Sistema Socio Sanitario
Ospedale Papa Giovanni XXIII
Regione Lombardia
ASST Papa Giovanni XXIII

Regione Lombardia
ASL Bergamo

Profilassi della riattivazione di HBV

Stefano Fagiuoli
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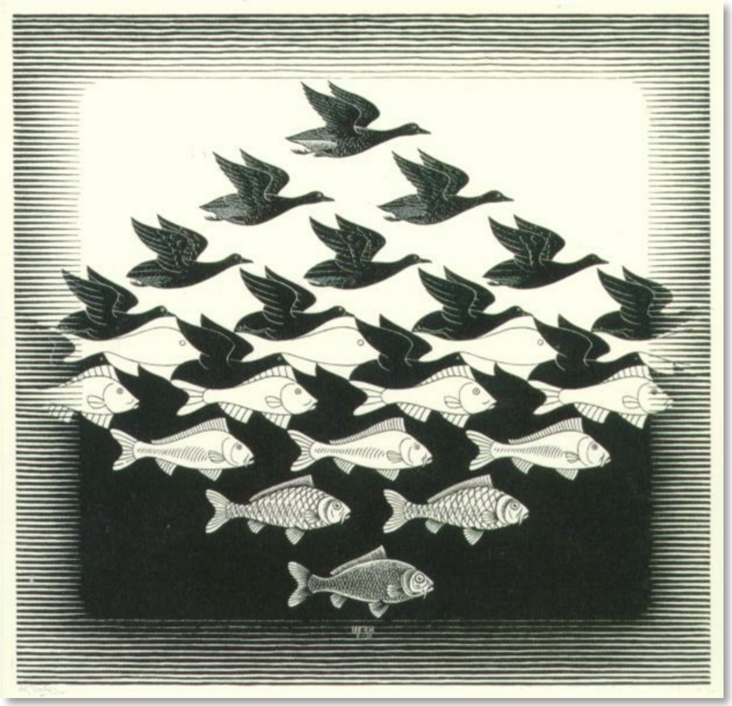

Gastroenterol Clin Biol 2006;30:307-309

CLINICAL CASE

Fatal hepatic decompensation in a bone marrow transplant recipient with HBV-related cirrhosis following lamivudine withdrawal

Annarosa FLOREANI (1), Sara BONINSEGNA (1), Salvatore LOBELLO (2), Diego CAROLI (1), Stefano FAGIUOLI (1)

(1) Department of Surgical and Gastroenterological Sciences,University of Padova ; (2) S. Antonio Hospital, ASL 16, Padova, Italy.

A 56-year-old Caucasian male with HBV-related cirrhosis was admitted to hospital in July 2004 with high ALT/AST.

- **Regularly attending a liver outpatient clinic since 1981 (HBsAg(+), HBeAg(-) anti-Hbe(+), HBV-DNA (-) (??), normal transaminases.**
- **LFT's remained stable until 1997: "hepatitis flare" (ALT x 10) HBV-DNA (+)**
- **HCV, HDV, HIV: neg**
- **June 1997: liver biopsy: Grading 10/18 Staging 6/6 (Ishak modified histology)**
- **No IFN treatment because of the prompt resolution of the flare with negativization of HBV-DNA by PCR.**

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January 2003: Diagnosis of multiple myeloma

- 100 mg a day of **lamivudine** (prophylaxis against HBV reactivation)
- One month after starting lamivudine, **three cycles of chemotherapy** with doxorubicin, vincristine and dexamethasone were given, leading to **complete remission** within six months.
- **Then an autologous bone marrow transplantation was performed.**

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2003

What to do with LAMIVUDINE????

1. **STOP (4 months from BMT)**
2. **Continue lifelong**
3. **Stop 6 months after BMT**
4. **Stop 12-18 months after BMT**

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Lamivudine was continued for a total of one year and was stopped 4 months after the bone marrow transplantation

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56-year-old Caucasian male with HBV-related cirrhosis was admitted to hospital in July 2004 with high ALT/AST.

Biochemical tests revealed: **AST 1960** U/L (N < 45), **ALT 1711** U/L (N < 50), **total bilirubin 169.8** µmol/L, **conjugate bilirubin 130.7 µmol/L**, **PT 59 %**

HBeAg (-)

HBV-DNA > 10^6 copies/mL. **no YMDD mutants**

HAV, HDV, HCV, and HIV: neg

Lamivudine 100 mg /day was started

Prophylaxis against viral, fungal, and bacterial infections was also given.

During the next 10 days: **AST/ALT peak to 3901 U/L and 2508 U/L in ALT. Total bilirubin rose to 500 µmol/L PT: 37%.**

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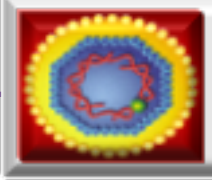
56-year-old Caucasian male with HBV-related cirrhosis was admitted to hospital in July 2004 with high ALT/AST.

On the 15th day in hospital:

- Developed fever (T = 38o),
- Chest X-ray revealed bilateral pulmonary interstitial pneumonia,
- The temperature chart suggested a septic clinical picture.

On the 23rd day: Exitus



HBV carrier

Decreased immune recognition of HBV-infected hepatocytes

While on Chemotherapy Immunosuppression

Increased HBV replication

- ↑ Serum HBV DNA
- ↑ Intrahepatic HBcAg
- ↑ Number of productively HBV-infected hepatocytes *(FCH-like)*

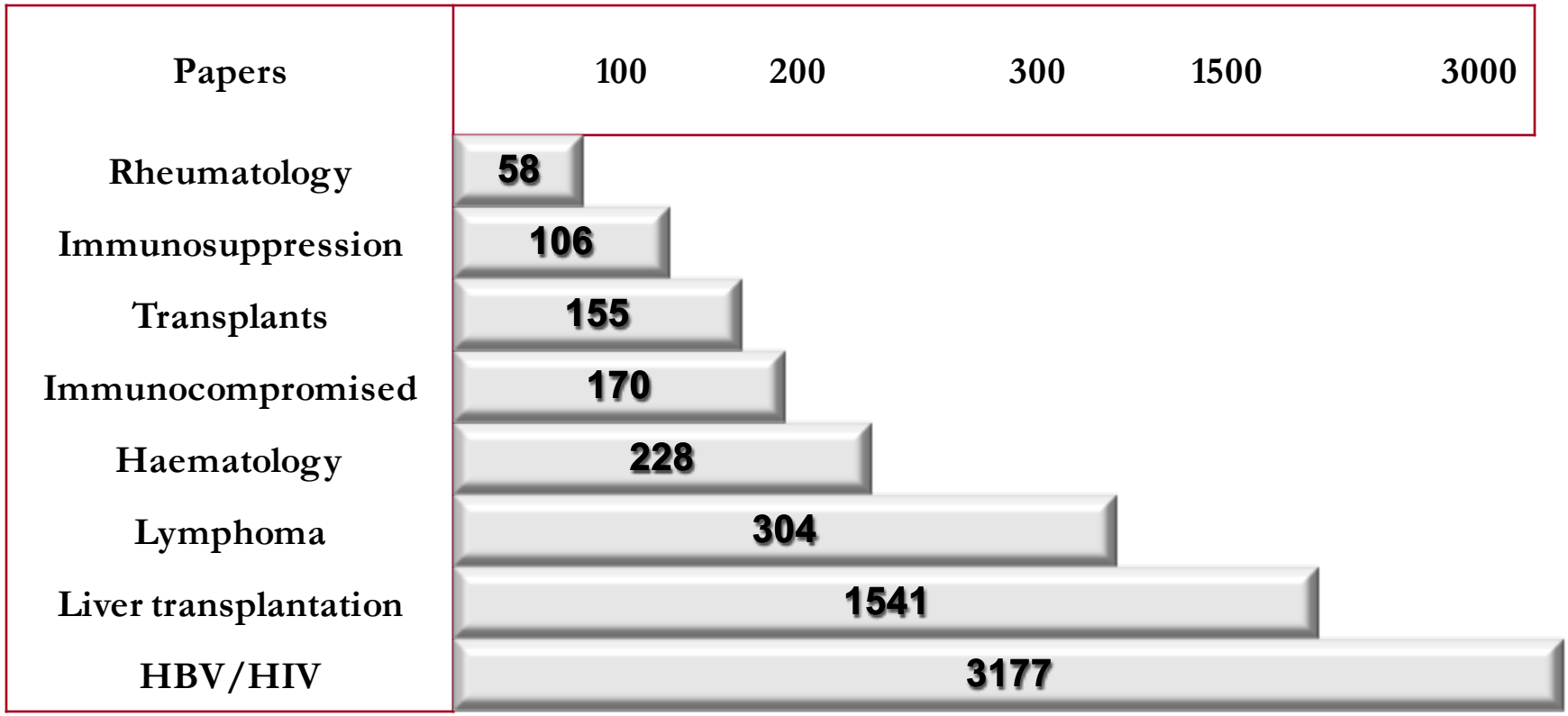
Rebound immune Recognition of HBV-infected Hepatocytes

After restored T-cell function upon Immunosuppression withdrawal (+++)

Hepatitis Flare*

**Severity according with pre-existing liver disease*

PubMed 25/9/2011
HBV and….



Speakers: 2008-2011 update

Basal Evaluation in immunocompromised patients – Virological Categories

	Active carrier
HBsAg	**+**
HBeAg	**-/+**
antiHBe	**-/+**
antiHBc	**+**
antiHBs	**-**
qHBsAg	**≥1000**
ALT	**Increased** *(persistent or intermittent)*
HBV DNA *(IU/mL) serum*	**> 2000**
HBV DNA *(IU/mL) liver*	+
Liver Stiffness *(kPa)*	**> 6 o ≤ 6^**

* *In absence of other causes of liver disease; steatosis*

°° *In the Mediterranea area about 1/3 of the Inactive Carriers maintains qHBsAg>1000 IU/mL and/or HBV DNA > 2,000/mL (grey zone*

^ *Normal transaminases in immunotollerant HBeAg-positive patients*

Basal Evaluation in immunocompromised patients – Virological Categories

	Active carrier	Inactive carrier
HBsAg	+	+
HBeAg	-/+	-
antiHBe	-/+	+
antiHBc	+	+
antiHBs	-	-
qHBsAg	≥1000	< 1000°°
ALT	**Increased** *(persistent or intermittent)*	**Normal***
HBV DNA *(IU/mL) serum*	> 2000	≤ 2000°°
HBV DNA *(IU/mL) liver*	+	+
Liver Stiffness *(kPa)*	> 6 o ≤ 6^	< 6*

* *In absence of other causes of liver disease; steatosis*

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Basal Evaluation in immunocompromised patients – Virological Categories

	Active carrier	Inactive carrier	pOBI (anti-core)
HBsAg	+	+	-
HBeAg	-/+	-	-
antiHBe	-/+	+	+
antiHBc	+	+	+
antiHBs	-	-	±
qHBsAg	≥1000	< 1000°°	-
ALT	**Increased** *(persistent or intermittent)*	**Normal***	**Normal***
HBV DNA *(IU/mL) serum*	> 2000	≤ 2000°°	-
HBV DNA *(IU/mL) liver*	+	+	+
Liver Stiffness *(kPa)*	> 6 o ≤ 6^	< 6*	<6*

* *In absence of other causes of liver disease; steatosis*

°° *In the Mediterranea area about 1/3 of the Inactive Carriers maintains qHBsAg>1000 IU/mL and/or HBV DNA > 2,000/mL (grey zone*

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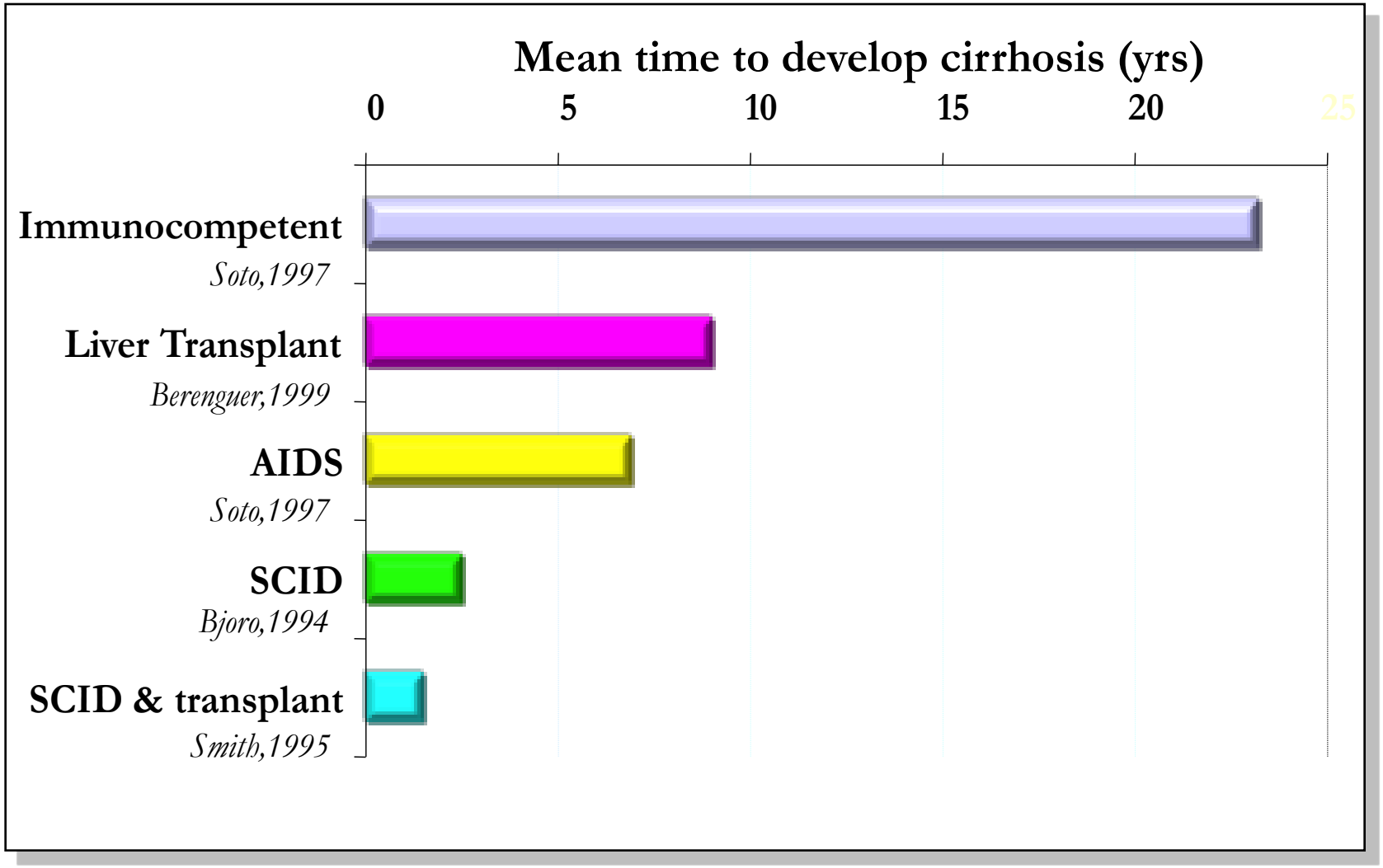
Disease evolution in immunocompromized individuals



***SCID**, Severe Combined Immuno Deficiencies*

HBcAb positive

The finding of **isolated anti-HBc** can occur for a variety of reasons:

(1) Anti-HBc may be an indicator of **chronic HBV infection** *(HBsAg had decreased to undetectable levels but HBVDNA often remains detectable, more so in the liver than in serum).*

(2) Anti-HBc may be a marker of **immunity** after recovery from a prior infection *(anti-HBs had decreased to undetectable levels but anamnestic response can be observed after one dose of HBV vaccine).*

(3) Anti-HBc may be a **false positive** test result particularly in persons from low prevalence areas with no risk factors for HBV infection.*(These individuals respond to hepatitis B vaccination similar to persons without any HBV seromarkers)*

(4) Anti-HBc may be the only marker of HBV infection during the **window phase** of acute hepatitis B *(These persons should test positive for anti-HBc IgM)*

AASLD PRACTICE GUIDELINES Chronic Hepatitis B: Update 2009 Anna S. F. Lok1 and Brian J. McMahon2

Haematology

Prevalence of HBV in Haematology

	HBV			
	HBsAg+		HBsAg- anti-HBc+	
	Europe	China	Europe	China
Range	**5.5-12.2%**	**30-40%**	**20-40%**	**70-80%**
Italy	**8.8%(I)- 12.2%(Gr)°**		**41.7%°**	
HBV Reactivation^	**24-88%** *(median 50%)*		**14-50%** *(HSCT-BMT)*	
Mortality	**20%**			
Lymphoma in carriers	OR 2.6 (China)-2.8 (USA) in B-NHL *Wang F et al, Cancer 2007; Ulcickas YM et al, Hepatology 2007*			

° *Marcucci et al ,Haematologica 2006*

Gadi Lalazar,[1] Deborah Rund[2] and Daniel Shouval[1]

2007 Blackwell Publishing Ltd, *British Journal of Haematology*, **136**, 699–712

Table II. Chemotherapeutic and immune modulating agents involved in hepatitis B virus reactivation and their potential for hepatotoxicity*.

Class	Agents associated with HBV reactivation	Potential hepatotoxicity
Alkylators	Cyclophosphamide	VOD, hepatocellular injury
	Ifosfamide	Hepatocellular injury, cholestasis
	Chlorambucil	Hepatocellular injury
	Carboplatin, cisplatin	hepatocellular injury, cholestasis, steatosis, peliosis
Antimetabolites	Cytarabine	VOD, hepatocellular injury
	Fluorouraril	Hepatocellular injury
	Gemcitabine	Hepatocellular injury, cholestasis
	Mercaptopurine	Hepatocellular injury, cholestasis
	Methotrexate	Hepatocellular injury, steatosis, fibrosis, hepatic neoplasm
	Thioguanine	VOD, hepatocellular injury, NRH, peliosis
Antitumor antibiotics	Anthracyclines	Hepatocellular injury, VOD
	Bleomycin	Steatosis
	Mitomycin C	VOD, steatosis
	Actinomycin D	VOD, steatosis
Corticosteroides	Prednisone/dexamethasone etc.	hepatomegaly (rare association)
Immunotherapy	Rituximab (anti-CD20)	Hepatocellular injury
	Alemtuzumab (anti-CD52)	Hepatocellular injury
	Infliximab (anti-TNF)	Hepatocellular injury, steatosis
Plant Alkaloids	Vincristine	VOD, hepatocellular injury
	Vinblastine	Hepatocellular injury
Others	Asparginase	Hepatocellular injury, steatosis
	Procarbazine	VOD
	Docetaxel	Hepatocellular injury
	Etoposide	Hepatocellular injury
	Fludarabine	Hepatocellular injury
	Imatinib Mesylate	Hepatocellular injury, cholestasis
	Interferon alpha	Hepatocellular injury

MONOCLONAL ANTIBODY THERAPY (anti-CD20 e anti-CD52)

The most frequently experienced **viral infections** were:

- ✓ **HBV (39.1%,** n=25)
- ✓ CMV (23.4%, n = 15)
- ✓ VZV (9.4%, n = 6)
- ✓ others (28.1%, n = 18)

- **HBV reactivation** accounted for **39%** of the reported cases

- About **52%** of the rituximab-related HBV reactivation resulted in **death** as a result of hepatic failure

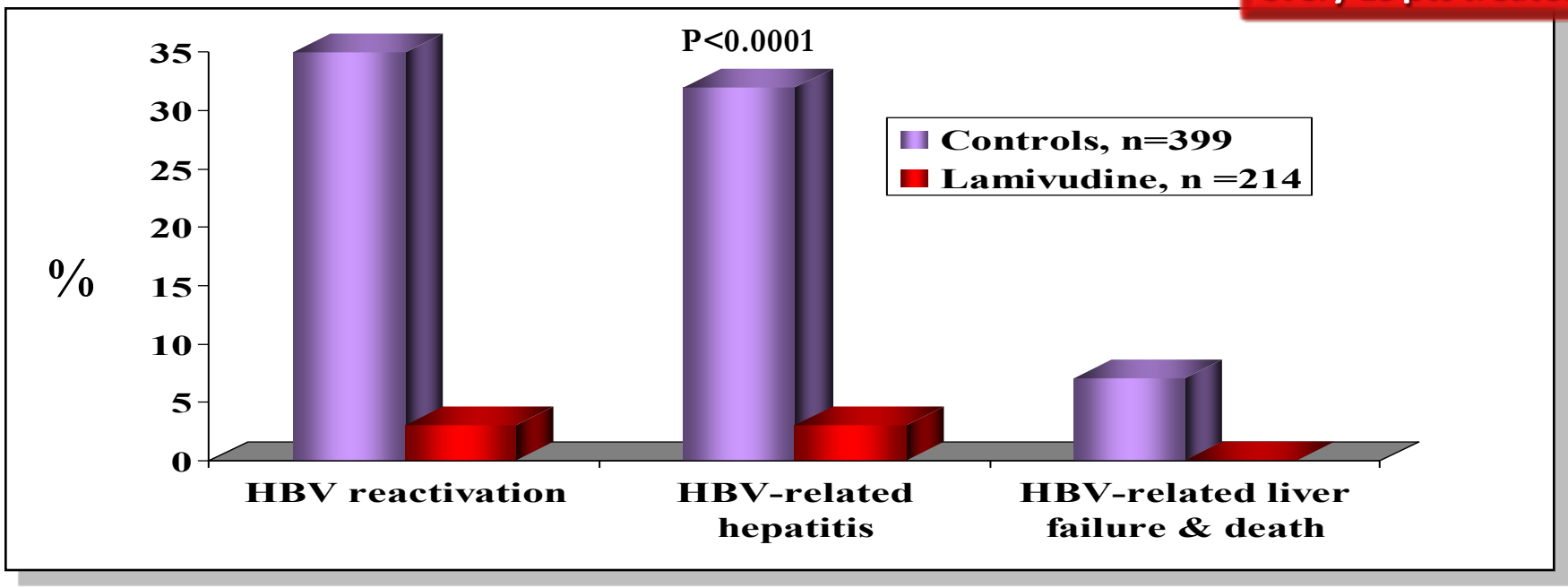
Blood, Nov 2009

Immunosuppressive drugs, virological category and risk of HBV reactivation

Risk grading	Drugs	HBsAg-positive	pOBI
High risk (≥ 10%)	Rituximab, Ofatumumab	X	X
	Anthracycline, Steroids > 10-20 mg > 4 weeks	X	
	Anti-TNF	X	
	Biological	X	
Medium risk (< 10%)	Steroids < 10 mg > 4 weeks	X	
	Steroids >10 mg > 4 weeks	X	X
Low risk (< 1%)	Traditional immunosuppressants *(Azathioprine, Methotrexate, 6 MP)*, Intra-articular steroids: • Steroids < 1 week, • Steroids < 10 mg > 4 weeks	X	X

- A **Meta-analysis** of all studies available on the Web, to estimate the beneficial effect of **pre-emptive Lamivudine in HBsAg+ cancer patients undergoing chemo-therapy**
- 12 trials evaluated, including 2 RCT, mostly in the Orient
- Data on 219 patients treated with pre-emptive lamivudine and 399 controls

LAM therapy:
1 death prevented every 15 pts treated



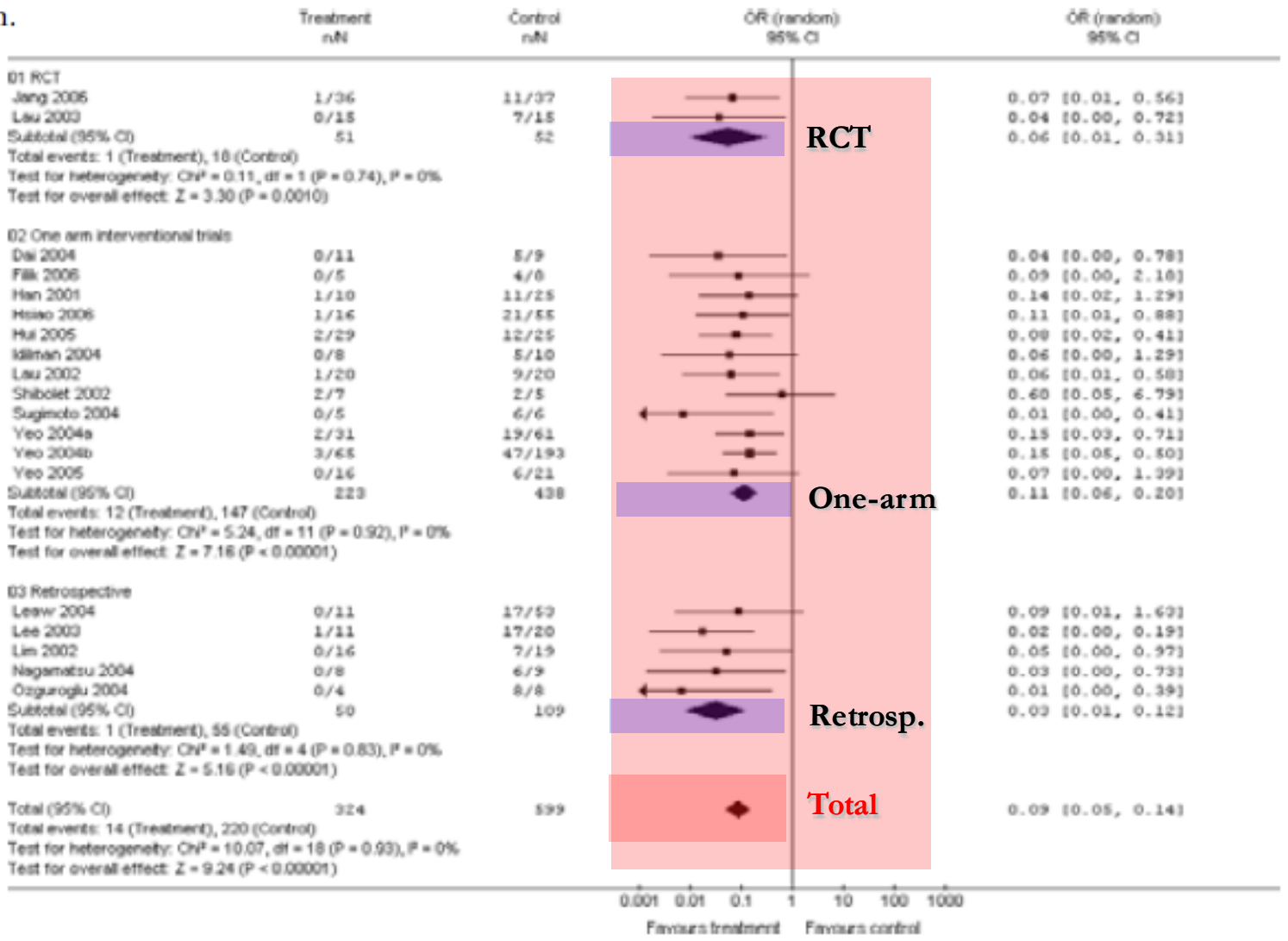
Loomba et al, Hepatology 2007; 657A (Boston 2007)

Lamivudine prevents reactivation of hepatitis B and reduces mortality in immunosuppressed patients: systematic review and meta-analysis

L. H. Katz,[1,4] A. Fraser,[2] A. Gafter-Gvili,[3,4] L. Leibovici[3,4] and R. Tur-Kaspa[1,4] [1]Department of Medicine

Journal of Viral Hepatitis, 2008, 15, 89–102

Clinical reactivation of hepatitis-B: lamivudine *vs* placebo or no intervention.



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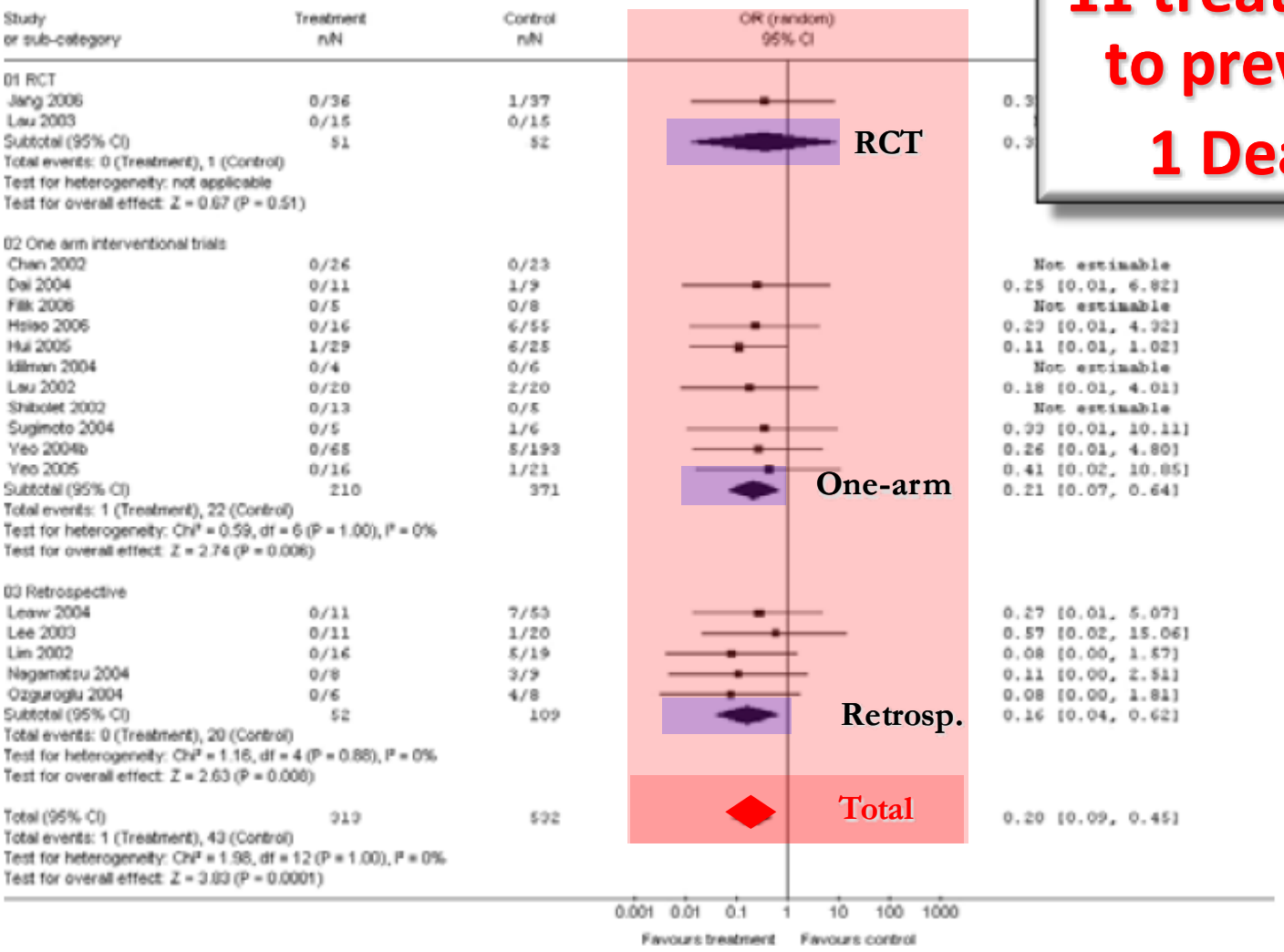
HBV-related mortality: lamivudine *vs* placebo or no intervention.



11 treatment to prevent 1 Death

Biol Blood Marrow Transplant 17: 1630-1637 (2011)

Changes of Hepatitis B Virus Serologic Status after Allogeneic Hematopoietic Stem Cell Transplantation and Impact of Donor Immunity on Hepatitis B Virus

Silvia Park,[1] Kihyun Kim,[1] Dong Hwan Kim,[1] Jun Ho Jang,[1] Seok Jin Kim,[1] Won Seog Kim,[1] Chul Won Jung,[1] Kwang Cheol Koh[2]

Reverse Seroconversion (RS) of HBV after ALLOGENEIC Transplantation:

Incidence 14 – 86%

Role of:

- Endemic areas
- Criteria for HBV screening
- Adoption of prophylaxis

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Reverse Seroconversion (RS) of HBV after ALLOGENEIC Transplantation: Incidence 14 – 86%

Role of:

- Endemic areas
- Criteria for HBV screening
- Adoption of prophylaxis

Reverse seroconversion (RS) of Hepatitis B virus (HBV) has been reported after allogeneic transplantation with an incidence of 14% to 86%. However, most prior studies on HBV RS were performed in HBV nonendemic areas. In this study, the frequency of HBV RS at a single center in Korea, endemic for HBV, was evaluated. Also, the influence of the donor's immunity for HBV on posttransplantation HBV serologic changes in recipients was also investigated. A total of 288 patients underwent allogeneic transplantation between February 1996 and June 2008. We retrospectively reviewed the medical records of 288 patients and their paired donors. Among the 268 HBsAg(−) patients, 205 were assessed for posttransplantation HBsAg, and 114 (55.6%) of 205 had HBcAb before transplantation. With a median follow-up of 77.9 months, 3 of 114 patients experienced HBV RS (2.6%). With regard to donor immunity, significantly more patients with anti-HBs(−) donors experienced anti-HBs loss ($P = .006$), and the donor anti-HBs showed significant protective effects against the anti-HBs loss with an HR of 0.4. HBV RS after allogeneic transplantation may not be as common in HBV endemic areas. Also, donor anti-HBs showed a significant favorable effect on maintaining HBV immunity in recipients.

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Table 1-1. Hepatitis B Markers before HSCT in Recipients

HBsAg	Anti-HBs	Anti-HBc	No. of patients (%)
Negative (n = 268)	Positive (n = 240)	Positive	146 (50.7)
		Negative	85 (29.5)
		Unknown	9 (3.1)
	Negative (n = 28)	Positive	2 (0.7)
		Negative	23 (8.0)
		Unknown	3 (1.0)
Positive (n = 20)	Negative (n = 20)	Positive	18 (6.3)
		Unknown	2 (0.7)

Table 1-2. Hepatitis B Markers before HSCT in Donors

HBsAg	Anti-HBs	Anti-HBc	No. of patients (%)
Negative (n = 249)	Positive (n = 132)	Positive	60 (20.8)
		Negative	65 (22.6)
		Unknown	7 (2.4)
	Negative (n = 92)	Positive	10 (3.5)
		Negative	78 (27.1)
		Unknown	4 (1.4)
	Unknown (n = 25)	Unknown	25 (8.7)
Positive (n = 6)	Negative (n = 6)	Positive	6 (2.1)
		Unknown	0 (0)
Unknown (n = 33)	Unknown (n = 33)	Unknown	33 (11.5)

288 HSCT

1996-2008

↓

205

Tested post HSCT

↓

185 anti S e/o anti Core

↓

3 SR (1,6%)

114 anti Core alone

↓

3 SR (2,6%)

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- HBV RS after allogeneic transplantation may **not be as common** in HBV endemic areas.
- Also, **donor anti-HBs** showed a significant **favorable effect** on maintaining HBV immunity in recipients.

Biol Blood Marrow Transplant 17: 1630-1637 (2011)

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Table 6. Rate of HBV RS in Comparison with Other Literatures

References	Rate of HBV RS	Median F/U Period	Nationality
Dhedin et al., Transplantation 1998	20.5% (4 of 37)	20 months	France
Seth et al., Bone Marrow Transplant. 2002	14% (6 of 42)	16 months	Saudi Arabia
Knoll et al., Bone Marrow Transplant. 2004	50% (3 of 6)	30 months	Germany
Onozawa et al., Transplantation 2005	50% (7 of 14)	48 months	Japan
Knoll et al., J Viral Hepatol. 2007	85.7% (6 of 7)	53 months	Germany
Sarah et al., Blood Marrow Transplant. 2009	19.7% (12 of 61)	17 months	USA

HBV RS indicates hepititis B reverse seroconversion; F/U, follow-up.

…… different **epidemiology** for HBV infection, suggest to us that the **data from nonendemic regions might significantly differ** from the data collected in endemic regions.

In addition, it seems that HBV reactivation after allo-HSCT is a less common complication in HBV endemic areas.

HSCT and HBV: role of vaccination on RS

Transpl Infect Dis 2014: **16:** 797–801

Hepatitis B virus (HBV) reverse seroconversion (RS) can be prevented even in non-responders to hepatitis B vaccine after allogeneic stem cell transplantation: long-term analysis of intervention in RS with vaccine for patients with previous HBV infection

M. Takahata[1], S. Hashino[2], M. Onozawa[1], A. Shigematsu[1], J. Sugita[1], K. Fujimoto[1], T. Endo[1], T. Kondo[1], J. Tanaka[3], M. Imamura[4], T. Teshima[1]

Trial HSCT in anti Core +

21 vax vs **25** non vax

3-dose Vax:

After discontinuation of immunosuppression

Patient characteristics

	Non-vaccine group	Vaccine group	*P*-value
Number	25	21	
Male/Female	13/12	11/10	0.98
Median age, years (range)	38 (22–65)	51 (24–68)	0.02
Median follow-up, months (range)	49 (16–245)	67 (13–102)	0.15
Anti-HBs on pre-HSCT, mIU/mL (range)	112.9 (0.1–986)	20.6 (0.2–295)	0.094
MAC/RIC	20/5	8/13	0.004
Acute GVHD			
Grade 0–I	16	12	0.64
Grade II–IV	9	9	
Chronic GVHD	17	11	0.37
IST[1]	3[2]	2[3]	0.79

Characteristics of vaccine group

	Responder	Non-responder	*P*-value
Number	9	12	
Age, years (range)	51 (26–54)	51 (25–68)	0.73
Antibody value, IU/mL (range)			
Pre-HSCT	24.7 (5.6–295)	20.1 (0.2–128)	0.16
Pre vaccine	24.7 (0.2–150)	0.12 (0–12.7)	0.007
2nd line HB vaccine	1	4	0.24
MAC/RIC[1]	5/4	3/9	0.38
aGVHD	7	7	0.35
Grade II–IV	5	4	0.31
cGVHD	4	7	0.43
IST	1	1	0.83
HSCT-Vac (months)	12 (6–39)	17.5 (10–79)	0.52
CD4 (/μL)	274 (94–739)	354 (51–657)	0.45

MAC/RIC: myeloablative/reduced intensity conditioning;

HSCT and HBV: role of vaccination on RS

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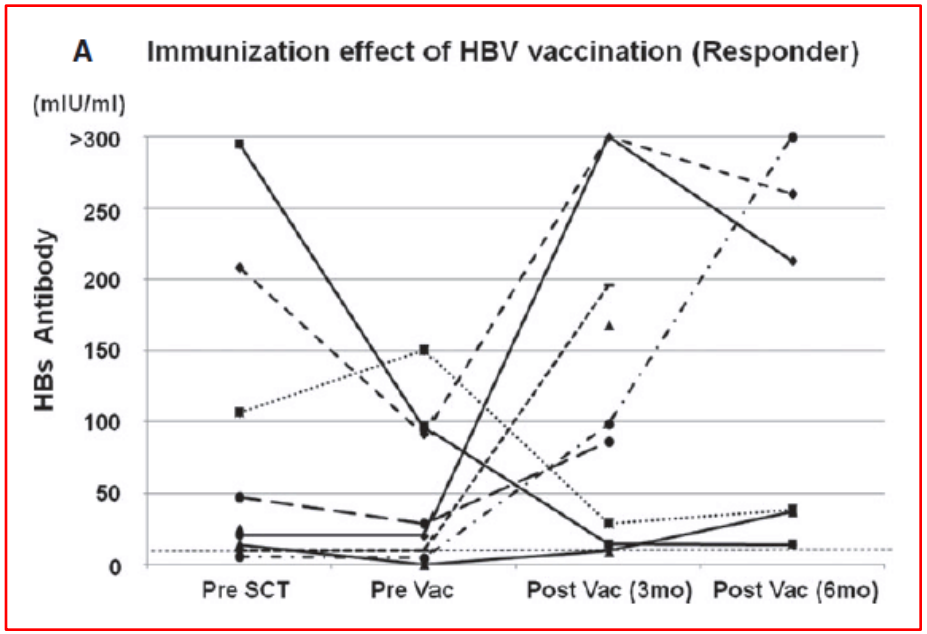
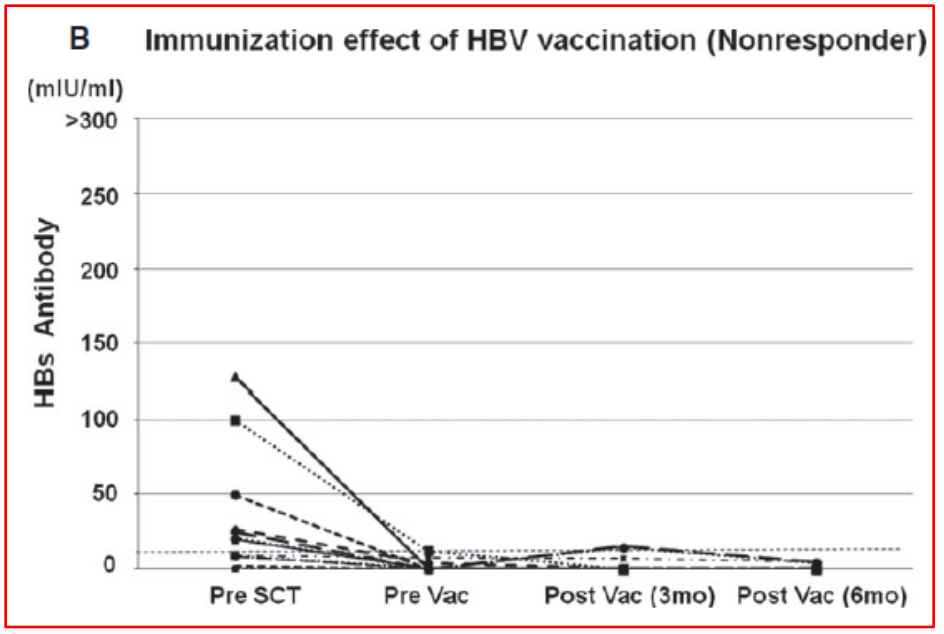
VAX:

Effect of vaccination on anti HBs levels





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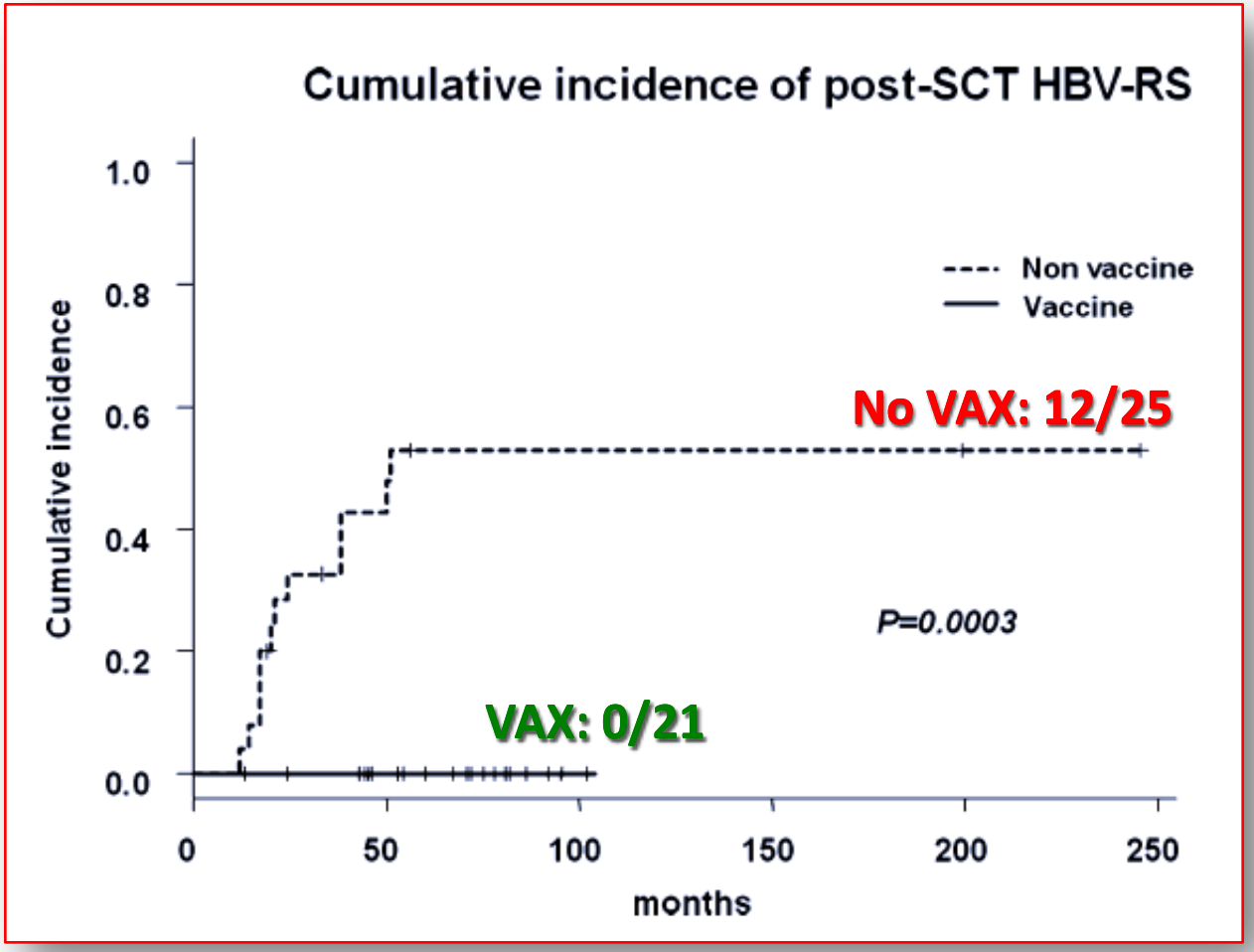

HSCT and HBV: role of vaccination on RS

Transpl Infect Dis 2014: **16:** 797–801

Hepatitis B virus (HBV) reverse seroconversion (RS) can be prevented even in non-responders to hepatitis B vaccine after allogeneic stem cell transplantation: long-term analysis of intervention in RS with vaccine for patients with previous HBV infection

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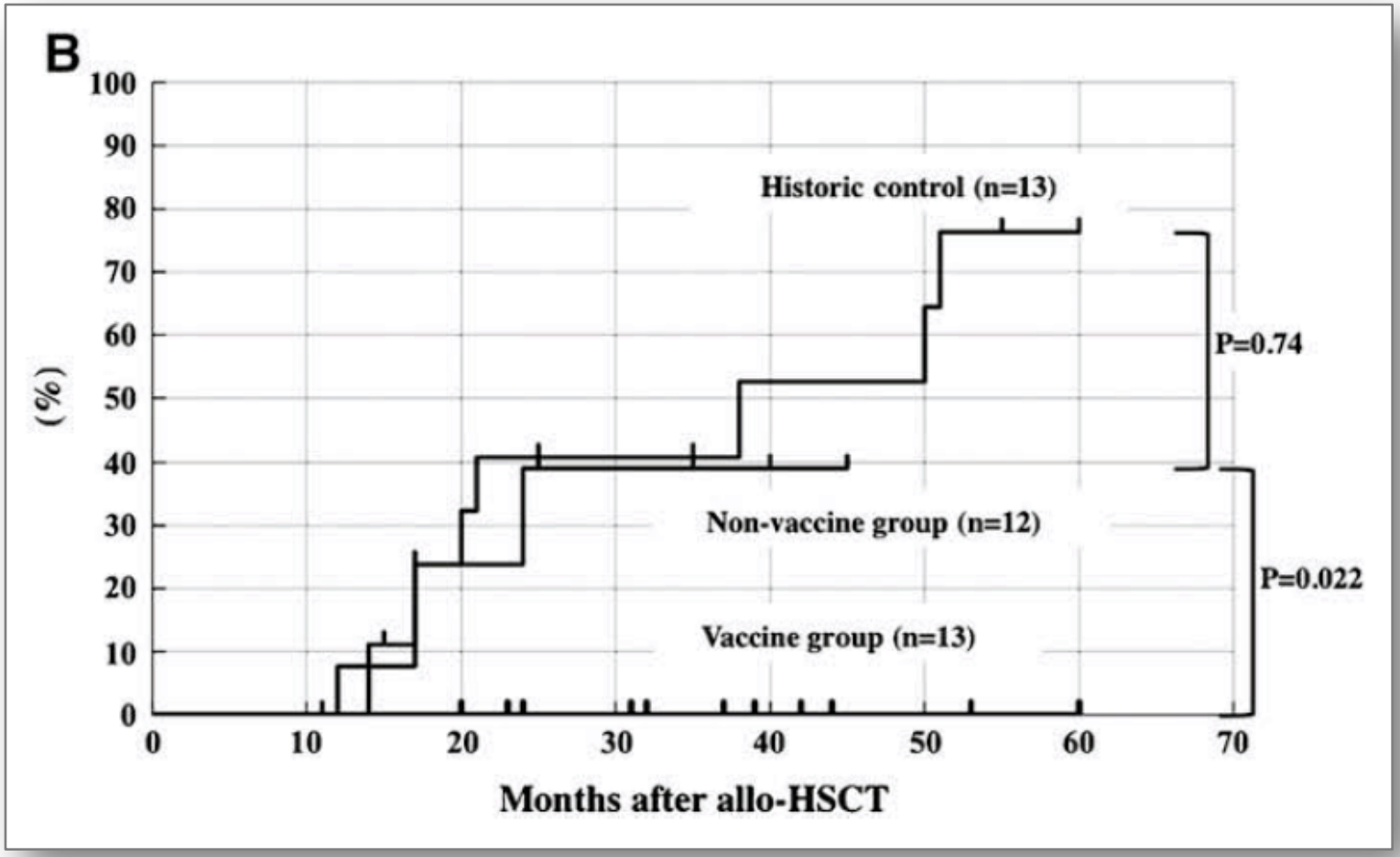
Conclusion. These results demonstrated the long-term effects of HBV vaccine for preventing HBV-RS after alloHSCT. Of note, no HBV-RS occurred, even in patients who did not achieve conversion into HBsAb positivity after vaccination.

HSCT and HBV: role of vaccination on RS

Biol Blood Marrow Transplant 14:1226-1230, 2008

HB Vaccination in the Prevention of Viral Reactivation in Allogeneic Hematopoietic Stem Cell Transplantation Recipients with Previous HBV Infection

Masahiro Onozawa,[1] Satoshi Hashino,[1] Stephanie Darmanin,[1] Kohei Okada,[1] Rena Morita,[1] Mutsumi Takahata,[1] Akio Shigematsu,[2] Kaoru Kahata,[1] Takeshi Kondo,[1] Junji Tanaka,[2] Masahiro Imamura,[2] Masahiro Asaka[1]

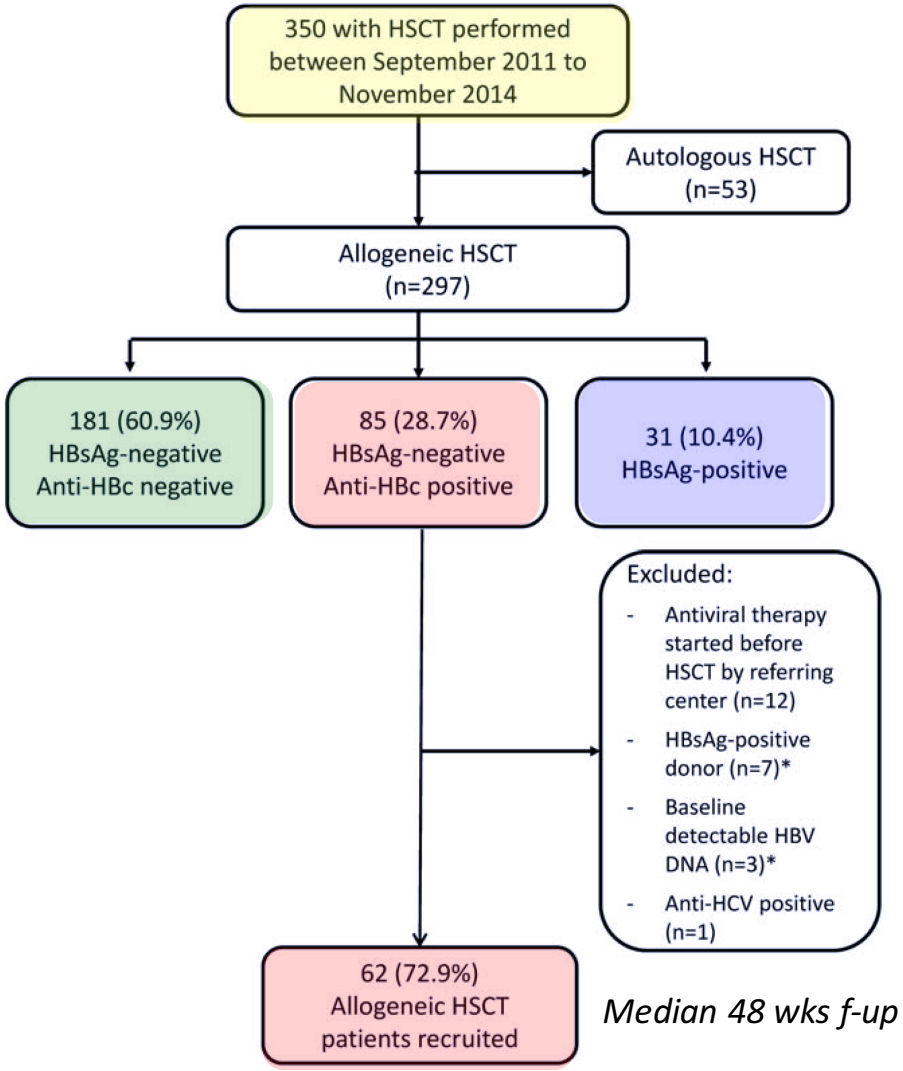


HSCT in anti HBc+ pts

HEPATOLOGY VOL. 65, NO. 5, 2017

Hepatitis B Reactivation in Occult Viral Carriers Undergoing Hematopoietic Stem Cell Transplantation: A Prospective Study

Wai-Kay Seto,[1,2] Thomas Sau-Yan Chan,[1] Yu-Yan Hwang,[1] Danny Ka-Ho Wong,[1,2] James Fung,[1,2] Kevin Sze-Hang Liu,[1] Harinder Gill,[1] Yuk-Fai Lam,[1] Eric H.Y. Lau,[3] Ka-Shing Cheung,[1] Albert K.W. Lie,[1] Ching-Lung Lai,[1,2] Yok-Lam Kwong,[1] and Man-Fung Yuen[1,2]



Median 48 wks f-up

Primary endpoint:

- HBV reactivation (*detectable HBV-DNA (10 IU/mL)*)

Secondary endpoints

- Overall survival,
- HBsAg positivity,
- Changes in liver biochemistry and antiHBs levels

HSCT in anti HBc+ pts

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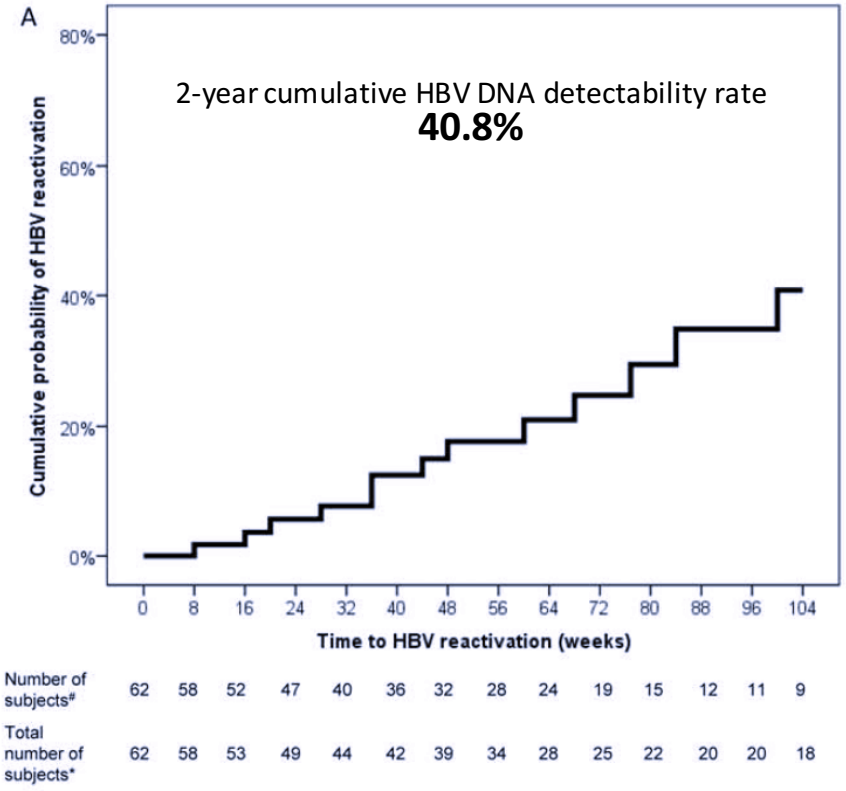
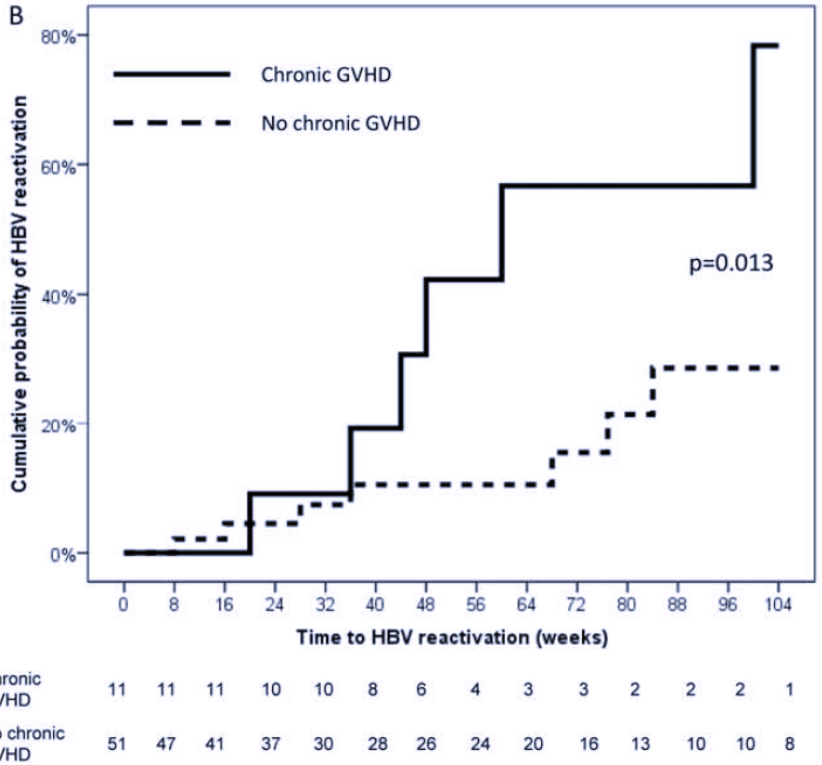
OVERALL

HBV DNA detectability rate



Chronic GVHD

HBV DNA detectability rate



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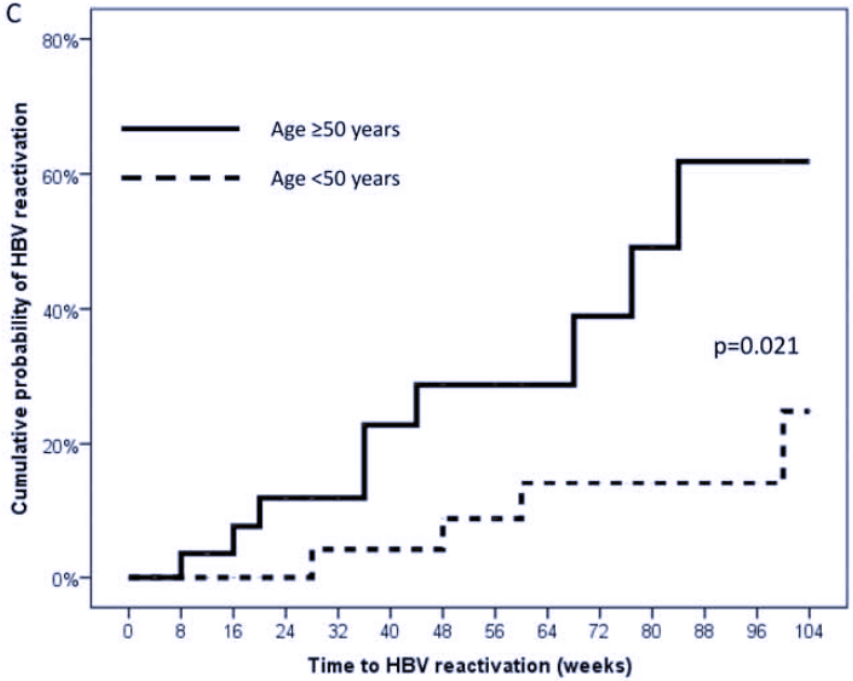
AGE

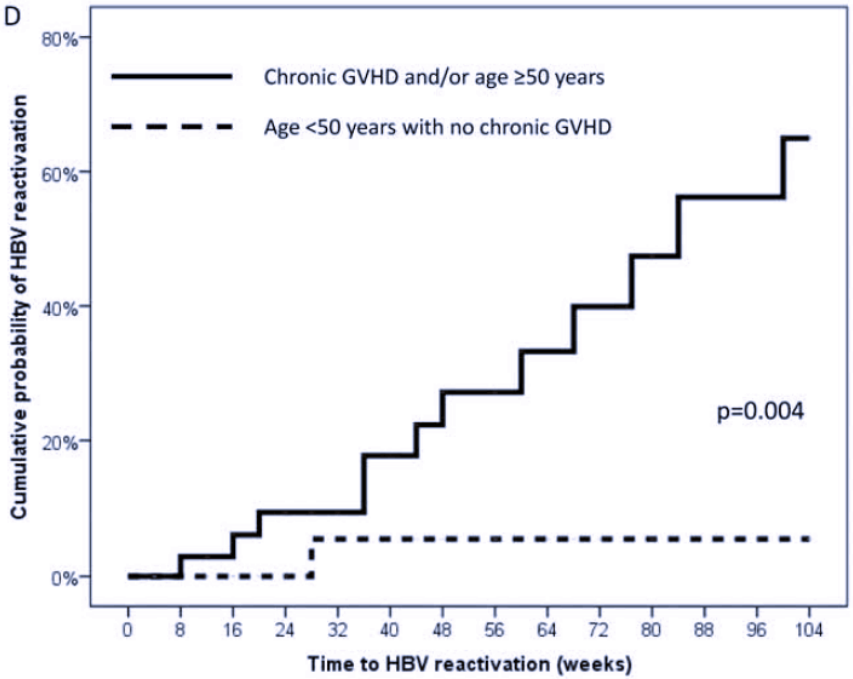
HBV DNA detectability rate



Age ≥50 years	28	28	24	22	17	13	11	9	7	6	5	3	3	2
Age <50 years	34	30	28	25	23	23	21	19	16	13	10	9	9	7

Chronic GVHD & AGE

HBV DNA detectability rate



Chronic GVHD and/or age ≥50 years	34	34	30	28	23	19	16	13	10	9	7	5	5	3
No chronic GVHD & age <50 years	28	24	22	19	17	17	16	15	13	10	8	7	7	6

HSCT in anti HBc+ pts

HEPATOLOGY VOL. 65, NO. 5, 2017

Hepatitis B Reactivation in Occult Viral Carriers Undergoing Hematopoietic Stem Cell Transplantation: A Prospective Study

NOT associated with reactivation

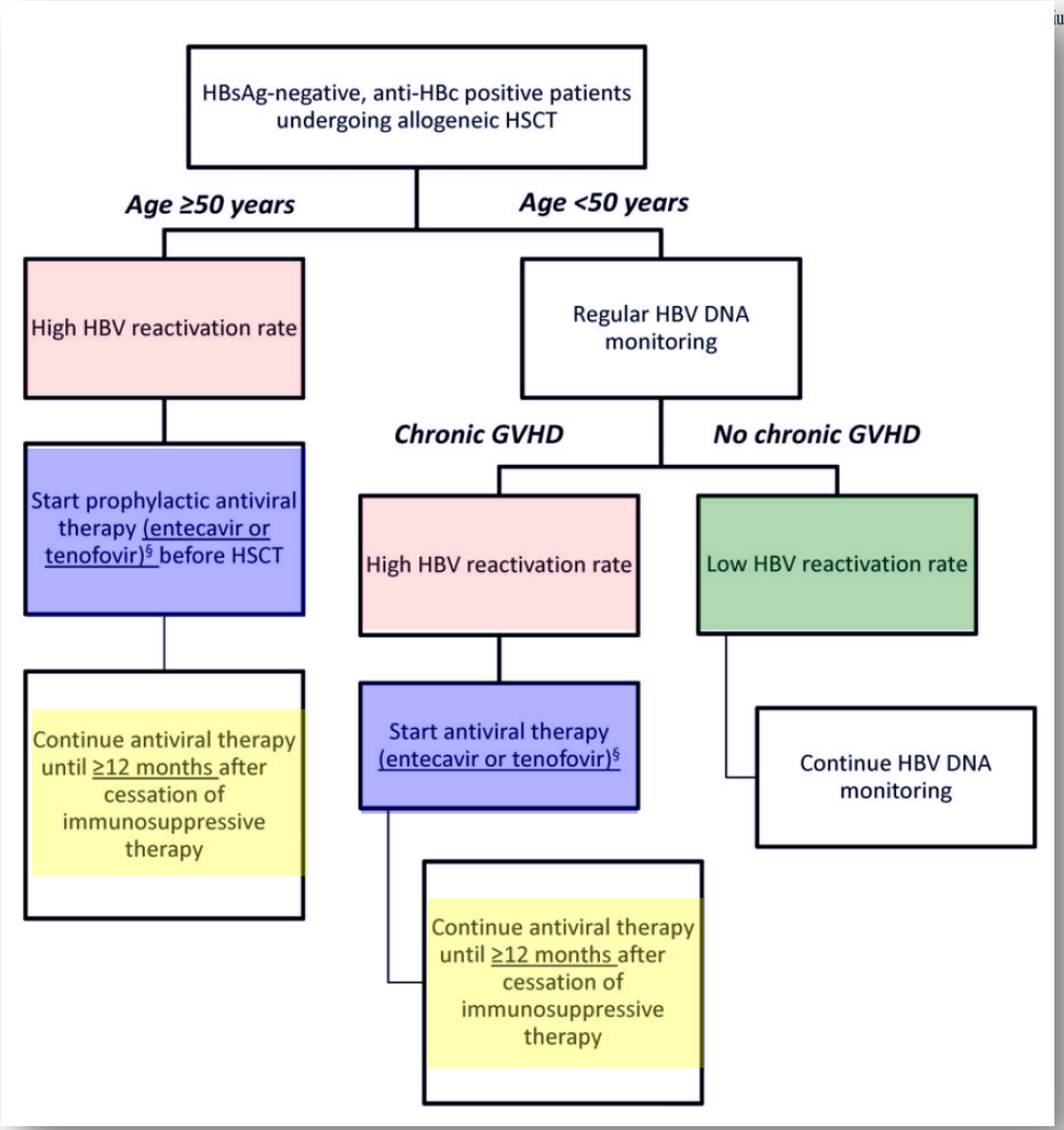
- *Baseline antiHBs ststus*
- *Serial changes in anti HBs levels*
- *Donor serology*

Age <50 yrs & No Chronic GVHD

Lower 2-yr HBV reactivation rate (**5.6%** versus **65.0%**, P 5 0.004).

Entecavir successfully suppressed HBV DNA to undetectable levels,

NO cases developing biochemical hepatitis.



HSCT in anti HBc+ pts

VIROLOGY *Clin Microbiol Infect* 2014; **20**: O694–O701

Hepatitis B reactivation in HBsAg-negative/HBcAb-positive allogeneic haematopoietic stem cell transplant recipients: risk factors and outcome

M. Mikulska[1,2], L. Nicolini[1], A. Signori[2], G. Rivoli[1], V. Del Bono[1], A. M. Raiola[3], C. Di Grazia[3], A. Dominietto[3], R. Varaldo[3], A. Ghiso[3], A. Bacigalupo[3] and C. Viscoli[1,2]

764 HSCT

↓

137 *(18%)*

HBsAg(-) / anti Core(+) pre tx

↓

14 (10%)

HBV reactivation *[median 19 m (9-77)]*

No difference between antiHBc(+) and anti HBc(-) in:

- *Survival*
- *NRM*
- *GVHD*

NRM: non-relapse mortality

HSCT in anti HBc+ pts

VIROLOGY Clin Microbiol Infect 2014; 20: O694–O701

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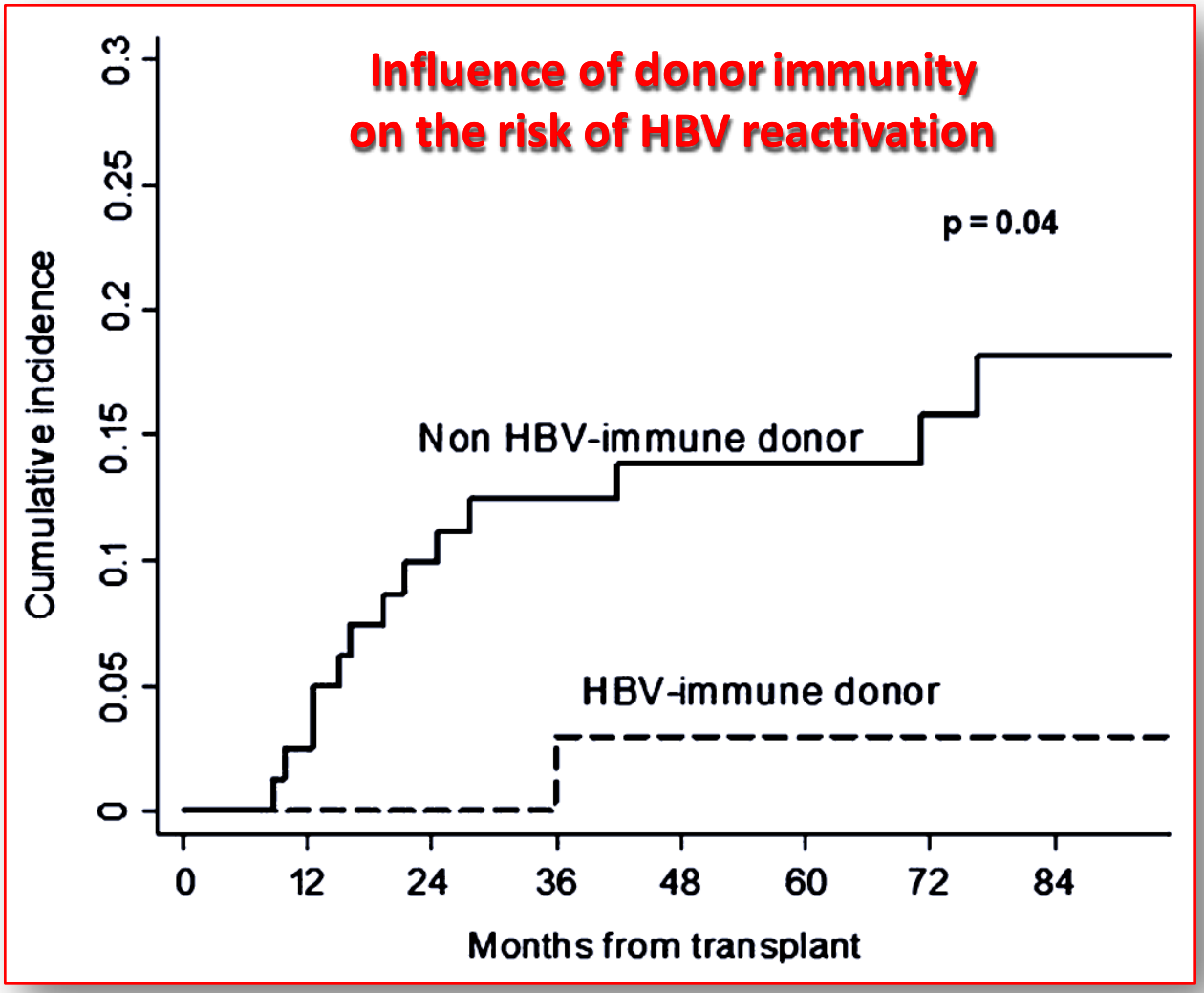

Cause-specific hazard for reactivation

- **Rituximab** treatment *(HR adjusted = 2.91; p 0.11).*
- **Length** of treatment with cyclosporine *(p <0.001)*

HSCT in anti HBc+ pts

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- No differences in **overall survival** and **NRM** were found between patients with and without **HBV reactivation**.
- **Donor's immunity** was independently and consistently associated with a **decreased risk of HBV reactivation**,
- **Rituximab** and **cyclosporine** treatments increased the probability.

HBV and HSCT

Clinical Microbiology and Infection 22 (2016) 946.e1–946.e8

Persistent risk of HBV reactivation despite extensive lamivudine prophylaxis in haematopoietic stem cell transplant recipients who are anti-HBc-positive or HBV-negative recipients with an anti-HBc-positive donor

C. Cerva [1,4], L. Colagrossi [2,4], G. Maffongelli [1], R. Salpini [2], D. Di Carlo [2], V. Malagnino [1], A. Battisti [2], A. Ricciardi [1], M. Pollicita [2], A. Bianchi [1], A. Picardi [3], L. Cudillo [3], R. Cerretti [3], G. De Angelis [3], M. Cantonetti [3], M. Andreoni [1], C.F. Perno [2], W. Arcese [3], V. Svicher [2,4], L. Sarmati [1,*,4]

57

10 Auto HSCT
27 Allo HSCT
Anti HBc +

2 Auto HSCT
3 Allo HSCT
Inactive Carriers

15 Allo HSCT
Anti HBc donor

47 (82,4%)
LAM prophylaxis

2 Reactivations
3,5%

320

Anti HBc - **Auto HSCT**

NO
LAM prophylaxis

2 Reactivations
0,6%

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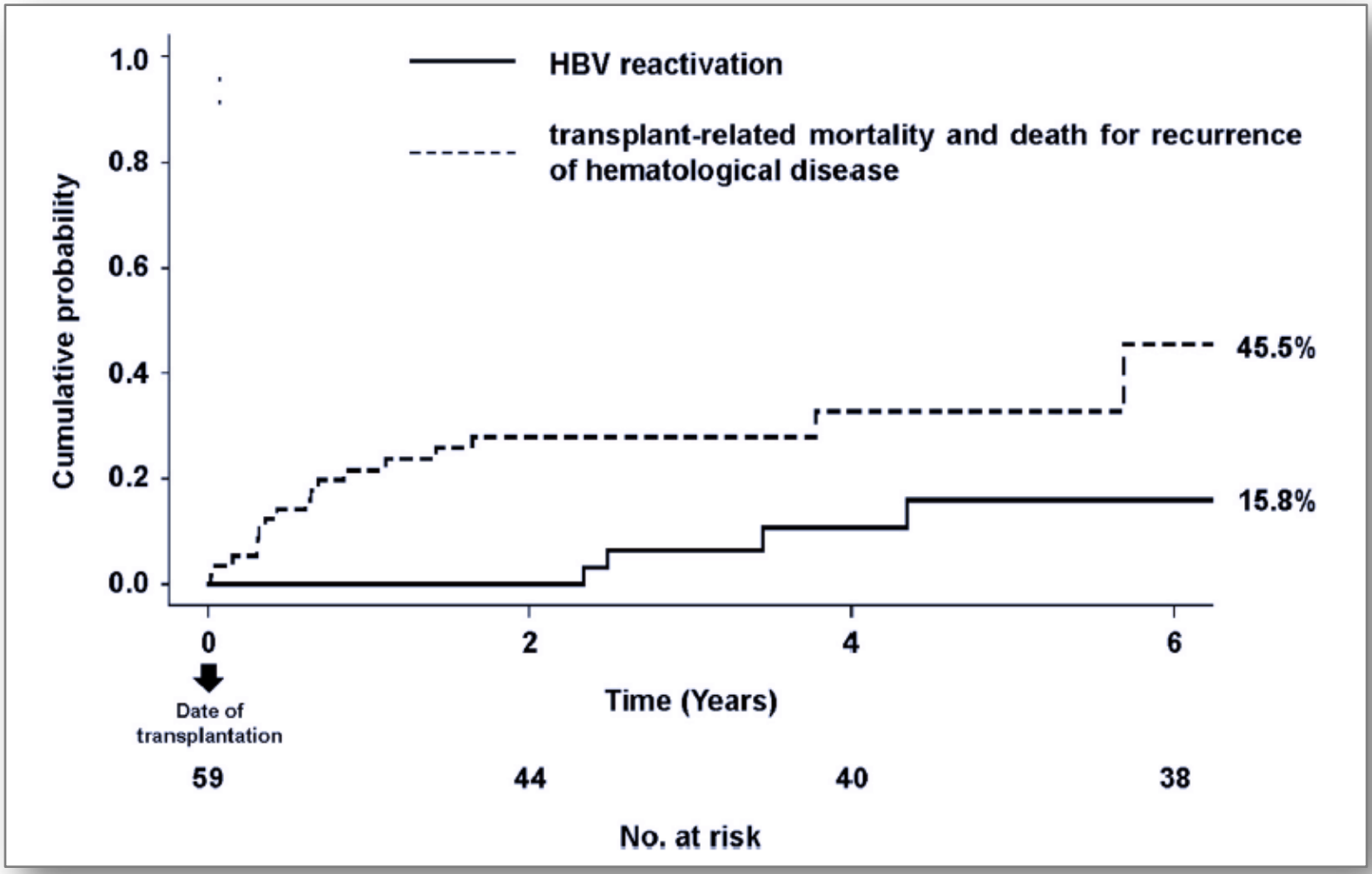
Cumulative Probability of events



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Features of the 4 HBV reactivating pts

ID_Patient	1	2	3	4
Clinical characteristics				
HBV serological status [a]	Anti-HBc and anti-HBs positive	Negative	Negative [a]	Negative
N of HSCT before HBV-R	2	1	2	1
HSCT type	Autologous/allogeneic	Allogeneic	Autologous/allogeneic	Autologous
Donor's HBV serological status [a,b]	NA/anti-HBc and anti-HBs positive	Anti-HBc alone	NA/negative	NA
Months from disease diagnosis to HBV-R	71	36	39	62
Months from first HSCT to HBV-R	41	30	12	52
Outcome	—	Dead	Dead	—
GvHD concomitant	Yes	No	Yes	—
LMV prophylaxis	Yes (41 months)	No	No	No
Virological characteristics				
Genotype	D	D	D	F
HBV-DNA Log (IU/mL)	5.97	3.24	5.08	8.94
ALT (U/L)	31	2159	361	61
AST (U/L)	29	2570	203	31
HBsAg quantitative (IU/mL)	>52 000	Negative	4029	>52 000
HBsAg mutations associated with immune escape	None	V96A/V, M103I, T123N, C124Y, T126I, G145 K/R	D144E	R122K, T140S
RT mutations associated with drug resistance	L80I	A181S, V214A	None	None

HBV and HSCT

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In a HSCT population carefully evaluated for HBV prophylaxis, a risk of HBV reactivation persisted in the group of patients who were **not LMV treated**.

Management strategies according with virological profile

	Active carrier
HBsAg	**+**
HBV DNA (IU/ml)	**> 2000**
LS (KPa)	**> 6 o < 6^**
Reactivation risk > 10%	**+++**
Drug treatment	ETV or TDF (TAF)
Duration of treatment	Indefinite

* in the absence of other causes of liver disease;
^ immunotolerant;
°° after discontinuation of immunosuppressant and regression/control of underlying disease:
§ anti-CD 20 used in onco-haematological disease.
** If a quarterly virologic monitoring cannot be guaranteed during prophylaxis;
IS: immunosuppression. TDF; tenofovir disoproxil fumarate; TAF: Tenofovir Alafenamide; ETV: Entecavir; LAM: Lamivudine; LS: Liver stiffness.

Management strategies according with virological profile

	Active carrier	Inactive carrier
HBsAg	**+**	**+**
HBV DNA (IU/ml)	**> 2000**	**Positive (≤2000)**
LS (KPa)	**> 6 o < 6^**	**<6***
Reactivation risk > 10%	**+++**	**++**
Drug treatment	ETV or TDF (TAF)	ETV
Duration of treatment	Indefinite	Prophylaxis for at least 12 months °°

* in the absence of other causes of liver disease;
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Management strategies according with virological profile

	Active carrier	Inactive carrier	Inactive Carrier
HBsAg	**+**	**+**	**+**
HBV DNA (IU/ml)	**> 2000**	**Positive (≤2000)**	**Negative (Undetectable)**
LS (KPa)	**> 6 o < 6^**	**<6***	**< 6***
Reactivation risk > 10%	**+++**	**++**	**+**
Drug treatment	ETV or TDF (TAF)	ETV	LAM *(HBV DNA monitoring)* or ETV**
Duration of treatment	Indefinite	Prophylaxis for at least 12 months °°	Prophylaxis for at least 12 months °°

* in the absence of other causes of liver disease;

^ immunotolerant;

°° after discontinuation of immunosuppressant and regression/control of underlying disease:

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Management strategies according with virological profile

	Active carrier	Inactive carrier	Inactive Carrier	pOBI (anti-core)
HBsAg	**+**	**+**	**+**	**-**
HBV DNA (IU/ml)	**> 2000**	**Positive (≤2000)**	**Negative (Undetectable)**	**Negative/detectable (≤200)**
LS (KPa)	**> 6 o < 6^**	**<6***	**< 6***	**<6***
Reactivation risk > 10%	**+++**	**++**	**+**	**+§/-**
Drug treatment	ETV or TDF (TAF)	ETV	LAM *(HBV DNA monitoring)* or ETV**	LAM (HBsAg monitoring)
Duration of treatment	Indefinite	Prophylaxis for at least 12 months °°	Prophylaxis for at least 12 months °°	Prophylaxis for at least 18 months °°

* in the absence of other causes of liver disease;

^ immunotolerant;

°° after discontinuation of immunosuppressant and regression/control of underlying disease:

§ anti-CD 20 used in onco-haematological disease.

** If a quarterly virologic monitoring cannot be guaranteed during prophylaxis;

IS: immunosuppression. TDF; tenofovir disoproxil fumarate; TAF: Tenofovir Alafenamide; ETV: Entecavir; LAM: Lamivudine; LS: Liver stiffness.

Management strategies IN HSCT

Auto-HSCT

Virological profile:
- Antiviral Therapy in AC
- Prophylaxis in pOBI

Anti HBV Vaccination

Recipients:
Whenever possible!!

Donor:
Strongly Advised

Allo-HSCT

HBV in Donor IS NOT a contraindication

HBsAg + DONOR
Assess for AT

HBsAg + Recipient
According to virological profile

pOBI Recipient /HBsAg- Donor
LAM for 18 m after*
Swithch to ETV/TDF if long IS

Naive Recipient /pOBI Donor
Pre-emptive strategy

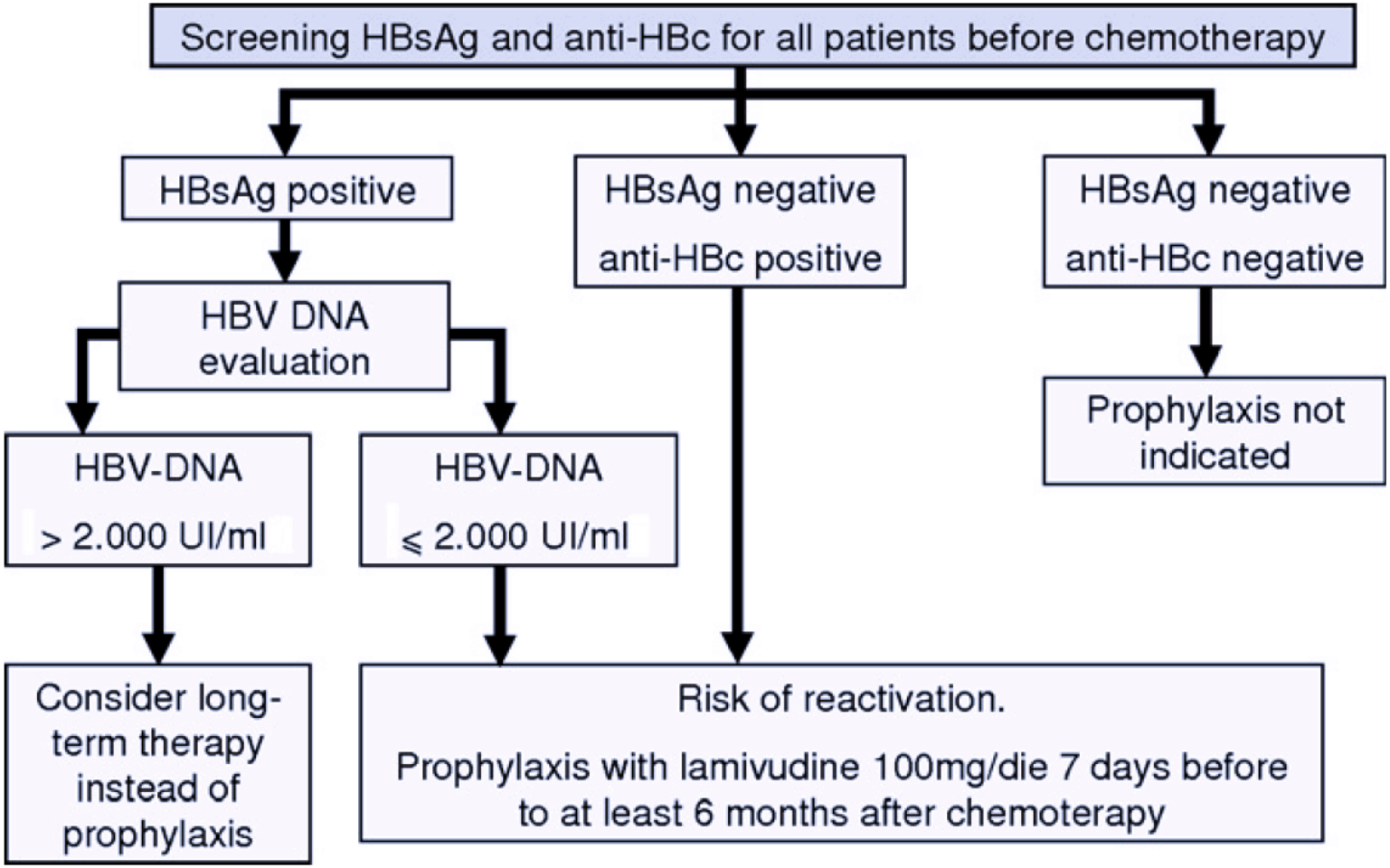
Naive Recipient /Naive Donor
Monitor ALT

The benefit of a good choice lasts forever……

Digestive and Liver Disease 43S (2011) S49–S56

HBV disease: HBsAg carrier and occult B infection reactivation in haematological setting

Carlo Marinone*, Monica Mestriner



General statements in allogenic HSCT

1. Vaccination of the recipients (BIII) and donors (AV) not immunized with accelerated protocols
2. Treatment of HBsAg+ donors with lamivudine and universal prophylaxis of recipients (AIV)
3. Preferential allocation of anti-HBc+ positive organs to vaccinated recipients or those with markers of prior contact with HBV (BV)
4. HBIG during infusion of HSCT in HBsAg- recipients of HBsAg+ donors (CVI)

The panel agrees that because of the actual results of the hepatologic and haematologic therapy there is no reason to deny a HSCT from a HBV positive donor (any form) if the risk-benefit ratio is in favour of transplantation. Moreover in the case of a HLA identical family HBV positive member there is no point in wasting time and resources in searching for an unrelated donor in the international bone marrow donor bank.

Digestive and Liver Disease 43S (2011) S49–S56

HBV disease: HBsAg carrier and occult B infection reactivation in haematological setting

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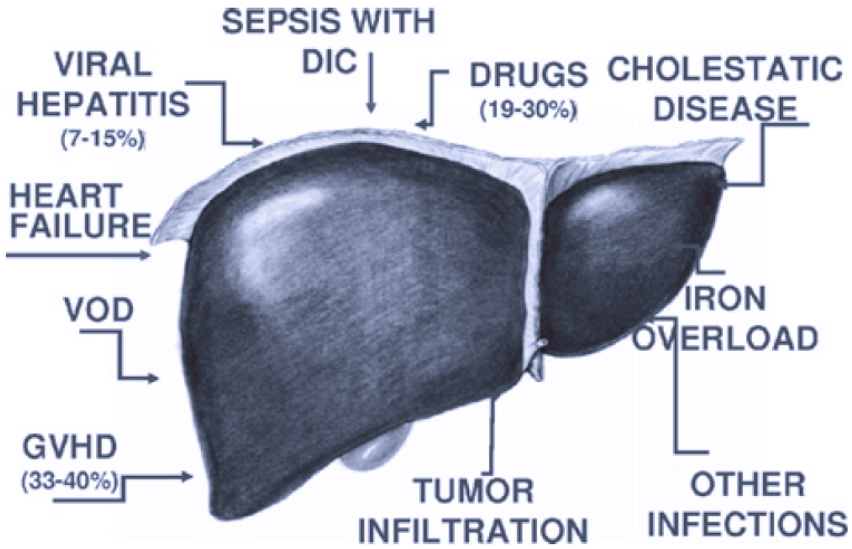

Fig. 1. Liver complication after stem cell transplantation/immuno-chemotherapy. DIC: disseminated intravascular coagulation; VOD: veno-occlusive disease; GVHD: graft vs. host disease.

Journal of Clinical Virology 57 (2013) 209–214

Contents lists available at SciVerse ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

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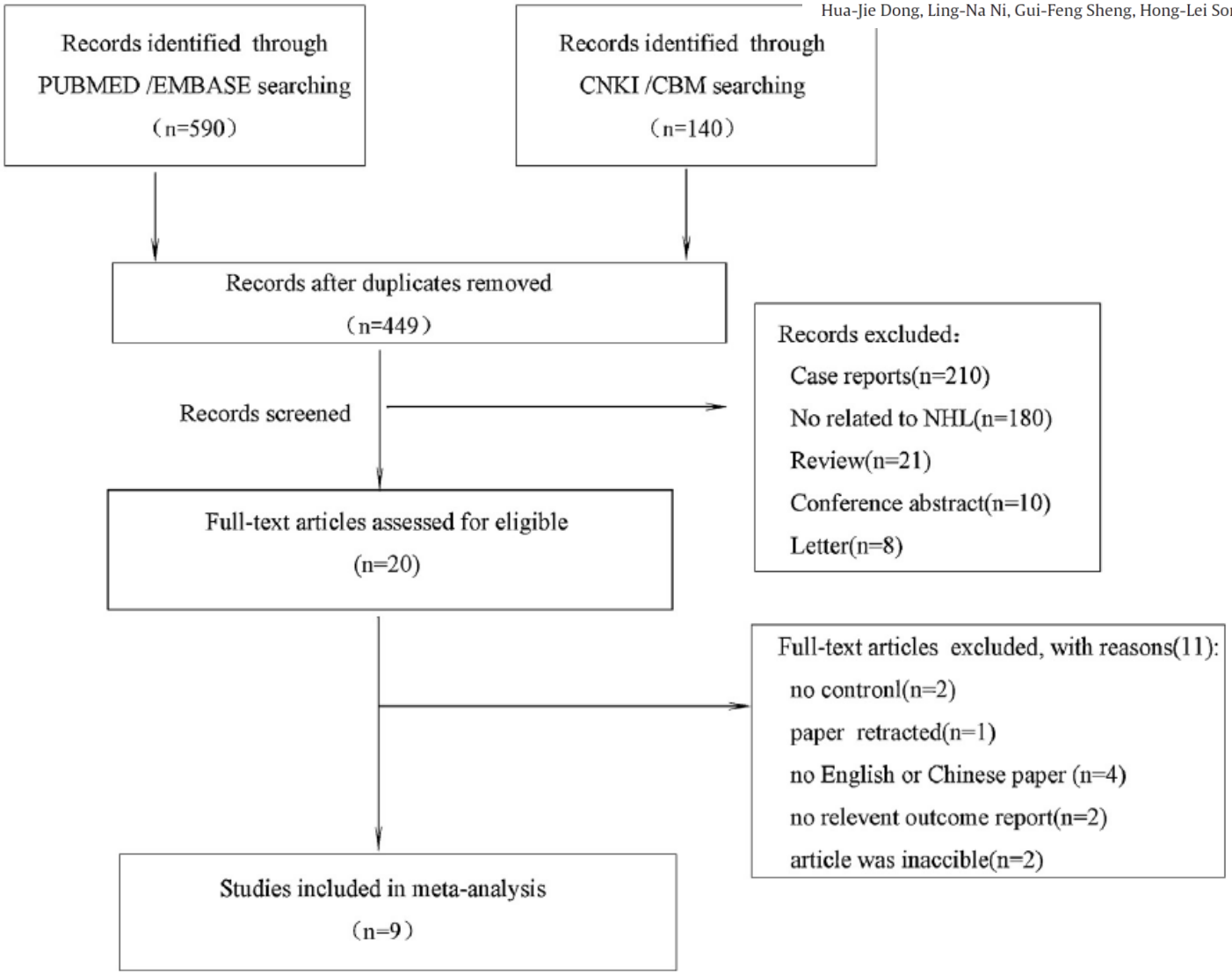
Hua-Jie Dong, Ling-Na Ni, Gui-Feng Sheng, Hong-Lei Song, Jian-Zhong Xu, Yang Ling*



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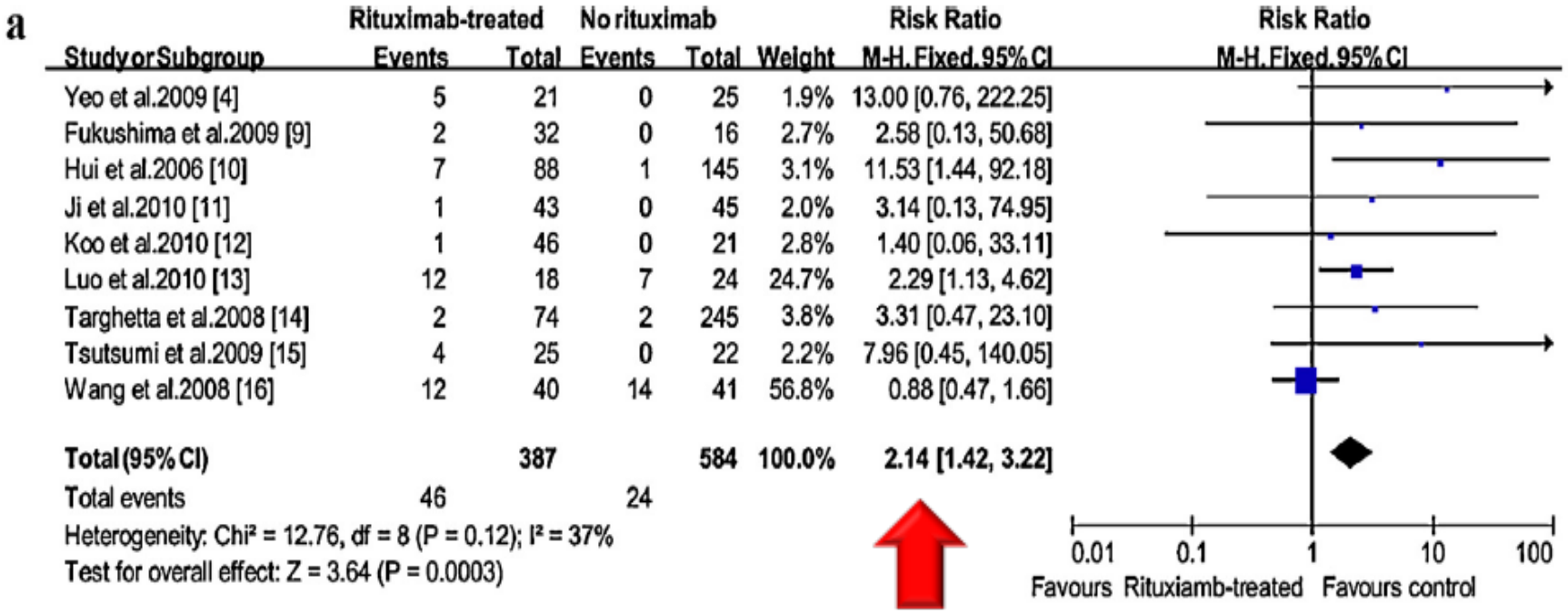
Forest plot showing the prevalence of HBV reactivation in HBsAg(+) and HBcAb(+) patients with non-Hodgkin lymphoma (NHL): rituximab based therapy versus non-rituximab controls



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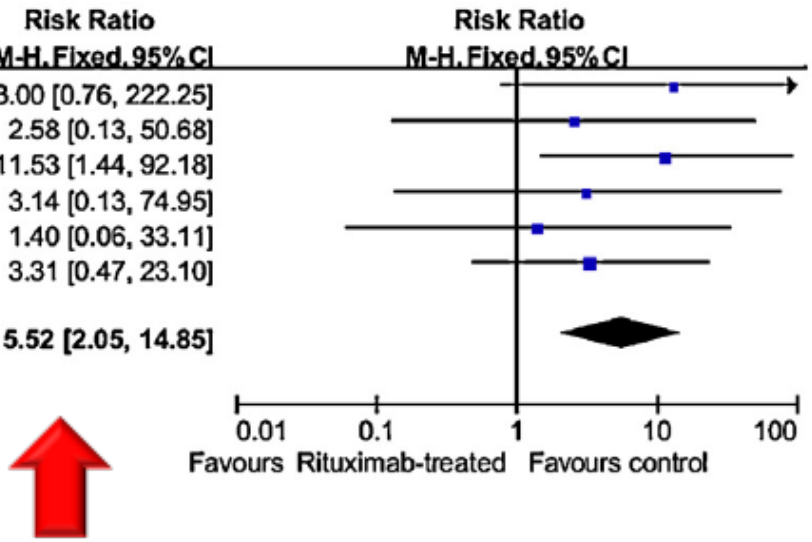
Forest plot showing the prevalence of HBV reactivation in HBsAg(-) and HBcAb(+) patients with non-Hodgkin lymphoma (NHL): rituximab based therapy versus non-rituximab controls

b

Study or Subgroup	Rituximab-treated Events	Total	No rituximab Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Yeo et al.2009 [4]	5	21	0	25	11.5%	13.00 [0.76, 222.25]
Fukushima et al.2009 [9]	2	32	0	16	16.6%	2.58 [0.13, 50.68]
Hui et al.2006 [10]	7	88	1	145	19.0%	11.53 [1.44, 92.18]
Ji et al.2010 [11]	1	43	0	45	12.3%	3.14 [0.13, 74.95]
Koo et al.2010 [12]	1	46	0	21	17.2%	1.40 [0.06, 33.11]
Targhetta et al.2008 [14]	2	74	2	245	23.4%	3.31 [0.47, 23.10]
Total (95% CI)		**304**		**497**	**100.0%**	**5.52 [2.05, 14.85]**
Total events	18		3			

Heterogeneity: Chi² = 2.19, df = 5 (P = 0.82); I² = 0%

Test for overall effect: Z = 3.39 (P = 0.0007)



Journal of Clinical Virology 57 (2013) 209–214

Contents lists available at SciVerse ScienceDirect

Journal of Clinical Virology

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Hua-Jie Dong, Ling-Na Ni, Gui-Feng Sheng, Hong-Lei Song, Jian-Zhong Xu, Yang Ling*

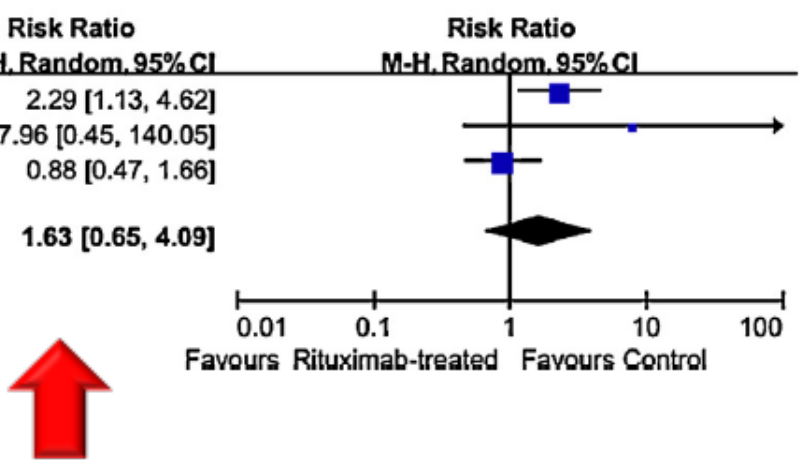
Forest plot showing the prevalence of HBV reactivation in HBsAg(+) patients with non-Hodgkin lymphoma (NHL): rituximab based therapy versus non-rituximab controls

c

Study or Subgroup	Rituximab-treated Events	Total	No rituximab Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Luo et al.2010 [13]	12	18	7	24	44.5%	2.29 [1.13, 4.62]
Tsutsumi et al.2009 [15]	4	25	0	22	8.8%	7.96 [0.45, 140.05]
Wang et al.2008 [16]	12	40	14	41	46.7%	0.88 [0.47, 1.66]
Total (95% CI)		**83**		**87**	**100.0%**	**1.63 [0.65, 4.09]**
Total events	28		21			

Heterogeneity: $Tau^2 = 0.37$; $Chi^2 = 5.37$, df = 2 (P = 0.07); $I^2 = 63\%$

Test for overall effect: Z = 1.04 (P = 0.30)



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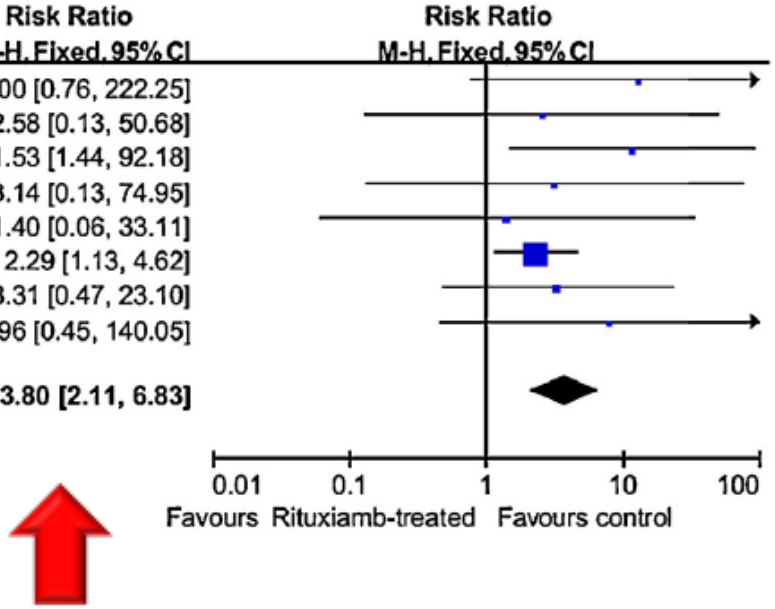
Forest plot showing the prevalence of HBV reactivation in HBsAg(+) and HBcAb(+) patients with non-Hodgkin lymphoma (NHL): rituximab based therapy versus non-rituximab controls (after adjustment for heterogeneity).

Study or Subgroup	Rituximab-treated Events	Total	No rituximab Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Yeo et al.2009 [4]	5	21	0	25	4.4%	13.00 [0.76, 222.25]
Fukushima et al.2009 [9]	2	32	0	16	6.3%	2.58 [0.13, 50.68]
Hui et al.2006 [10]	7	88	1	145	7.2%	11.53 [1.44, 92.18]
Ji et al.2010 [11]	1	43	0	45	4.7%	3.14 [0.13, 74.95]
Koo et al.2010 [12]	1	46	0	21	6.5%	1.40 [0.06, 33.11]
Luo et al.2010 [13]	12	18	7	24	57.1%	2.29 [1.13, 4.62]
Targhetta et al.2008 [14]	2	74	2	245	8.8%	3.31 [0.47, 23.10]
Tsutsumi et al.2009 [15]	4	25	0	22	5.1%	7.96 [0.45, 140.05]
Total (95% CI)		**347**		**543**	**100.0%**	**3.80 [2.11, 6.83]**
Total events	34		10			

Heterogeneity: $Chi^2 = 4.55$, df = 7 (P = 0.71); $I^2 = 0\%$

Test for overall effect: Z = 4.45 (P < 0.00001)



Rituximab-associated HBV-R

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Pooled effect: **Relative risk (RR) 2.14**, *95%CI 1.42–3.22, P = 0.0003*

In subgroup analysis:

1. in **isolated HBcAb (+) RR was 5.52** *(95%CI 2.05–14.85, P = 0.0007).*
2. In **HBsAg (+) RR was 1.63**

Conclusions:

Rituximab therapy increase the risk of developing HBV-R in NHL patients with HBcAb(+).

HEPATOLOGY
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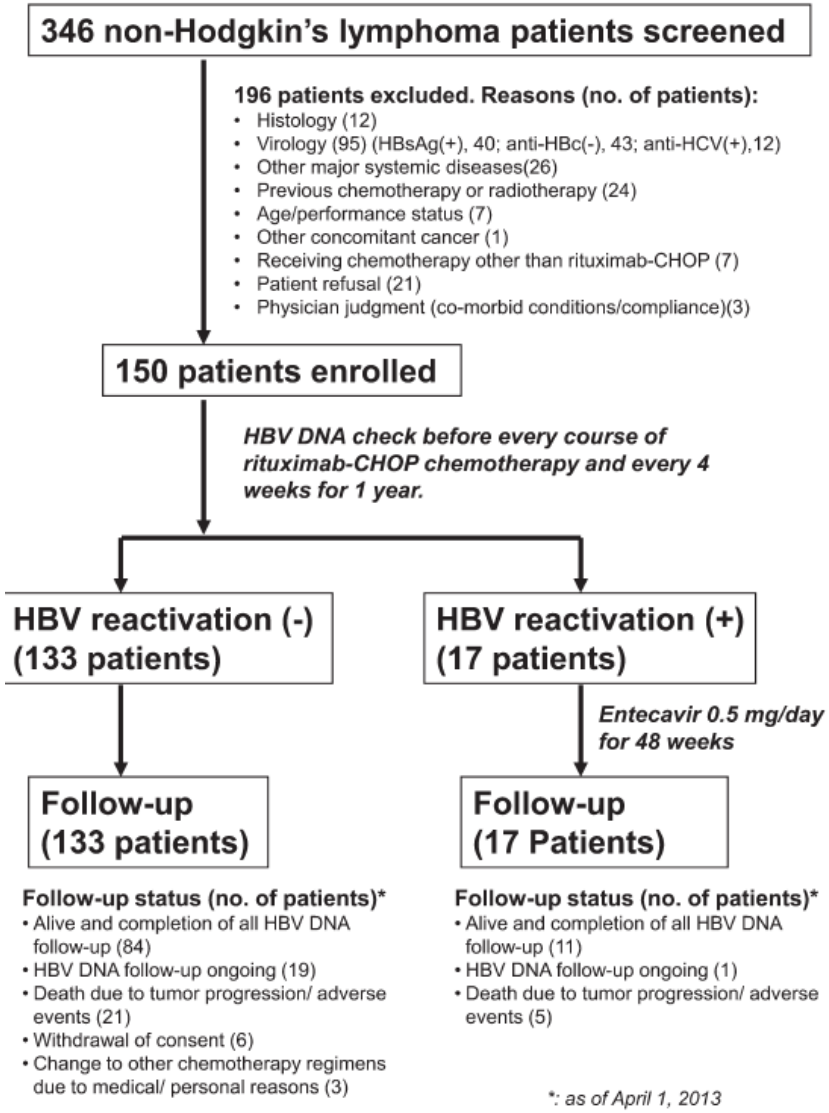

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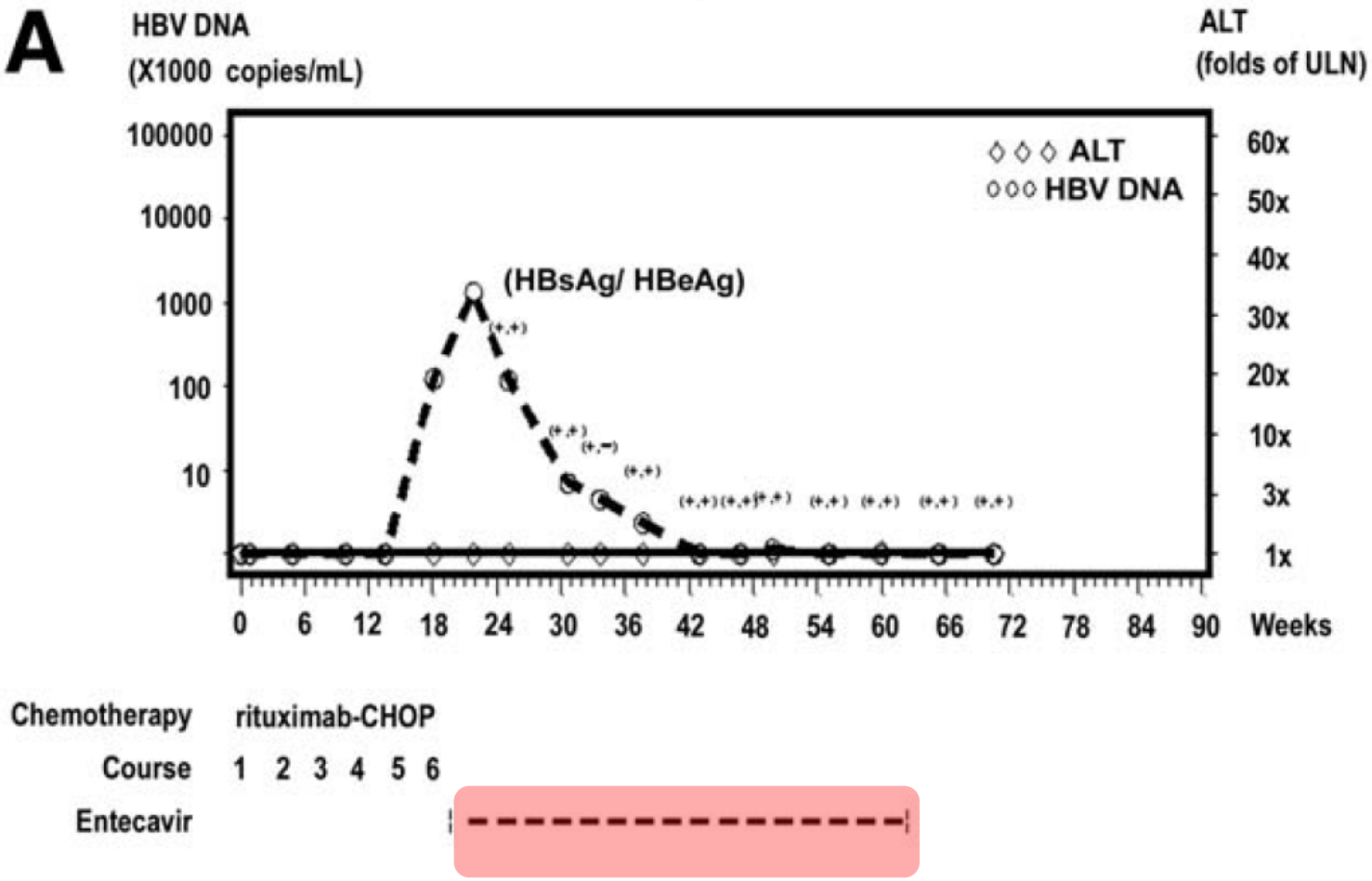
HBV- R during rituximab-CHOP
without hepatitis flare



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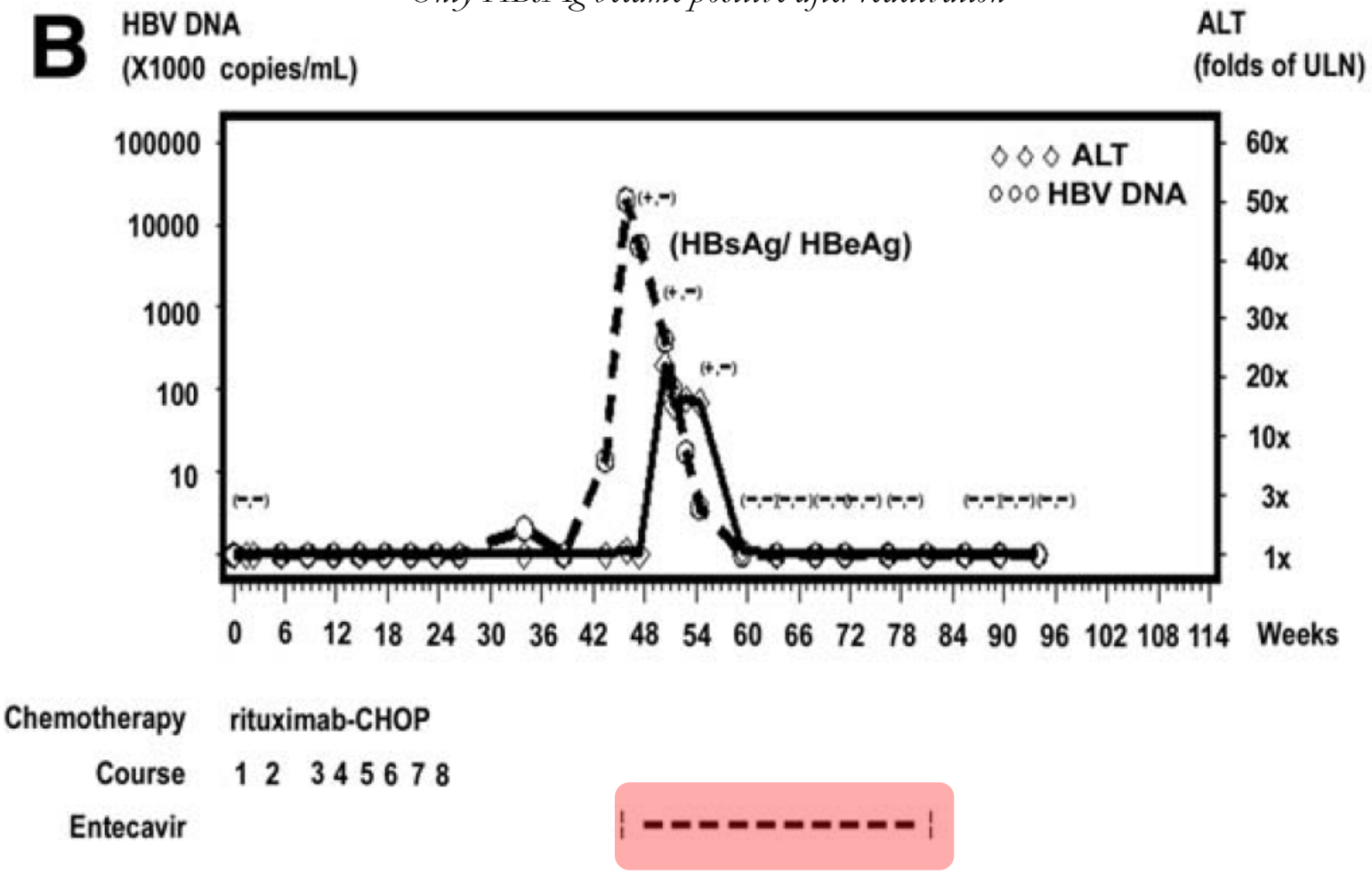
HBV- R after completion of rituximab-CHOP with hepatitis flare.

Only HBsAg became positive after reactivation



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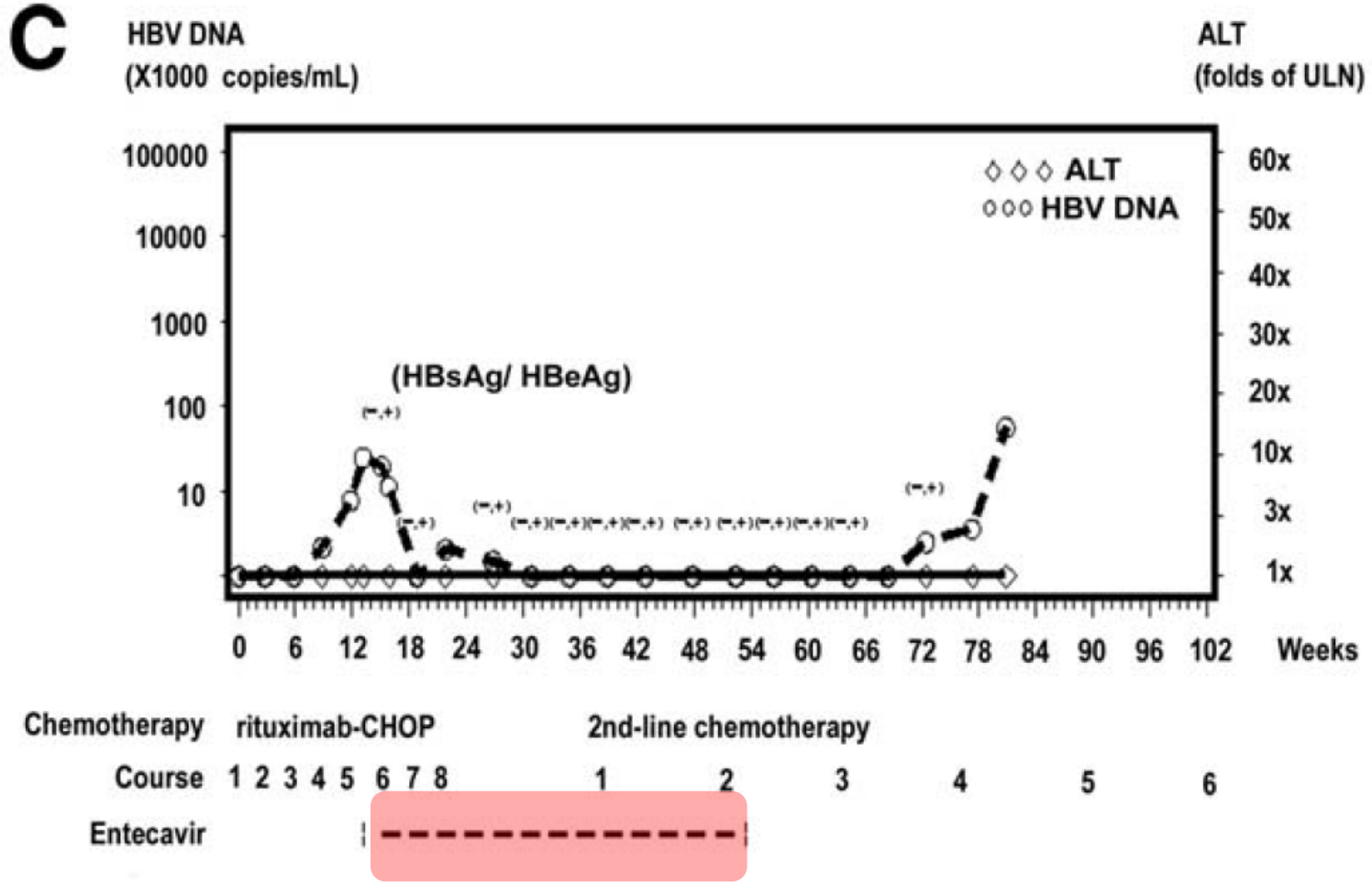
2nd episode of HBV-R after completion of entecavir treatment, *(induced by second-line chemotherapy?)*



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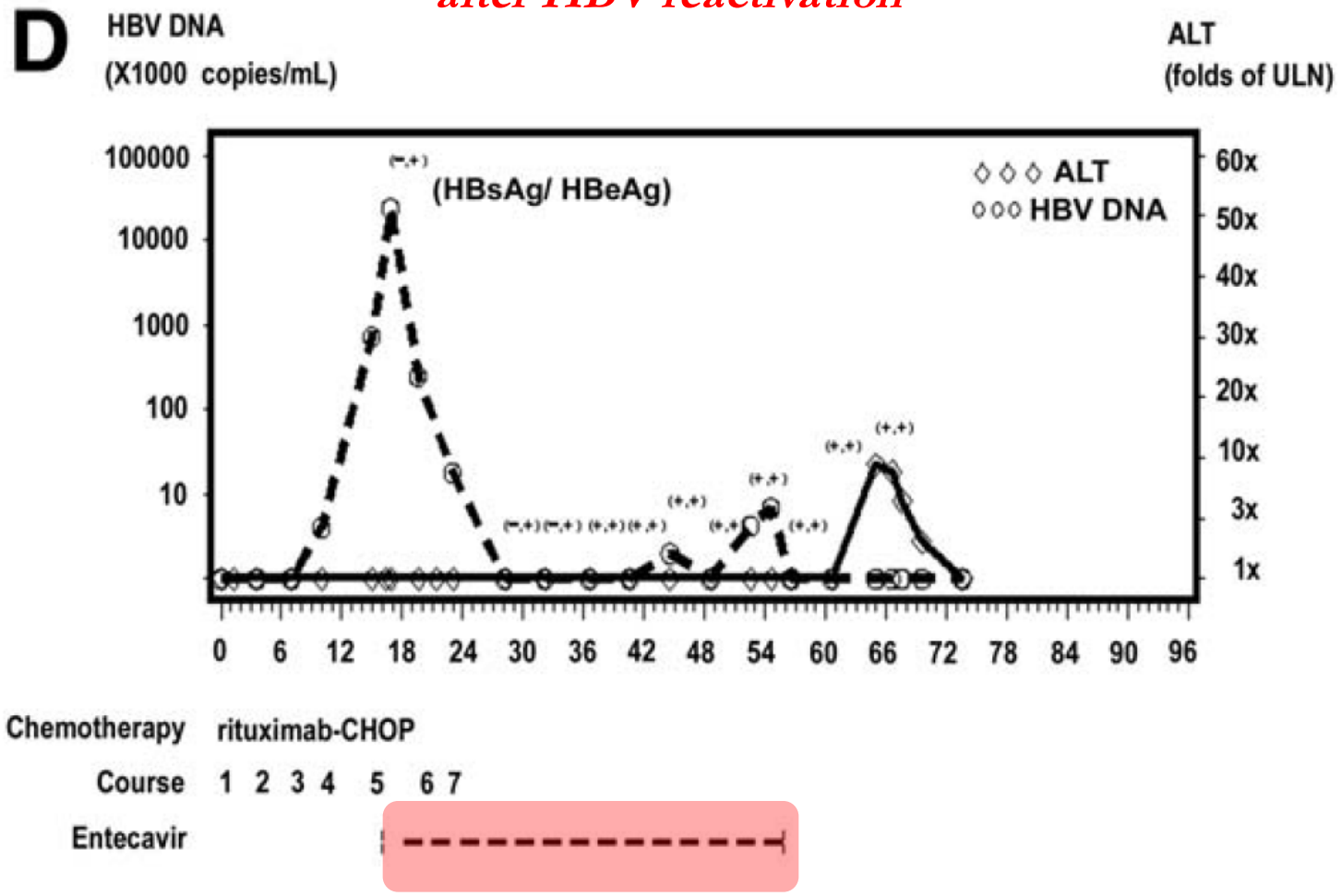
Delayed hepatitis flare
after HBV reactivation



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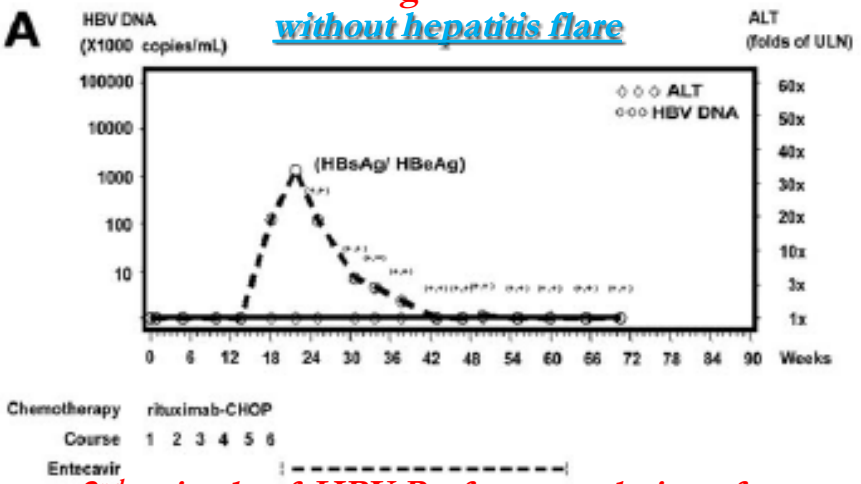

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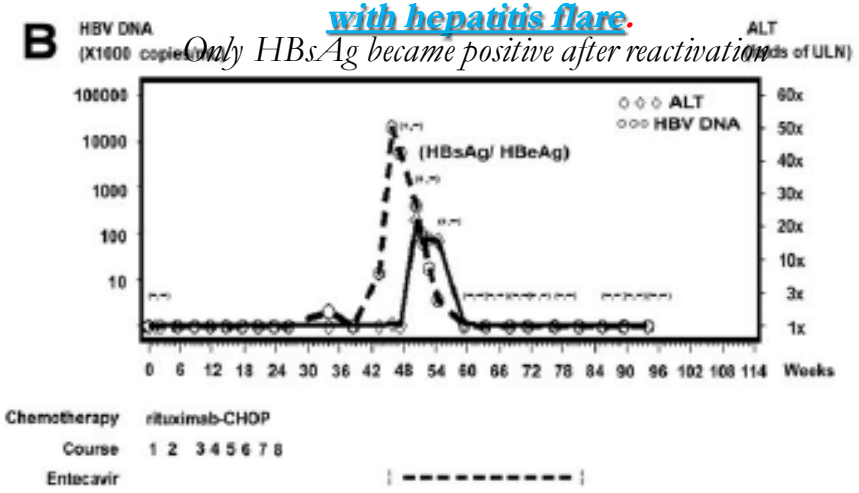
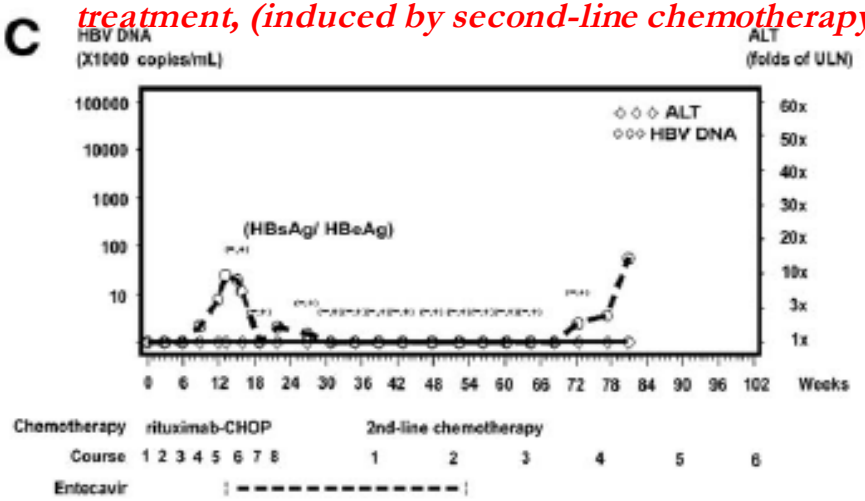
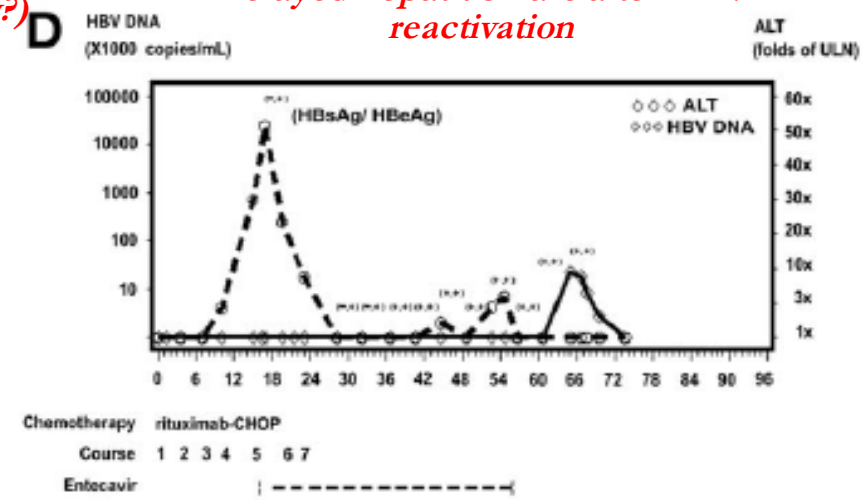


2nd episode of HBV-R after completion of entecavir treatment, (induced by second-line chemotherapy?)



Delayed hepatitis flare after HBV reactivation



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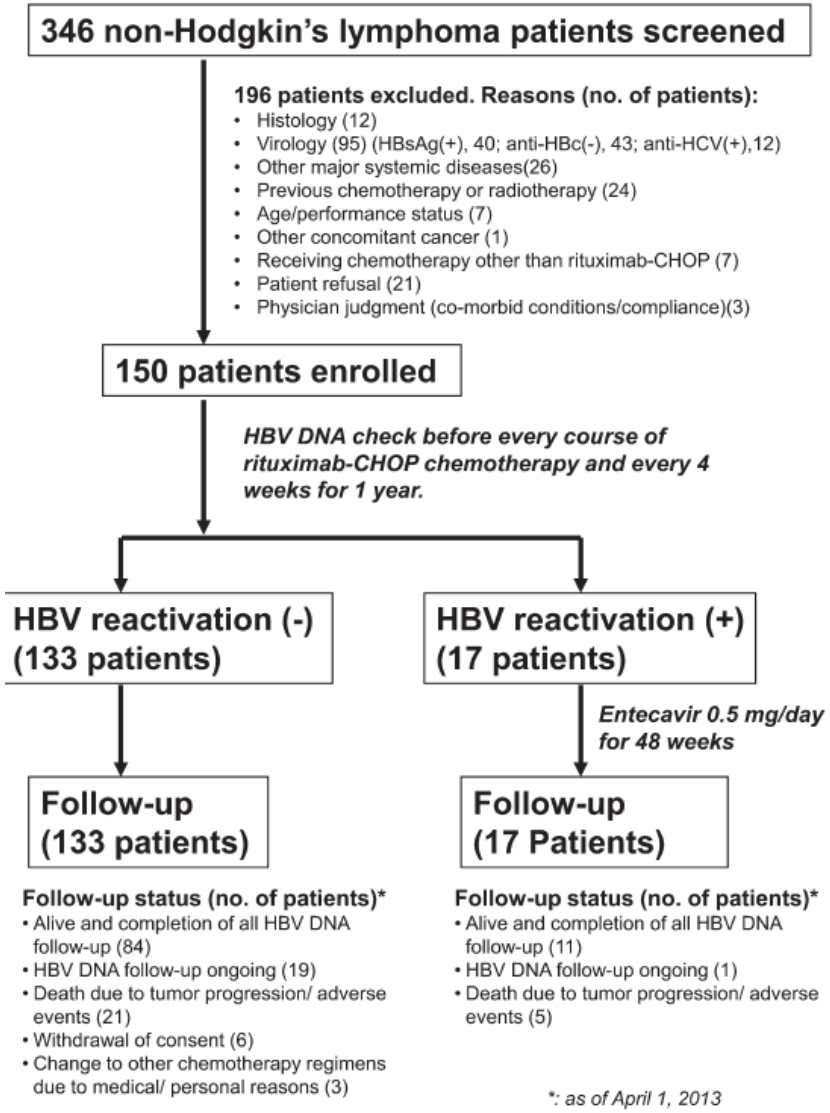

- HBV-related severe hepatitis: **7(4,6%)**
- Chemotherapy delay: **2 (1,3%)**

Severe HBV-related hepatitis *(ALT >10-fold of upper limit of normal)* occurred in **4 patients**, despite entecavir treatment.

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Critical Reviews in Oncology/Hematology 87 (2013) 12–27

CRITICAL REVIEWS IN
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Hepatitis B in immunosuppressed cancer patients: Pathogenesis, incidence and prophylaxis

Mario Mandalà[a,*], Stefano Fagiuoli[b], Daniela Francisci[c], Raffaele Bruno[d], Barbara Merelli[a], Luisa Pasulo[b], Carlo Tondini[a], Roberto Labianca[a], Fausto Roila[e]

Screening for hepatitis B in cancer patients receiving immunosuppressive therapy.

Scientific society	Recommendation	
	Oncologic	Hematologic
AASLD [61]	HBsAg, anti-HBc	HBsAg, anti-HBc
EASL [64]	HBsAg, anti-HBc	HBsAg, anti-HBc
CDC [85]	HBsAg, anti-HBc, HBsAb	HBsAg, anti-HBc, HBsAb
Scottish Liver Society [63]	None	HBsAg, HBcAb
NIH Consensus [86]	HBsAg	HBsAg
Italian Guidelines [7]	HBsAg	HBsAg, anti-HBc, HBsAb
ASCO [62]	Only patients who undergo certain "highly" cytotoxic or immunosuppressive therapies (i.e., stem cell transplants or treatment with rituximab) and patients "at risk" for HBV (HBV infection or prior exposure to HBV): HBsAg, anti-HBc	
APASL [87]	HBsAg	HBsAg
Canadian Guidelines [88]	HBsAg, anti-HBc, HBsAb	HBsAg, anti-HBc, HBsAb

(b) Management of patients with haematologic tumors suitable for immunosoppressive therapy

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Critical Reviews in Oncology/Hematology 87 (2013) 12–27
CRITICAL REVIEWS IN Oncology Hematology Incorporating Geriatric Oncology
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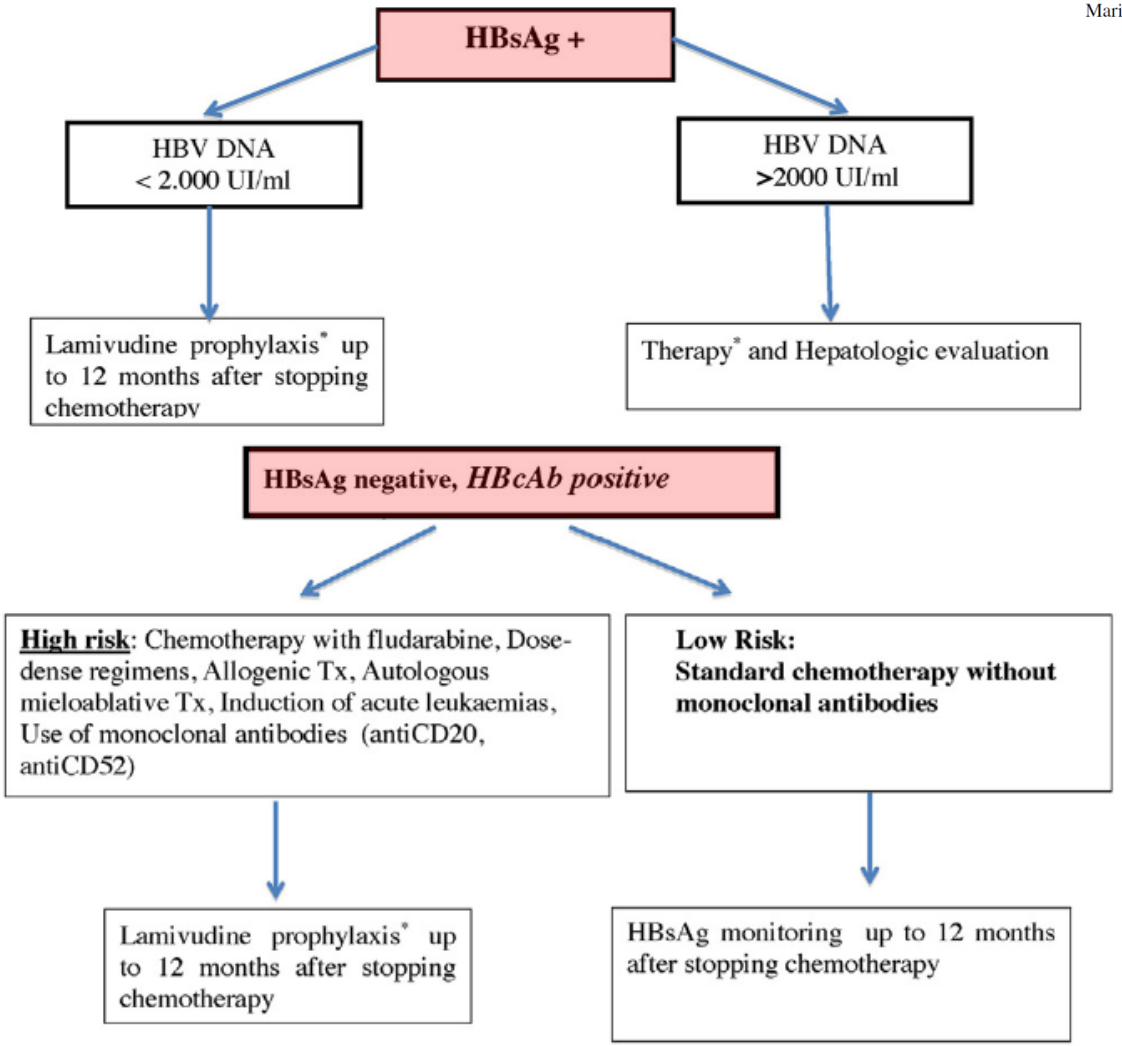
Screening for HBsAg (if HBsAg +: HBVDNA), HBcAb and HBsAb



Hepatitis B in immunosuppressed cancer patients: Pathogenesis, incidence and prophylaxis

Mario Mandalà[a,*], Stefano Fagiuoli[b], Daniela Francisci[c], Raffaele Bruno[d], Barbara Merelli[a], Luisa Pasulo[b], Carlo Tondini[a], Roberto Labianca[a], Fausto Roila[e]

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Hepatitis B in immunosuppressed cancer patients: Pathogenesis, incidence and prophylaxis

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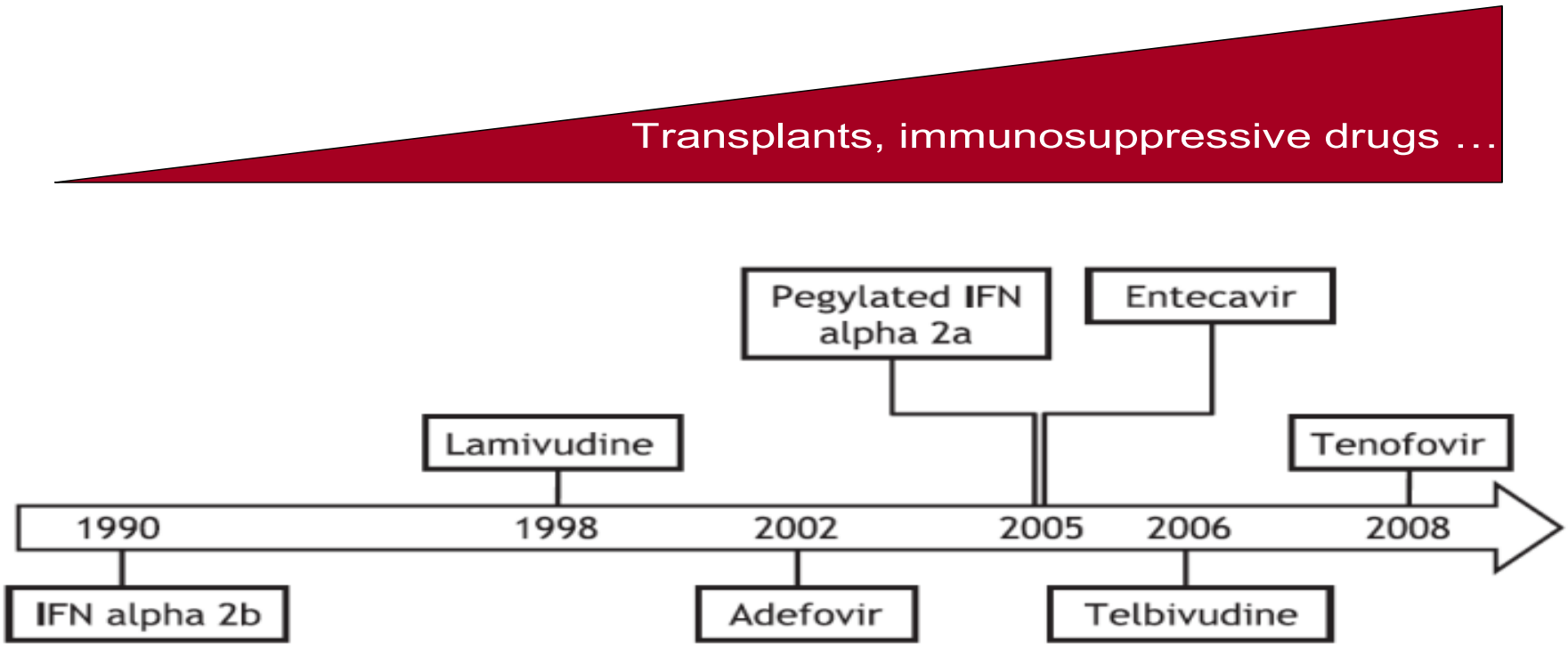
Management strategy for immunosuppressed hematologic cancer patients.

Active carrier	Inactive carrier	Anti-core
HBsAg+/HBVDNA > 2000 IU/ml Therapy (entecavir or tenofovir)	HBsAg+/HBVDNA < 2000 IU/ml Universal prophylaxis 6–12 months after the end of therapy	HBsAg−/anti-HBc+ Universal prophylaxis[a] or monitoring and targeted prophylaxis (after seroreversion HBsAg− → HBsAg+)

[a] High risk (hematology): chemotherapy with fludarabine, dose-dense regimens, allogenic Tx, autologous mieloablative Tx, induction of acute leukemias, use of monoclonal antibodies (antiCD20, antiCD52): prophylaxis for 12–18 months.

Why HBV and immunocompromised?



1. Definitions

A. Virological categories

Virological categories

	Active carrier	Inactive carrier	Anti-HBc positive (anti-core)
HBsAg	Positive	Positive	Negative
HBeAg	Positive or negative	Negative	Negative
Anti-HBs	Negative	Negative	Positive or negative
Anti-HBc	Positive	Positive	Positive
HBV DNA serum	**>2.000 IU/ml**	**>2.000 IU/ml**	Negative (>90%)
ALT[b]	Persistently or intermittently increased	Persistently normal[c]	Persistently normal[c]
HBV DNA tissue	Positive	Positive	Positive
Liver damage[d]	Yes (>90%)	No (>90%)[c]	No[c]

Basal Evaluation in immunocompromised patients – Virological Categories

	Active carrier	Inactive carrier	pOBI (anti-core)
HBsAg	+	+	-
HBeAg	-/+	-	-
antiHBe	-/+	+	+
antiHBc	+	+	+
antiHBs	-	-	±
qHBsAg	≥1000	< 1000°°	-
ALT	Increased (persistent or intermittent)	Normal*	Normal*
HBV DNA (IU/mL) serum	> 2000	≤ 2000°°	-
HBV DNA (IU/mL) liver	+	+	+
Liver Stiffness (kPa)	> 6 o ≤ 6^	< 6*	<6*

2.1 Definitions 2017

	Virologic events
Active carriers	Significant viremia Progressive CH (AIII)
Inactive carriers	**Virologic** reactivation (viremia > 2,000 IU); **clinical** (HBV DNA < 2000 IU and ALT UNV) (AIII)
OBI (anti-core)	Seroreversion (HBsAg+) (AIII)
Virologic response	HBV DNA negative by PCR (AIII)
Virologic BK	1 log increase of HBV DNA (AV)

	Clinical definitions
Baseline	Hepatogic assessment (underlying liver disease)
Infection	HBV DNA and or HBsAg+ in originally negative patients (not necessarily associated with reactivation of hepatitis)
Hepatitis B reacivation	Viremia (> 2000 IU)and ALT levels above the UNV

Table 4
Treatment strategies

		Original virological condition		
		Active carriers	Inactive carriers or anti-core positive	
Clinical condition	Infection	Yes	Yes	
	Hepatitis	Yes	No	
Treatment		Therapy	Prophylaxis	
			All the population	Only in patients with infection markers[a]
			Universal	Targeted

[a] Infection markers: evidence of HBV DNA or HBsAg in serum in originally negative patients.

3.1 Treatment options 2011

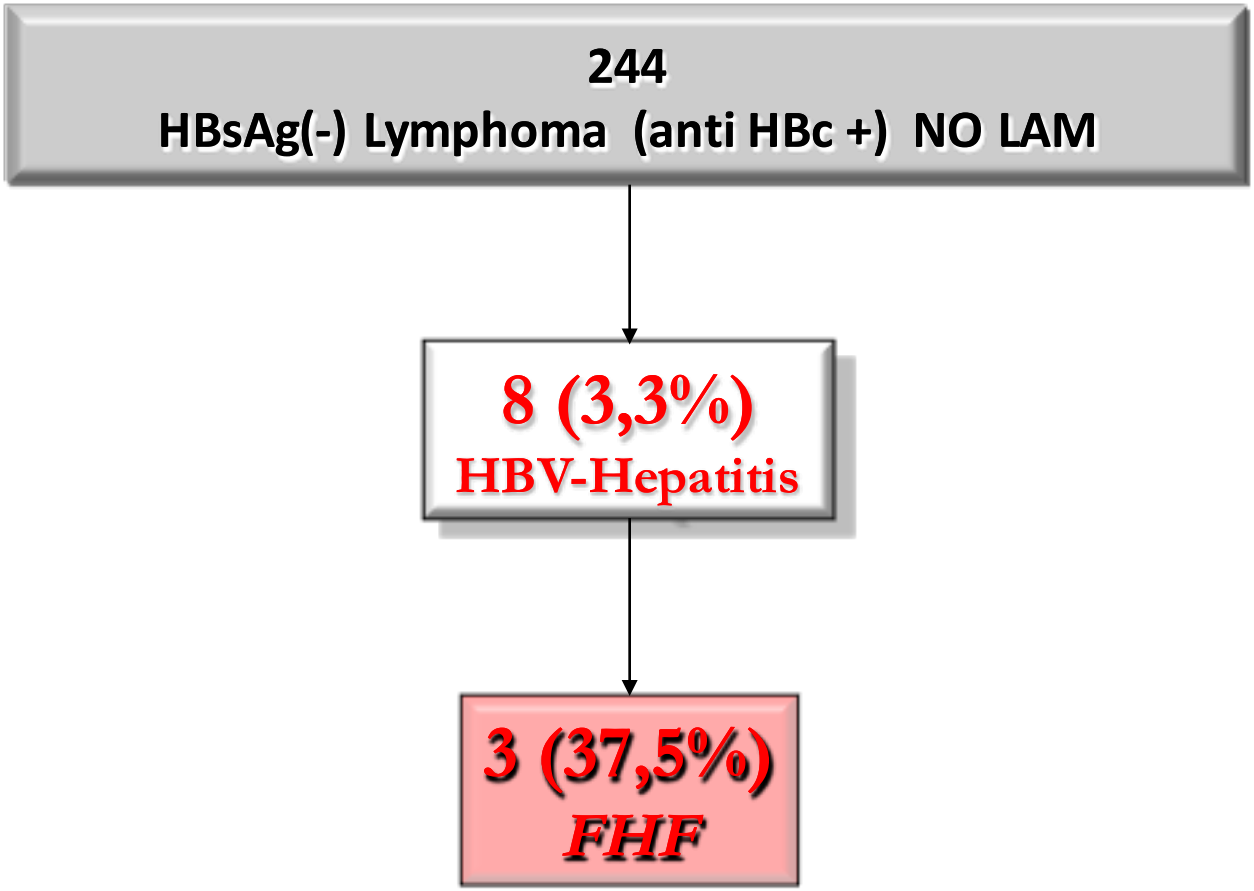
Lamivudine	GlaxoSmithKline	Only prophylaxis (long term in Inactive carriers?)
Tenofovir	(± emtricitabina) GILEAD	HBV or HIV/HBV
Entecavir	Bristol-Myers Squibb	HBV
Telbivudine	NOVARTIS	HIV (no ART)

HBV reactivation in HBsAg (-) individuals

blood
2009 113: 3147-3153
Prepublished online Jan 14, 2009;
doi:10.1182/blood-2008-10-163493

How I treat and monitor viral hepatitis B infection in patients receiving intensive immunosuppressive therapies or undergoing hematopoietic stem cell transplantation

Raymond Liang



Liang R. Blood, 2009

HEPATOLOGY VOL. 65, NO. 5, 2017

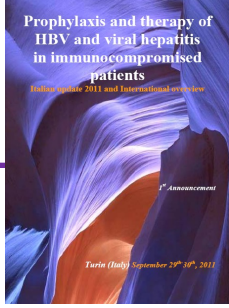
Hepatitis B Reactivation in Occult Viral Carriers Undergoing Hematopoietic Stem Cell Transplantation: A Prospective Study

Wai-Kay Seto,[1,2] Thomas Sau-Yan Chan,[1] Yu-Yan Hwang,[1] Danny Ka-Ho Wong,[1,2] James Fung,[1,2] Kevin Sze-Hang Liu,[1] Harinder Gill,[1] Yuk-Fai Lam,[1] Eric H.Y. Lau,[3] Ka-Shing Cheung,[1] Albert K.W. Lie,[1] Ching-Lung Lai,[1,2] Yok-Lam Kwong,[1] and Man-Fung Yuen[1,2]

Digestive and Liver Disease 43S (2011) S49–S56

HBV disease: HBsAg carrier and occult B infection reactivation in haematological setting

Carlo Marinone*, Monica Mestriner



Haematology:

Proposed statement

1. Clinicians caring for patients with hematologic malignancies need to be fully aware of the methods to identify, control and treat viral hepatitis in their patients, and to work in a **multidisciplinary team** in cooperation with a liver disease specialist (A-VI)

Proposed statement

2. Patients with hematologic malignancies undergoing immunosuppressive treatment or chemotherapy **should be screened for HBsAg, anti-HBc, and anti-HBs** *(and HBV DNA if HBsAg is already positive)* because of the high risk of viral reactivation with severe hepatic flares **(A-III)**.
3. Patients with B-cell NHL should be screened for anti-HCV **(A-III).**

Active carrier	Inactive carrier	Anti-core
HBsAg+	HBsAg+	HBsAg(-) antiHBc+
Therapy	Universal Prophylaxis (6-12 months after the end of treatment)	Universal prophylaxis* or HBsAg monitoring** (*targeted prophylaxis*) (low immunosuppressive potential as the ABVD of the CHOP 21 days scheme)
AIII	BV	BVI

*High risk (haematology): Chemotherapy with fludarabine, Dose-sense regimes, Allogenic Tx, Autologous mieloablative Tx, Induction of acute leukaemias, Use of monoclonal antibodies (antiCD20, antiCD52).
** HBV-DNA monitoring Controversial

Update 2011:

*High risk in CLL and myeloma, 1-3 months HBsAg monitoring in anti-core or UP in high risk, Prophylaxis/Monitoring 12-**18 months** after the end of the IS therapy, monitoring after the stop of prophylaxis*

SCID= Severe Combined ImmunoDeficiency

Conclusions

	Active carrier	Inactive carrier	Anti-core
Haematology	III generation NUC(s) ETV/TNF (AIII)	Prophylaxis LAM-NUCs?	Prophylaxis
Oncology			Monitoring
Nephrology		Monitoring	
Solid organ transplants		Prophylaxis LAM-NUCs?	
Liver transplantation			
Rheumatology (+IBD)		High/ low risk	
HIV			

LT: NUC(s) + low dose HBIg; anti-HBc+ livers → LAM prophylaxis

Conclusions

Prophylaxis and therapy in immunocompromised subjects

	Active carrier HBsAg positive	Inactive carrier	Anti-core HBsAg negative
Haematology and HSCT	T	UP	UP[a] High risk Monitoring low risk
Oncology	T	UP	Monitoring
Solid organ transplant	T	UP	Monitoring
Nephrology (dialysis)	T	Monitoring	Monitoring
Rheumatology	T	UP (high risk)[b] Monitoring (low risk)[c]	Monitoring
HIV	T (ART- and ART+)	Monitoring (ART−) UP (ART+)	Monitoring
Liver transplantation	T[d] (pre-LT) → UP[d] (post-LT)	UP[d,e] (pre-LT if PCR+) → UP[d,e] post-LT	Monitoring

Definitions 2011

	Virologic events
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