroenterology. 2004;126:1750-1758.

Reactivation



Disbalance between viral replication and immune response

↑ Increase Viral replication	↓ Decrease Immune response
Spontaneous	Spontaneous
Resistance to treatment	HIV infection
Stop Antiviral treatment	Solid Organ Trasplantation
	Hematologic malignancies
	Autoimmune disease

IMS= inmunosupresión
QMT= quimioterapia

Yeo ert al, Hepatology 2006; Lalazar et al, Br J Haematol 2007; Barclay et al, J Clin Virol 2008;
Hoofnagle JH, Hepatology 2009

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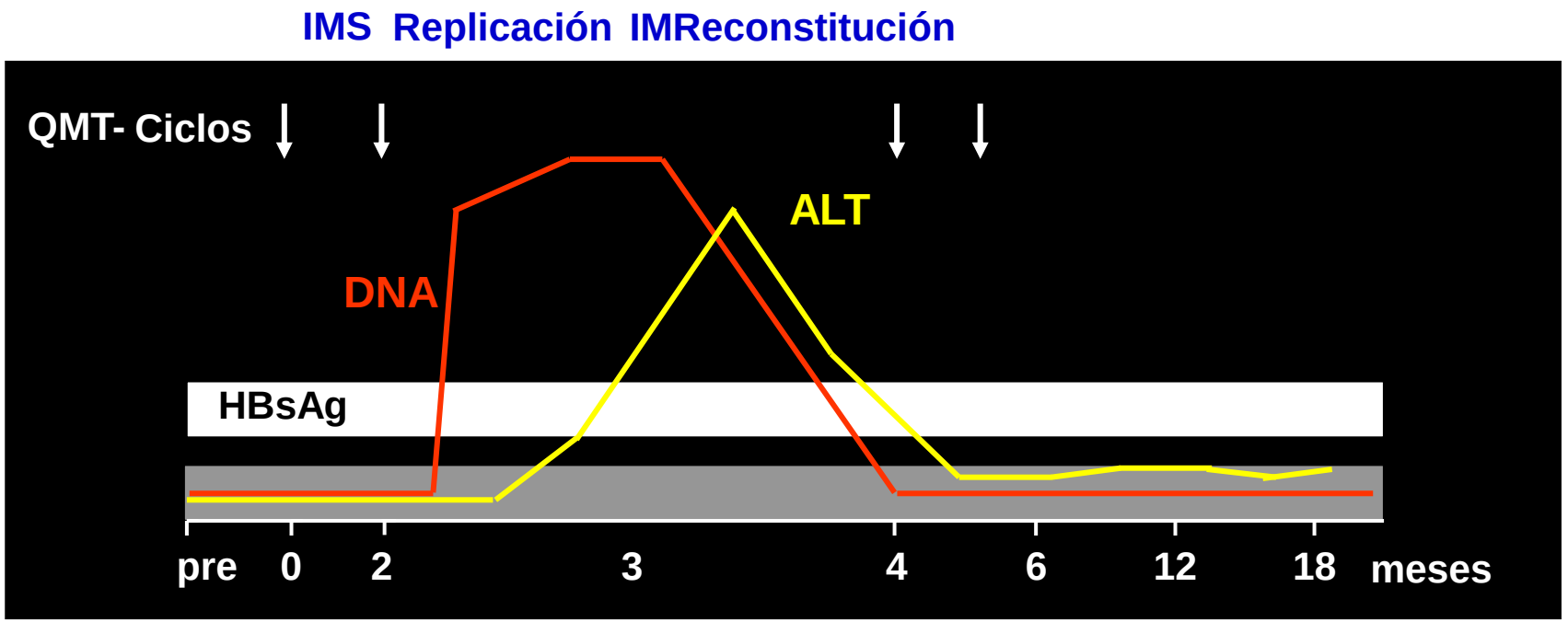
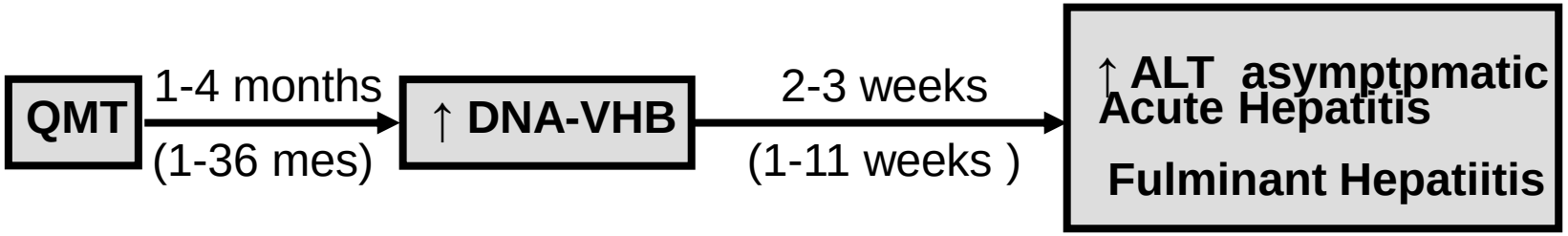
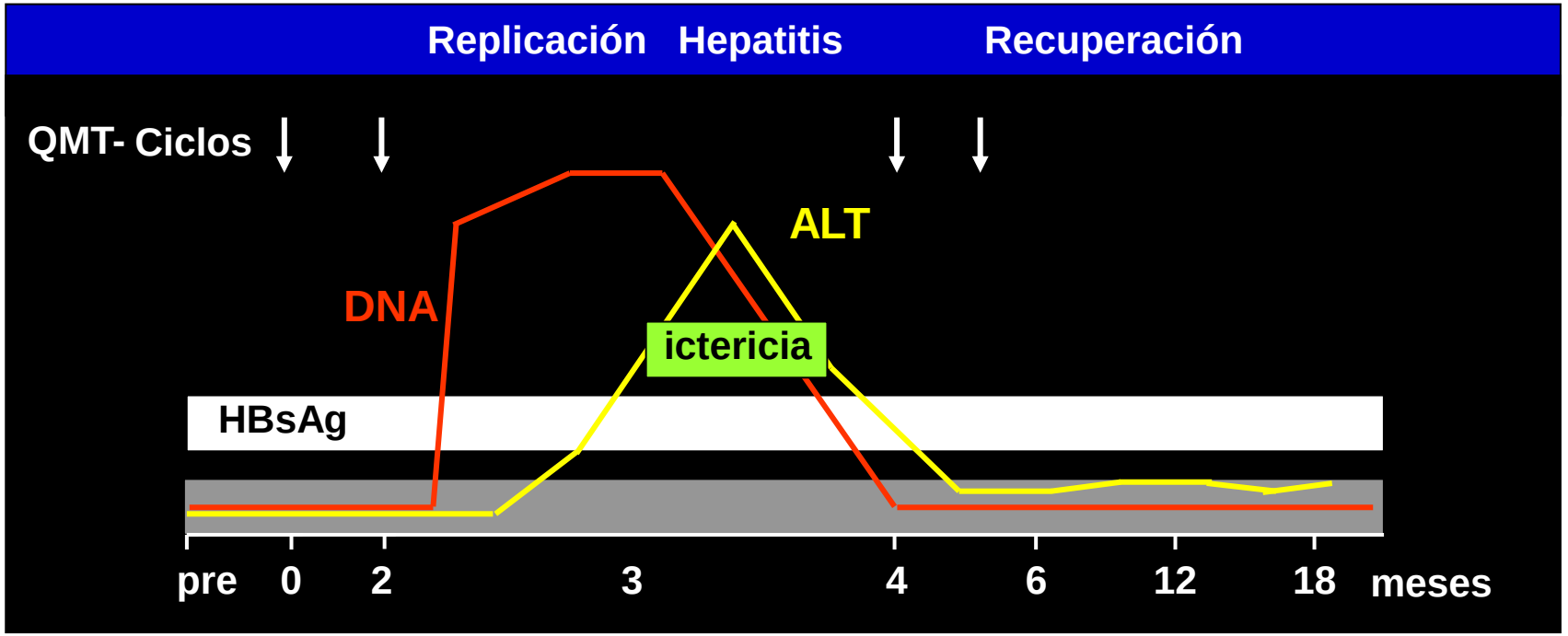
Clinical Course



Lau et al, Gastroenterology 2003; Lalazar et al, Br J Haematol 2007; Hoofnagle JH, Hepatology 2009

Clinical Course





Lau et al, Gastroenterology 2003; Lalazar et al, Br J Haematol 2007; Hoofnagle JH, Hepatology 2009

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Risk factors

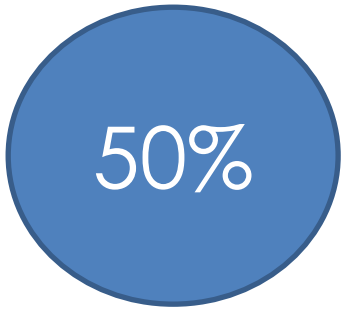
- **PATIENT**
  - MALE SEX
  - YOUNG
  - Hematologic disorders
- **VIRAL FACTORS**
  - DNA-VHB + (sobre todo si >20.000 UI/ml)
  - HBeAg +
- **TYPE OF DRUGS**
  - Corticosteroid Therapy
  - Rituximab

Cheng et al, Hepatology 2003; Sera et al, Intern Med 2006; Yeo et al, Hepatology 2006

Reactivation in Oncologic disorders

Inactive carriers HBs Ag positive

		HBsAg +	Hepatitis 2º reactivación
Lok 1991	lymphoma	27	67%
Yeo 2005	lymphoma	21	33%
Lau 2003	lymphoma	30	46%
Jang 2006	HCC	52	48%
Hsu 2008	lymphoma	73	29,7%



Reactivation in oncologic disorders

HBc Ac positive/HBs Ag negative

		n	Reactivación de VHB
Wands 1975	Quimioterapia	17	29%
Lok 1991	Quimioterapia	51	3,9%
Chen 1990	Quimiot+TMO	9	11%
Dhedin 1998	Quimiot+TMO	37	10,8%
Seth 2002	Quimiot+TMO	42	14,2%
Omaozawa 2005	Quimiot+TMP	14	50%
Knöll 2004	Quimiot+TMO	6	16%
Hui 2006	**Quimioterapia**	**152**	**6%**

Risk Factor : **Bone marrow TX**

- Carriers **HBsAg (+)** → **50-100%**
- Past Infection **(HBsAg -/antiHBc+)** → **11-50%**

Hoofnagle JH, Hepatology 2009

Estudios en HBsAg (-)/antiHBc+

Chen, 1990	9	**11%**
Dhedin, 1998	37	**10,8%**
Seth, 2002	42	**14,2%**
Onozawa, 2005	14	**50%** **40%/2 años** **70%/5 años**
Knöll, 2004	6	**16%**
Sugauchi, 2011	28	**10,7%**

Late Onset 1-3 years after TX (mean 18 meses)

Severe Liver disease

Chen et al, Transplantation 1990; Dhedin et al, Transplantation 1998; Seth et al, Bone Marrow Transplant 2002 Knöll et al, Bone Marrow Transplant 2004; Onozawa et al, Transplantation 2005

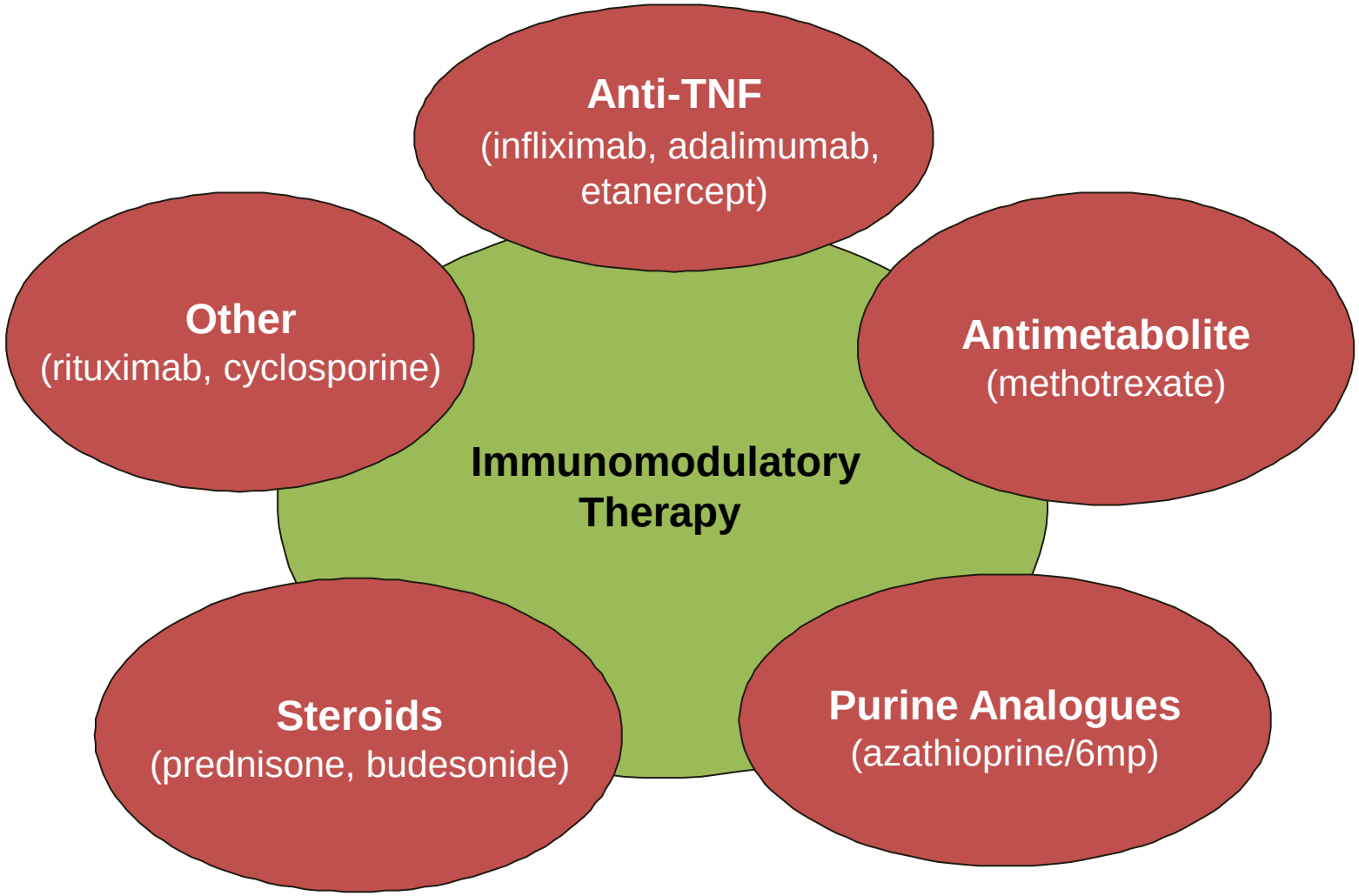
Risk of HBV reactivation in HBsAg+ vs HBsAg-

	HBsAg-positive	HBsAg-negative, anti-HBc-positive
Risk of HBV reactivation	20-50% on conventional chemotherapy	1.0-2.7% on conventional chemotherapy
	80% on rituximab-containing chemotherapy	12.2-23.3% on rituximab plus steroid combination
	> 50% on HSCT*	14-20% on HSCT*

*HSCT : Hematopoietic stem cell transplantation

Kusumoto S, et al. *J Gastroenterol* 2011;46:9-16.

Agents reported to cause HBV reactivation



IBD and reactivation

REPENTINA Study

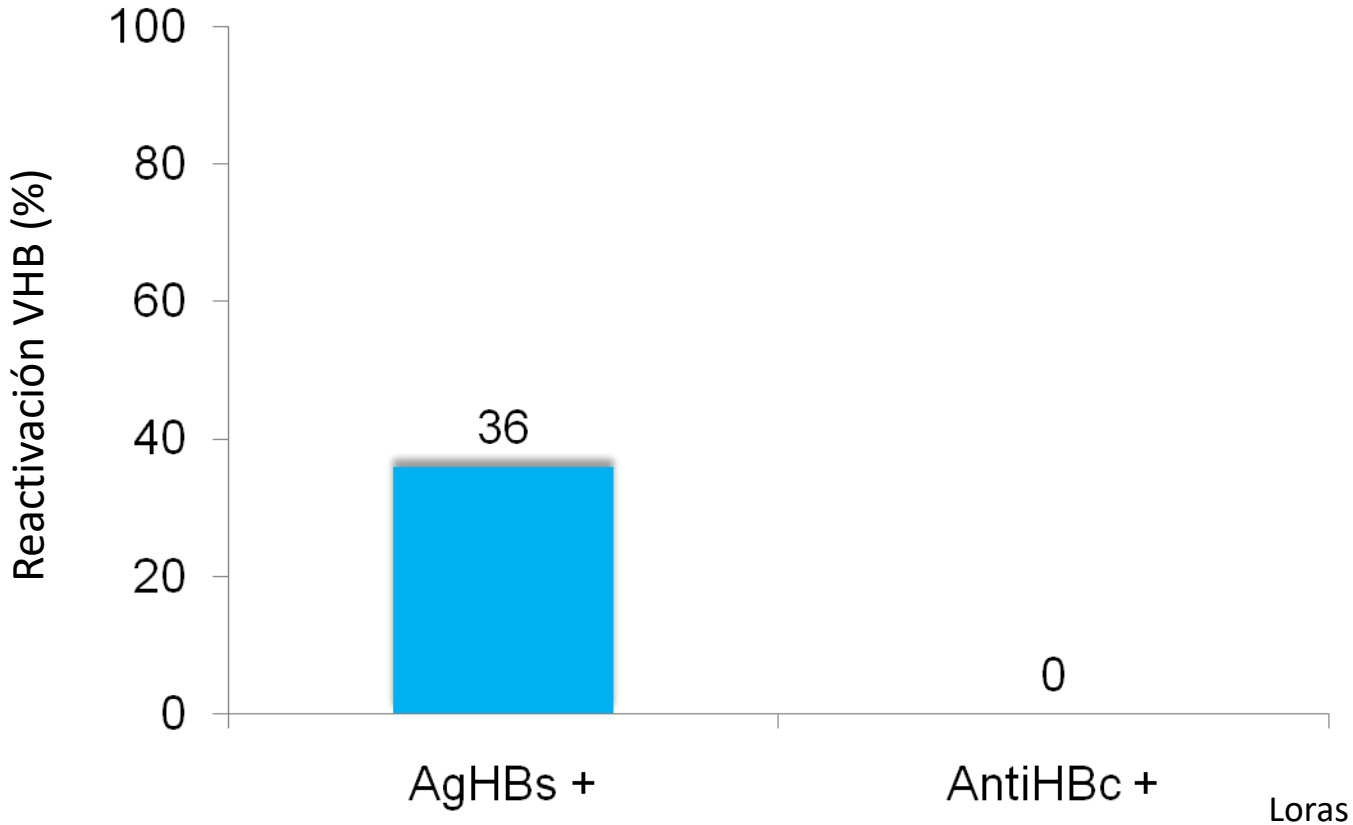
116 EII → 25 AgHBs +

79 AntiHBc +

→ Steroids (84%)

Azatihoprine (69%)

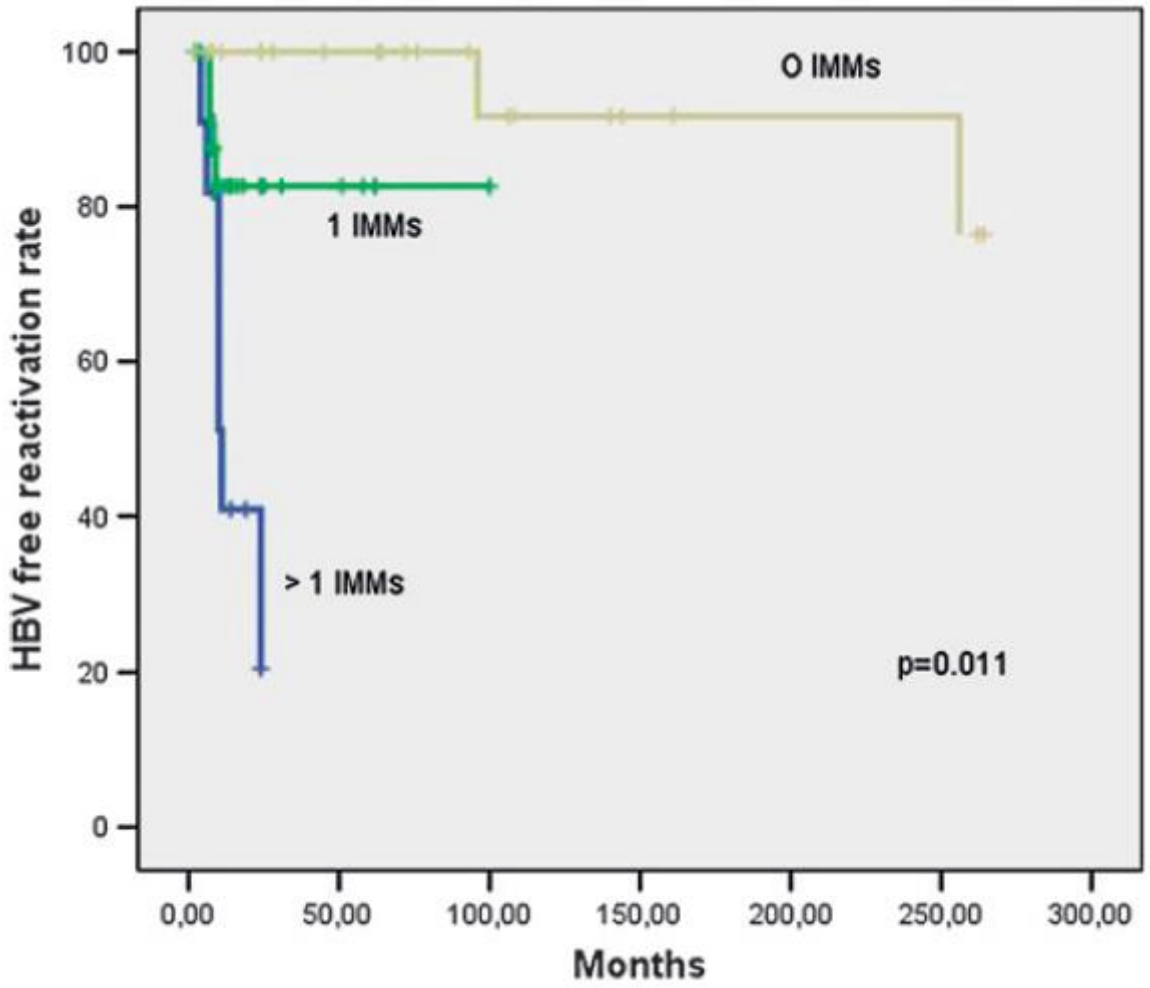
Infliximab (24%)



Loras et al. Gut 2010

IBD and reactivation

- Number of immunosupressors



IMMs: immunosuppressants

Loras et al. Gut 2010

Anti TNF and HBV reactivation

- Retrospective evaluatiuon of patients in Kaiser Permanente
- Receiving Anti-TNF for different autoimmune diseases

- 8887 patients evaluated
- Only 52% were screened for Hepatitis B

- 23 patients HBsAg + :
  - 9 reactivations (39%)
  - 8 without antiviral treatment
  - Mild disease in the majority of cases
- 178 patients HBsAg neg/ Hbc Ac + :
  - 0 % reactivation

Pauly MP Clin Gastro Hepatol 2018

Rheuma and reactivation

29 patients (AR/EA) AgHBs+

8 patients (AR/EA) AgHBs+

AR: Artritis reumatoide
EA: Espondilitis anquilosante

TNFα Inh

2/29
(**6.9%**)

REACTIVATION

1/8
(**12.5%**)

Infliximab 1/6 (**16.7%**)
Etanercept 1/19 (5.3%)
Adalimumab 0/4 (0%)

INFLIXIMAB

Infliximab 1/2 (**50%**)
Etanercept 0/4 (%)
Adalimumab 0/2 (0%)

Ryu et al. Clin Rheumatol 2012

Chung et al. J Rheumatol 2009

Consequences of Delayed Recognition of HBV Reactivation

Hepatitis

- May be severe or even fulminant
- Occasionally may miss HBV DNA spike because HBV DNA may fall when ALT rises
  - This may lead to misdiagnosis and, ultimately, may result in subsequent flares of HBV
- By the time ALT rises . . . may be too late to bring under control

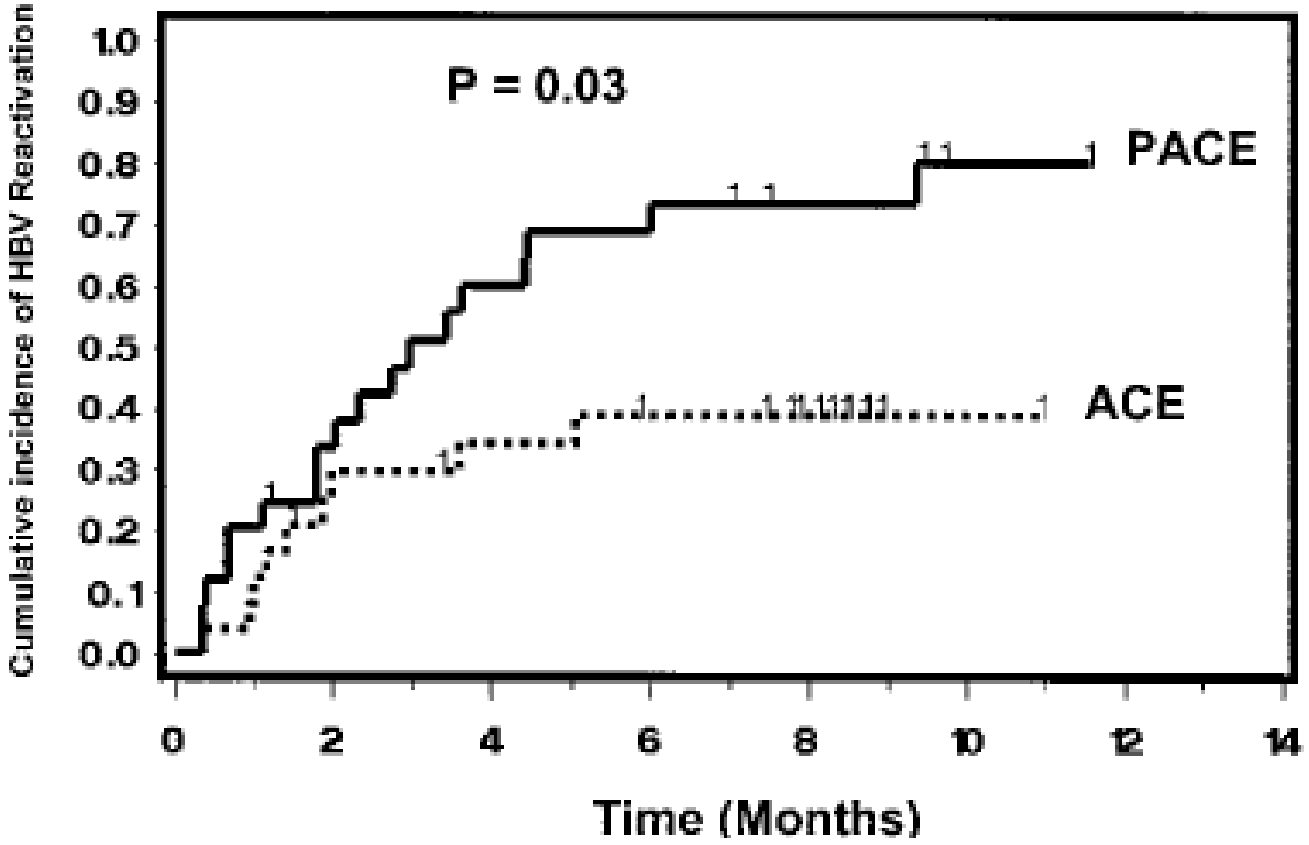
Interruption of chemotherapy

- Potential for poorer cancer-related outcome

Yeo W, et al. Hepatology. 2006;43:209-220.

Risk Factor: Corticosteroid therapy

Pacientes (N=50) AgHBs + Non Hodgkin Lymphoma



ACE= epirubicina, ciclofosfamida, etoposido

PACE= **prednisona** + ACE

Hepatology: 2003, 37: 1321

CASE REPORT Open Access

Fulminant hepatitis B reactivation leading to liver transplantation in a patient with chronic hepatitis C treated with simeprevir and sofosbuvir: a case report

Alexander R. Ende[1], Nina H. Kim[2], Matthew M. Yeh[3], Jason Harper[1] and Charles S. Landis[1*]

Abstract

Introduction: Hepatitis B and C coinfection is commonly seen in clinical practice. In coinfected individuals, high levels of hepatitis C viremia are often associated with low levels of serum hepatitis B DNA. Hepatitis B reactivation in hepatitis C-infected patients treated with pegylated interferon and ribavirin has been reported, but severe or fulminant reactivation is uncommon. Hepatitis C treatment-associated hepatitis B reactivation in patients with chronic hepatitis C and isolated core antibody has not been reported previously.

Case presentation: A 59-year-old white woman with chronic hepatitis C genotype 1B and isolated hepatitis B core antibody initiated treatment with simeprevir, sofosbuvir, and ribavirin for treatment of chronic hepatitis C. She responded very well to treatment initially with near normalization of aminotransferases and hepatitis C viral load suppressed to below the level of quantification after 4 weeks of treatment. At week 11 of a planned 12-week course, she developed fulminant hepatic failure due to hepatitis B reactivation and ultimately required liver transplantation. Fortunately, her posttransplant clinical course was unremarkable.

Conclusions: This is the first report of hepatitis B reactivation in a patient with isolated hepatitis B core antibody leading to fulminant hepatic failure and liver transplantation after initiation of treatment with sofosbuvir, simeprevir, and ribavirin for hepatitis C. This case raises the concern for the risk of severe hepatitis B reactivation in hepatitis B and C-coinfected patients or chronic hepatitis C-infected patients with isolated hepatitis B core antibody treated with direct-acting antiviral drugs for hepatitis C.

Keywords: Hepatitis B, Hepatitis C, Simeprevir, Sofosbuvir, Fulminant liver failure, Liver transplant, Hepatitis B reactivation

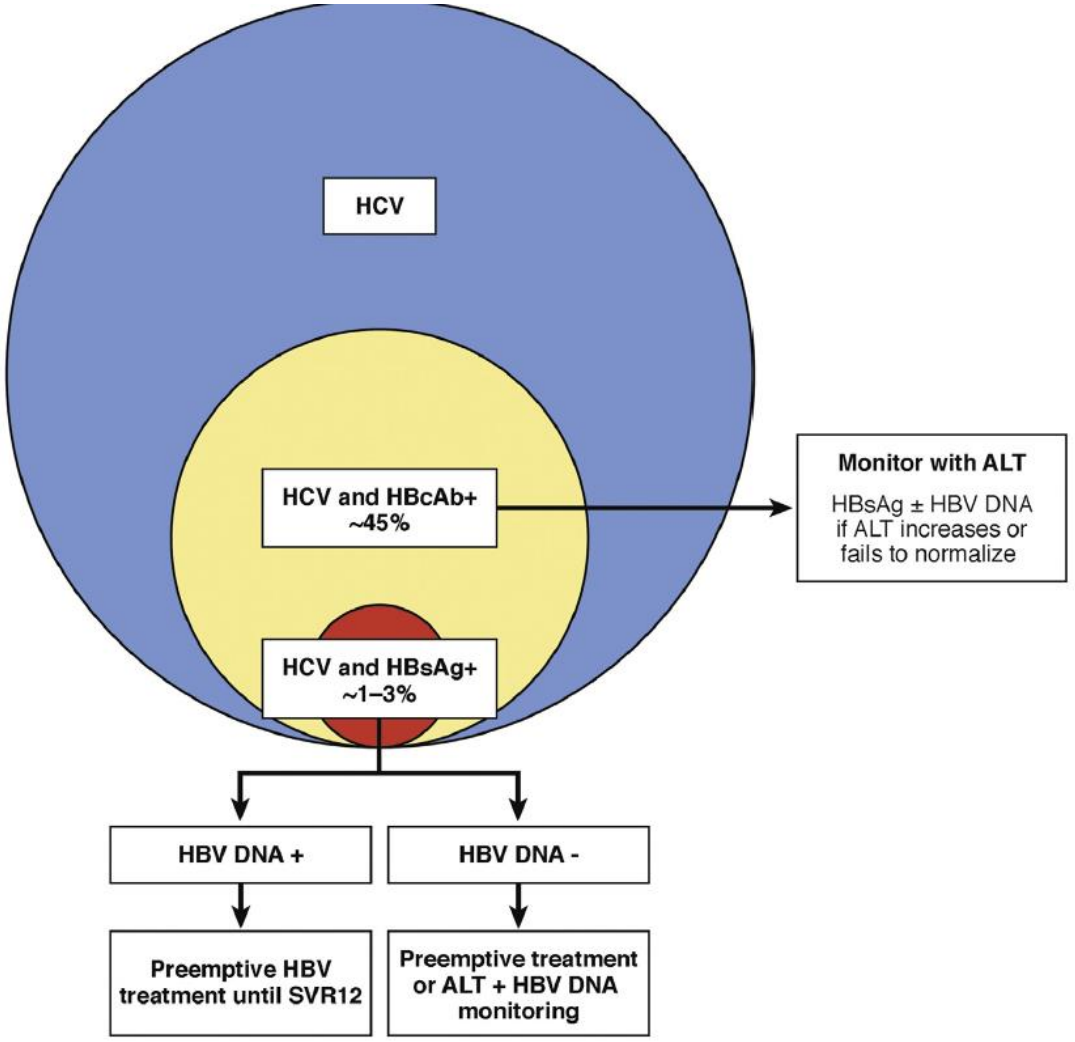
HBV Reactivation in the context of antiviral treatment for Hepatitis C

- 1,8-5,5 % of Hepatitis C patients are coinfected with Hepatitis B

- Prospective study
- 37 patients HBsAg + DNA neg. :
  - 84% showed positivization of DNA during or after therapy
- 74 patients HBsAg + DNA pos :
  - 54% increases more 1 log during or after therapy
- Majority of the cases only sublinical impact

Liu Gastroenterology 2018

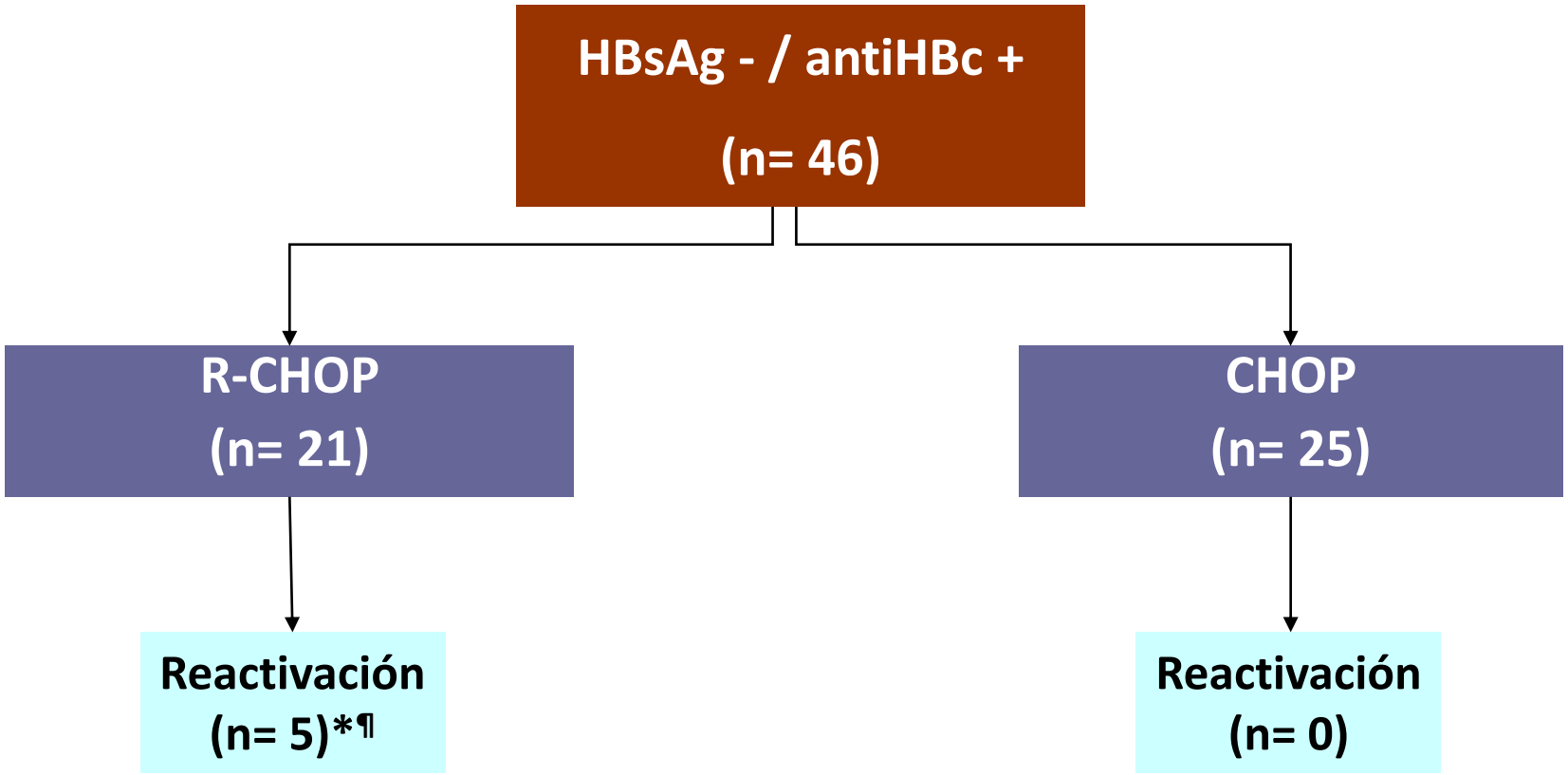
Proposed Algorithm



MA – Feld Gastroenterology 2018

Risk Factor : rituximab

Lymphoma



*Todos antiHBs negativo
¶Una muerte por IHA

Yeo W, et al. J Clin Oncol 2009

Factores de riesgo

- HbsAg +
  - Alto riesgo:
    - Rituximab y agentes depleccionante de linfocitos
    - Alta dosis esteroides
    - Antraciclinas
    - Terapia local para HCC
    - Anti TNF
  - Moderado riesgo
    - Quimioterapia
    - Inhibidor de la tirosin quinasa
    - Dosis moderada (10-20 mg/dia)
  - Bajo Riesgo
    - Azatioprina
    - Dosis bajas de corticoides

Loomba Gastroenterology 2017

Factores de riesgo

- Hbs Ag – HBc Ac +
  - Alto riesgo
    - Rituximab y agentes depleccionantes de linfocitos
  - Moderado riesgo
    - Altas dosis de corticoides
    - Antraciclinas
    - Anti TNF
    - Inhibidores de la tirosin quinasa
    - Quimioterapia sistémica
  - Bajo Riesgo
    - Dosis moderada y baja de corticoides
    - Azatioprina

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REACTIVATION

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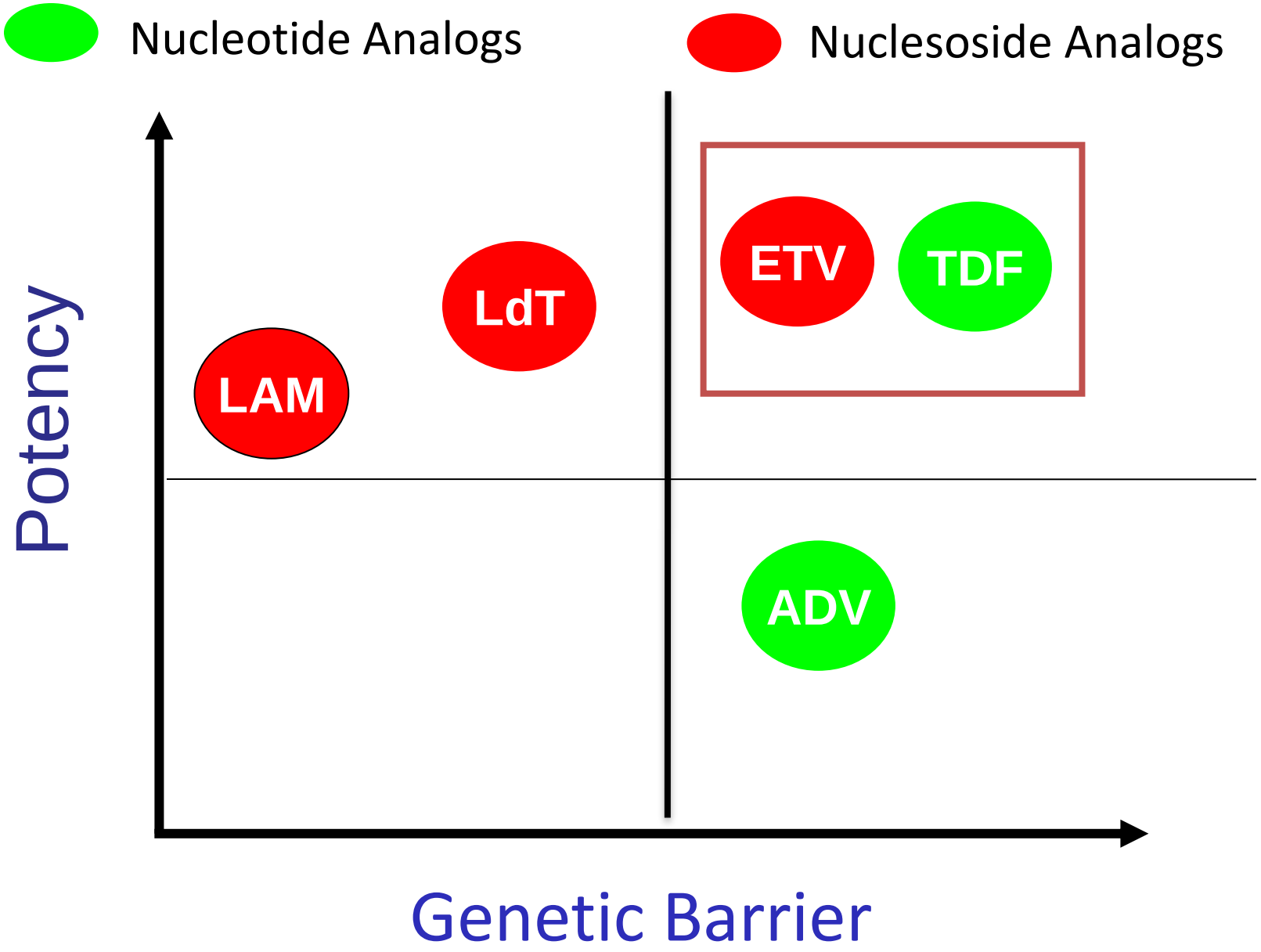
Treatment

1. STOP Chemotherapy

2. Antiviral Drugs


Nucleotide Analogs
Nucleososide Analogs
Potency
LAM
LdT
ETV
TDF
ADV
Genetic Barrier

Last generation antiviral grugs

Autor	Año	N	Tratamiento inmunosupresor	Serología basal	Respuesta virológica (ADN VHB -)
Colson[1]	2008	1	Rituximab	AgHBs-/AntiHBc+	1
Sanchez[1]	2009	1	Rituximab	AgHBs-/AntiHBc+	1
Ueda[1]	2009	1	Rituximab+TMO	AgHBs-/AntiHBc+	1
Brost[1]	2010	4	TMO(2), esteroides(1), bendamustine(1)	AgHBs-/AntiHBc+ (1)	3
Rago[2]	2010	1	Rituximab	AgHBs-/AntiHBc+	1
Milazzo[2]	2011	1	TMO	AgHBs-/AntiHBc+	1
Montineri[3]	2011	5	Rituximab	AgHBs-/AntiHBc+ (4) AgHBs+ (1)	5

[1] Monoterapia con entecavir
[2]Tratamiento combinado entecavir + tenofovir
[3] Monoterapia con lamivudina (1), telbivudina (2) y tenofovir (2)

Colson et al. Br J Haematol 2008
Sanchez et al. J Hepatol 2009
Ueda et al. Am J Haematol 2009
Rago et al. Antiviral ther 2010
Milazzo et al. Transplant Infect Dis 2011
Montineri et al. J Clinical Virol 2011

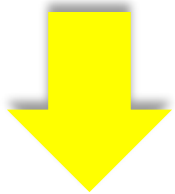
Limitations of Treatment

Mortality

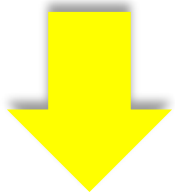
Author	year	N	Mortality (%)
Yeo	1999	8	1 (13)
Petrelli	2001	5	4 (80)
Liao	2002	5	1 (20)
Simpson	2003	4	2 (50)
TOTAL		22	8 (**36**)

Yeo et al. J Med Virol 1999
Petrelli et al. J Hepatol 2001
Liao et al. Br J Haematol 2002
Simpson et al. J Clin Gastreoenterol 2003

Mortality : 36%



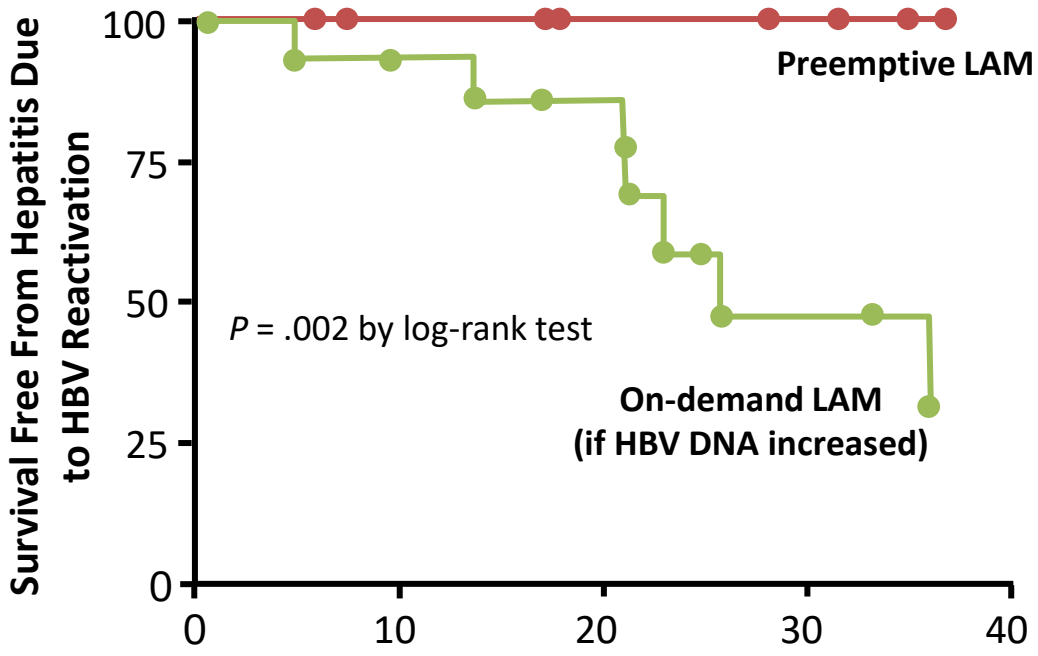
TOO LATE



¿Better Prophylaxis ?

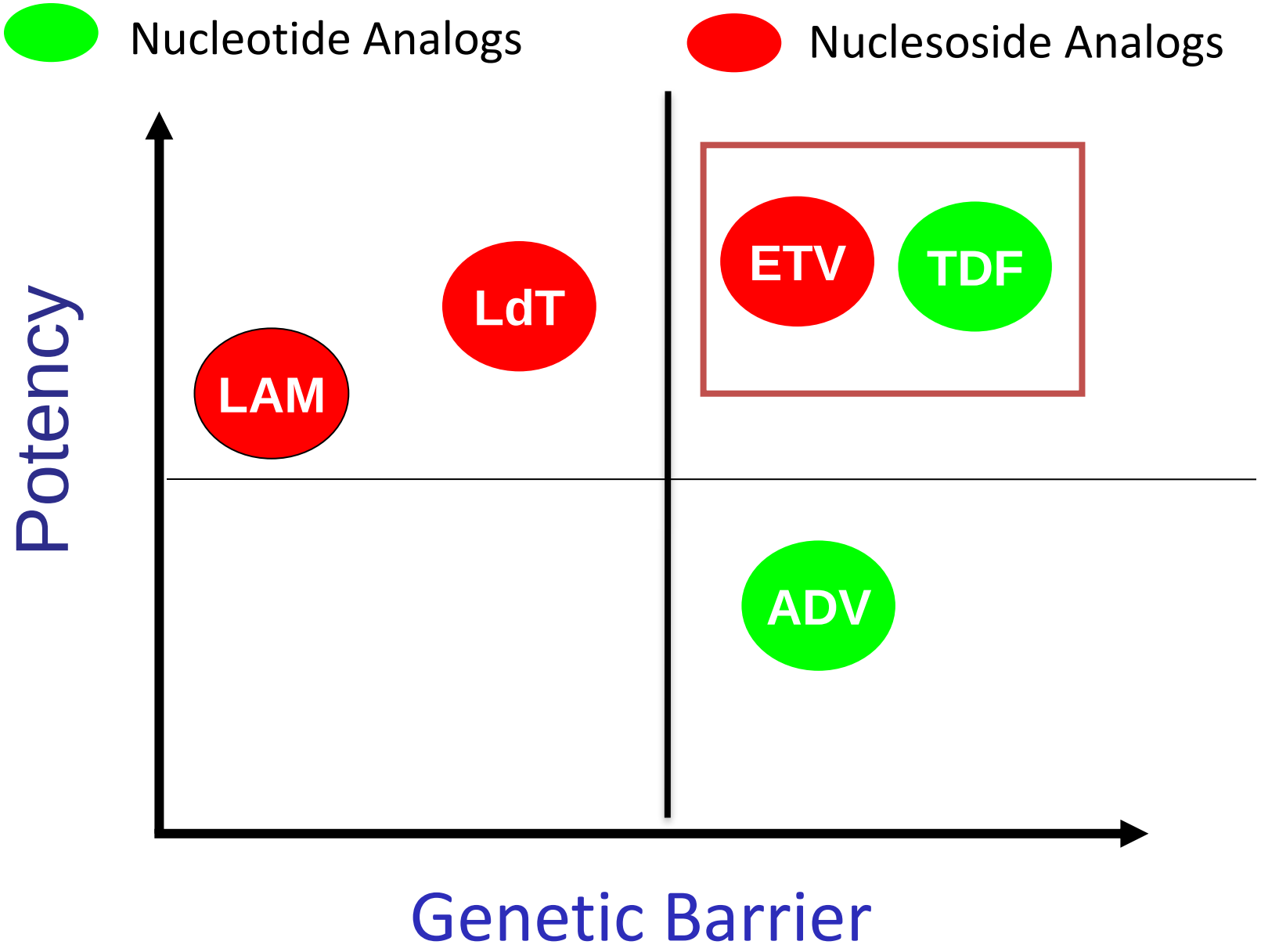
Use of Preemptive Lamivudine Reduces Risk of HBV-Related Hepatitis

- HBsAg-positive patients with lymphoma treated with high-dose chemotherapy randomized to “preemptive” vs “on-demand” lamivudine



Pts at Risk, n					
Preemptive LAM	15	12	10	9	6
On-demand LAM	15	13	10	4	2

Lau GK, et al. Gastroenterology. 2003;125:1742-1749.


Nucleotide Analogs
Nucleososide Analogs
Potency
LAM
LdT
ETV
TDF
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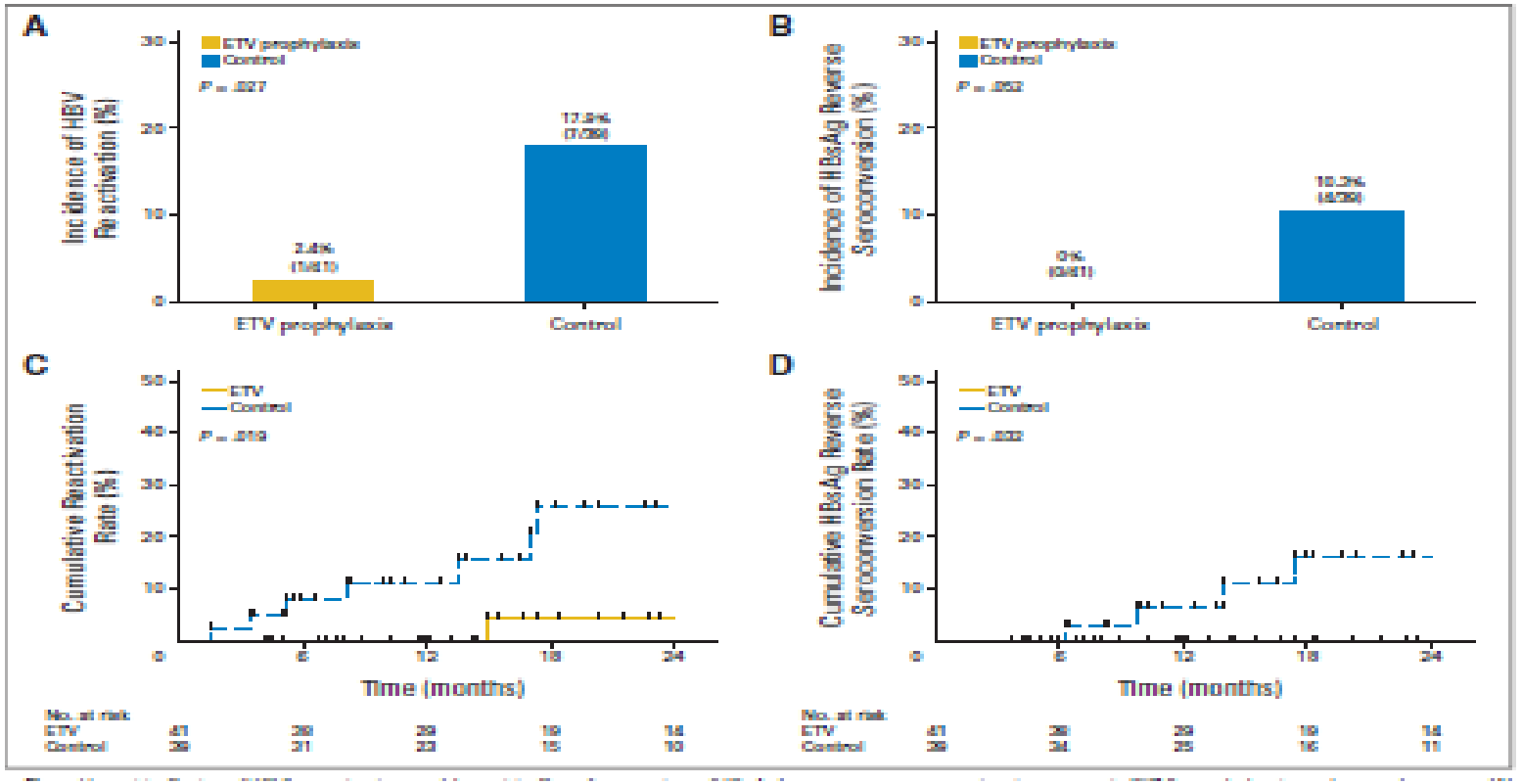
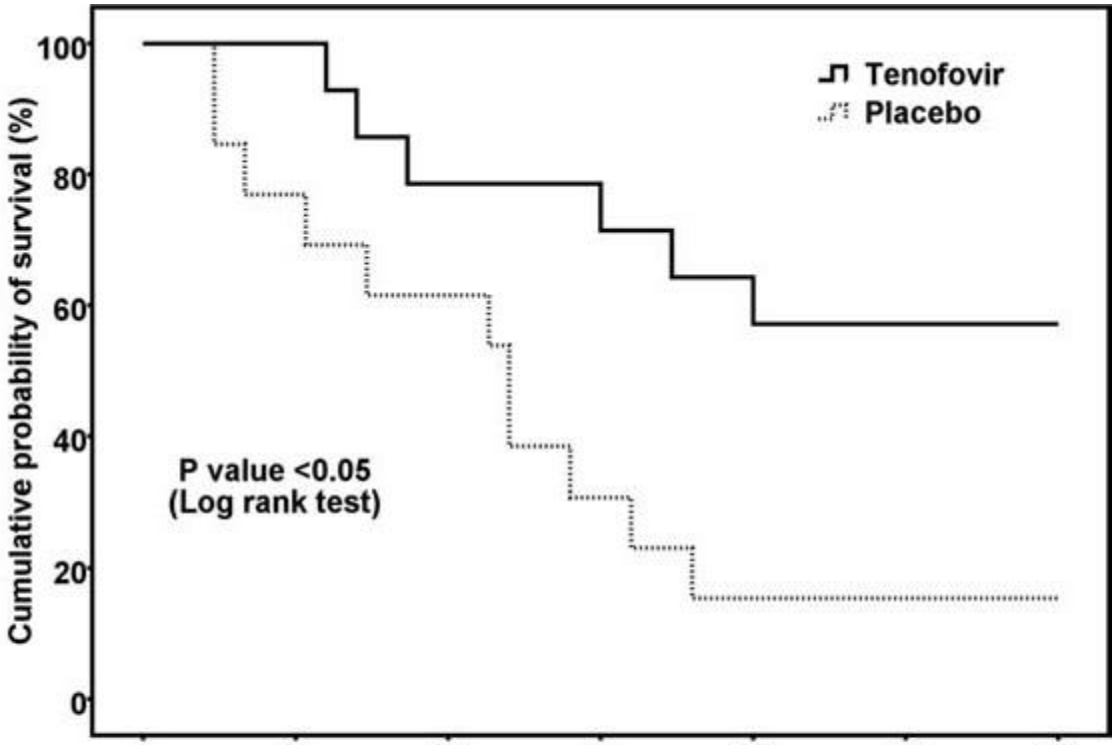
Genetic Barrier

ETV prophylaxis vs Treatment



Huang J Clin Oncol 2013

Tenofovir in prophylaxis



Number of patients:	27	24	19	14	11	10	10
Tenofovir:	14	14	11	10	9	8	8
Placebo:	13	10	8	4	2	2	2

Gang et al Hepatology 2011

Entecavir vs Lamivudine
RCT

	Patients With Event, No. (%)			
	Entecavir (n = 61)	Lamivudine (n = 60)	Difference (95% CI), %	*P* Value
HBV-related hepatitis	0	8 (13.3)	13.3 (4.7 to 21.9)	.003
HBV reactivation	4 (6.6)	18 (30.0)	23.4 (10.2 to 36.6)	.001
Chemotherapy disruption	1 (1.6)	11 (18.3)	16.7 (6.4 to 27.0)	.002
Treatment-related adverse events	15 (24.6)	18 (30.0)	5.4 (−10.5 to 21.3)	.50

Huang JAMA 2015

Timing of Antiviral Therapy

- When to start
  - Ideally before or together with chemotherapy
  - Do not delay start of chemotherapy
- When to stop
  - If baseline HBV DNA > 2000 IU/mL: high risk of withdrawal flare
    - Continue therapy as for chronic HBV infection
  - If baseline HBV DNA < 2000 IU/mL
    - 6-12 mos after end of chemotherapy
- Monitor for withdrawal flares with monthly HBV DNA and ALT

EASL. J Hepatol. 2009;50:227-242. Lok AS, et al. Hepatology. 2009;50:661-662.

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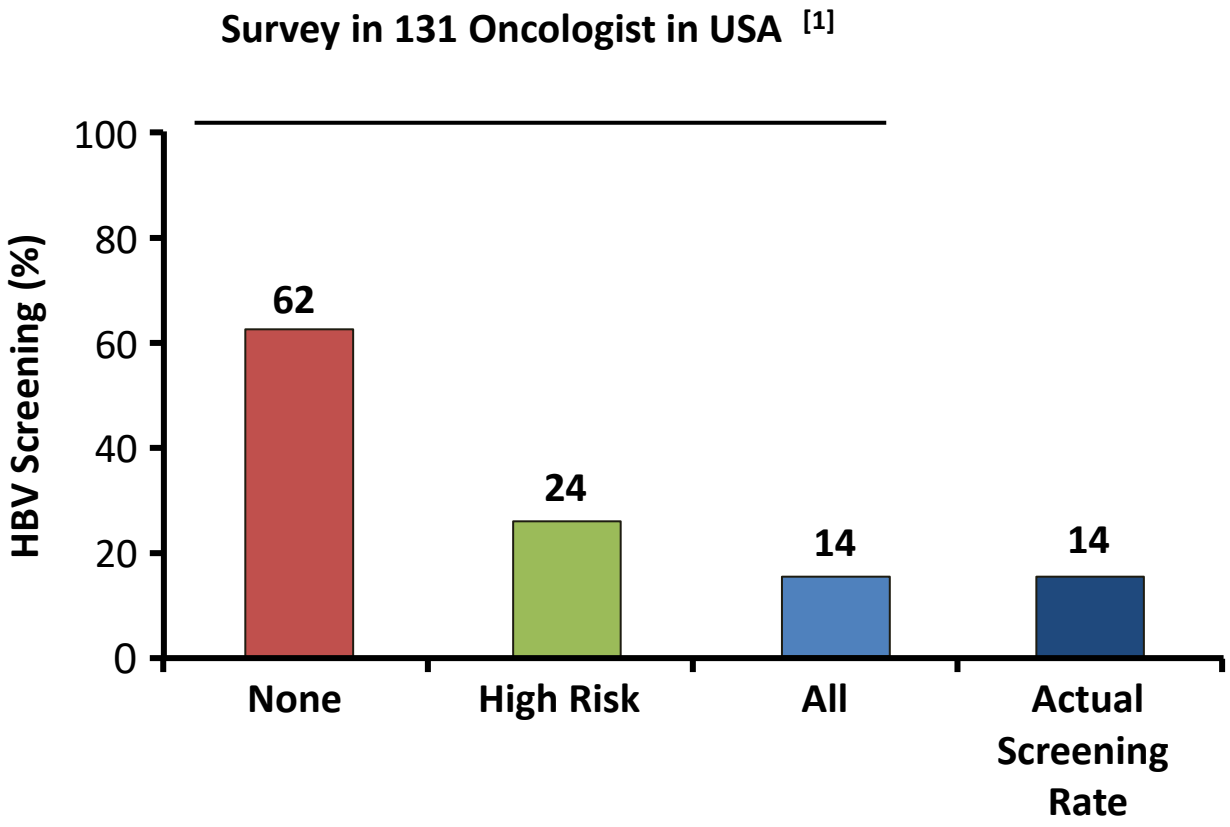
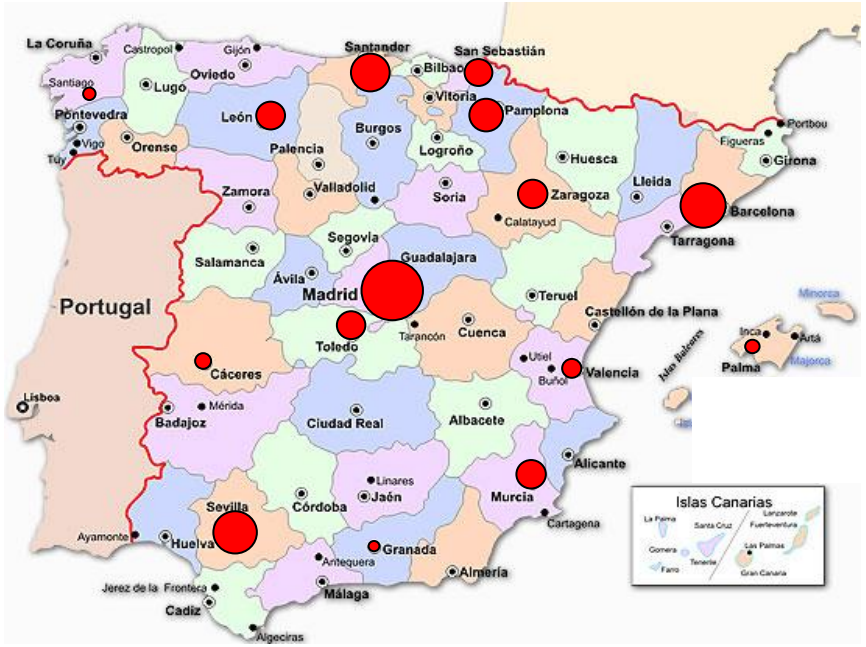
What we are doing ?



The majority of the Oncologist do not screen any patient for Hepatitis B

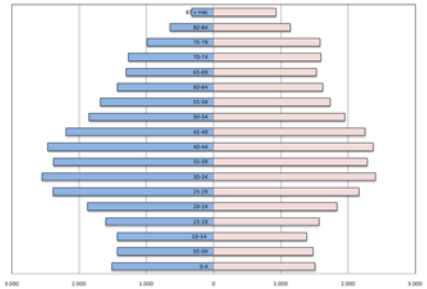
1. Khokhar OS, et al. Chemotherapy. 2009;55:69-75. 2. Lee R, et al. Curr Oncol. 2010;17:32-38.

HBV screening practices among 523 Medical Specialists in Spain: HEBRA Project



Specialty	n (%)
Hematology	131 (**25**)
Oncology	125 (**24**)
Gastroenterology	102 (**20**)
Rheumatology	68 (**13**)
Dermatology	63 (**12**)
Others	33 (**6**)

42 yr of age (25-68)



15 yr of professional experience

HBV screening practices among 523 Medical Specialists in Spain: HEBRA Project

- This surveys has noticed that **HBV screening practices vary among the medical specialties in Spain**.
- Of particular interest remark that **35% of respondents never or only sometimes requested the determination of HBsAg or anti-HBc**.
- This is particularly **evident in the oncology specialty** in which there was the lowest level of HBV screening (15 % of them).

Specialty	**Investigate risk factors linked to HBV infection**	**Request HBsAg**	**Request Anti-HBc**
All	*328 (63%)*	*341 (66%)*	*336 (65%)*
Hematology	94 (72%)	107 (82%)	107 (84%)
Oncology	**26 (21%)**	**18 (15%)**	**21 (17%)**
Gastroenterology	83 (82%)	90 (89%)	87 (85%)
Rheumatology	54 (79%)	52 (77%)	50 (75%)
Dermatology	46 (73%)	47 (75%)	48 (76%)
Chi square	**p<0.0001**	**p<0.0001**	**p<0.0001**

PRESCRIB Project: Phase 2 and 3; the CPOE

Phase 2: Implementation phase
(May - November 2012; N = 487)
VOLUNTARY SCREENING

↓

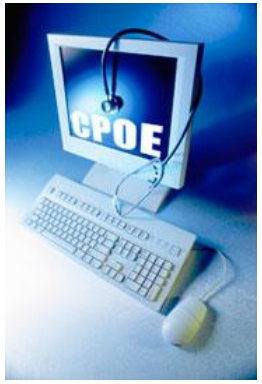
Phase 3: Universalization phase
(Nov. 2012 - May 2013; N = 506)
TARGETED SCREENING

- The **Phase 2 (Implementation Phase)** of this project started with the **creation of the new CPOE** (Computerized Physician Order Entry) **application**. This Phase took place from **May 2012 to November 2012 (6 months)** and specialists' participation was **voluntary**.

- In the **Phase 3 (Universalization Phase)** the participants were recruited with targeted screening conducted by the Hepatology Unit and had effect between **November 2012 and May 2013 (6 months)**.

- But, **what is exactly a CPOE system?**

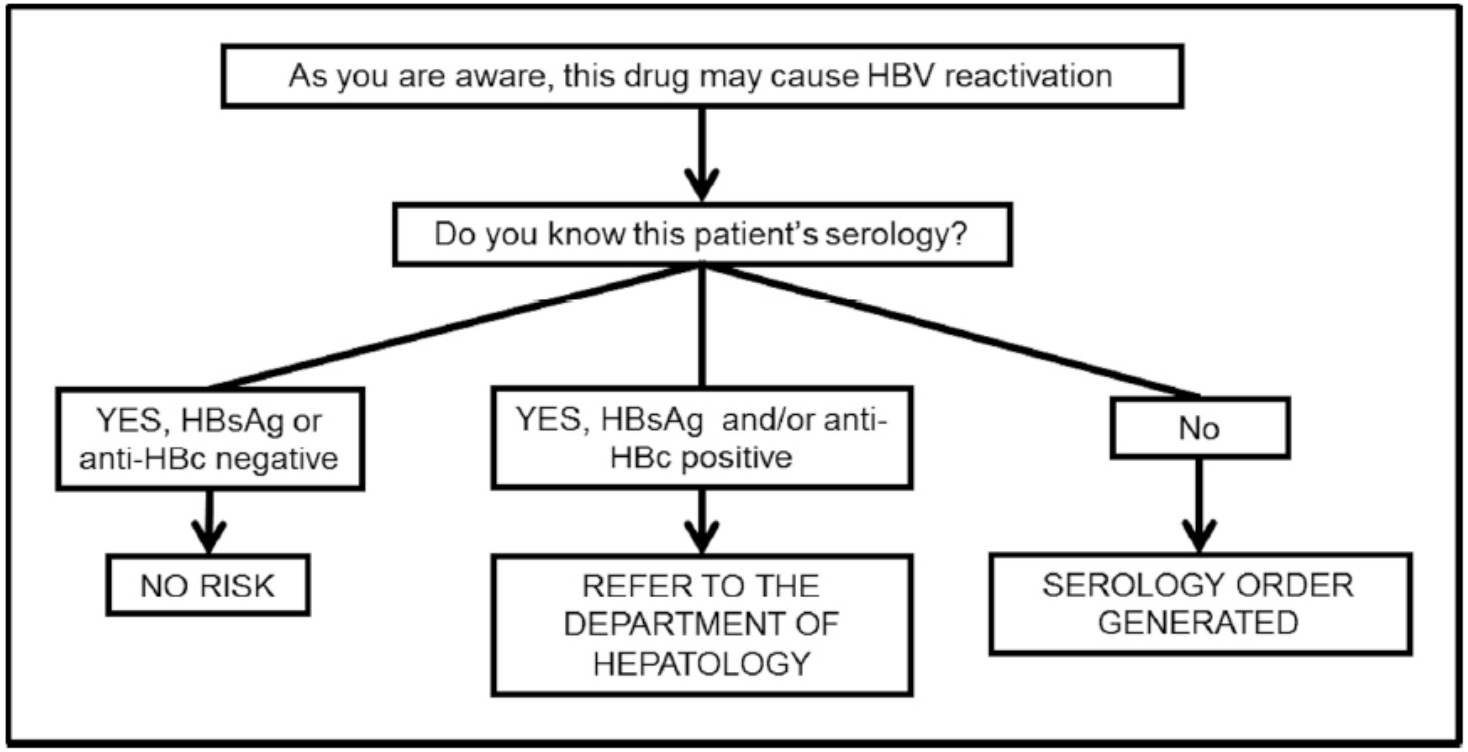
"CPOE is the process of entering medication orders and other physician's instructions electronically using a computer-based system to ensure standardized, legible and complete orders"



Sampedro Hepatology 2014; Al-Dorzi BMC Medical Informatics and Decision Making 2011

PRESCRIB Project: The CPOE system

- **Historically**, CPOE use has improved patient safety, **prevented medical errors**, and facilitated communication between physicians and pharmacists.
- The PRESCRIB Project established an **innovative strategy** which involves a protocol of **alerts for doctors who prescribe biological drugs (BDs), alerting them about the possibility of HBV reactivation**. The **algorithm** followed by the CPOE application for HBV screening is depicted below.



PRESCRIB Project: Impact and conclusions

- The PRESCRIB Project has shown that it is feasible to use CPOE in a 3rd level hospital, **increasing the HBV screening rate from less than 50% to 94% for HBsAg and from less than 30% to 85% for anti-HBc** in patients for whom a BD is prescribed.

- Consequently, this **cross-functional project demonstrates** the **feasibility of implementing a CPOE system*** in a hospital setting that has allowed **to increase the rate of HBV screening facilitating the identification of patients at high risk for HBV reactivation and permitted physicians to prescribe prophylactic measures** according to current guidelines.

- **Clinical pharmacologists in Europe** have a clear opportunity to lead this topic, thanks to our specific profile.

The AGA recommends antiviral prophylaxis over no prophylaxis for patients at high risk undergoing immunosuppressive drug therapy. *(Strong recommendation, Moderate-quality evidence)*

Comments: *Treatment should be continued for at least 6 months after discontinuation of immunosuppressive therapy (at least 12 months for B cell–depleting agents).*

The AGA suggests antiviral prophylaxis over monitoring for patients at moderate risk undergoing immunosuppressive drug therapy. (*Weak recommendation; Moderate-quality evidence)*

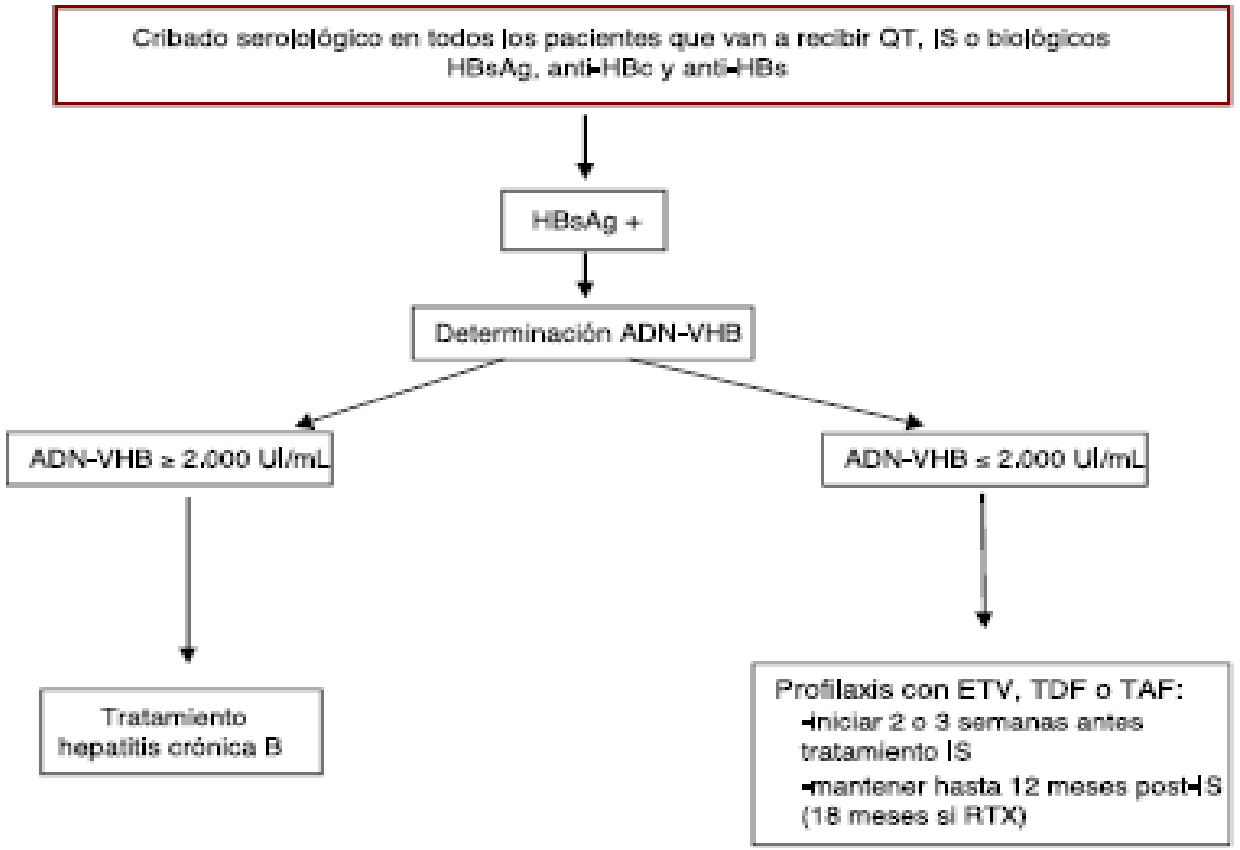
Comments: *Treatment should be continued for 6 months after discontinuation of immunosuppressive therapy. Patients who place a higher value on avoiding long-term use of antiviral therapy and the cost associated with its use and a lower value on avoiding the small risk of reactivation (particularly in those who are HBsAg negative) may reasonably select no prophylaxis over antiviral prophylaxis.*

The AGA suggests against routinely using antiviral prophylaxis in patients undergoing immunosuppressive drug therapy who are at low risk for HBVr. (*Weak recommendation; Moderate-quality evidence*)

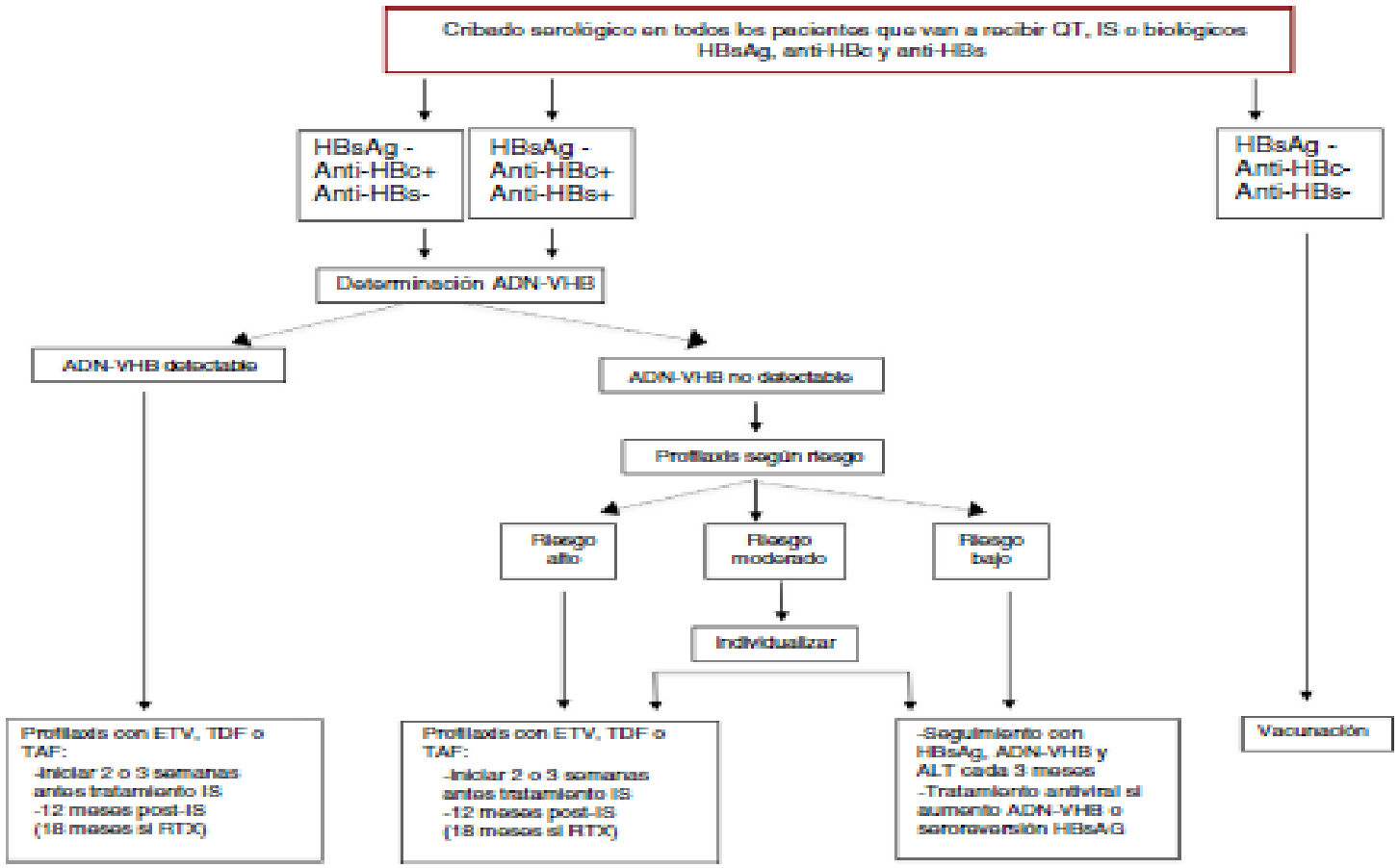
The AGA suggests use of antiviral drugs with a high barrier to resistance over lamivudine for prophylaxis in patients undergoing immunosuppressive drug therapy. (*Weak recommendation; Moderate-quality evidence*)

Reddy et al Gastroenterology 2015

Estrategia



Morillas RM Med Clin 2019



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VERY EASY CONCLUSIONS

- Screen ALL patients at risk
- Prophylaxis better than treatment
- Use last generation antiviral drugs
- Need for education and awareness in doctors, nurses and patients
- Electronic Prescription

MÁSTER EN HEPATOLOGÍA

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