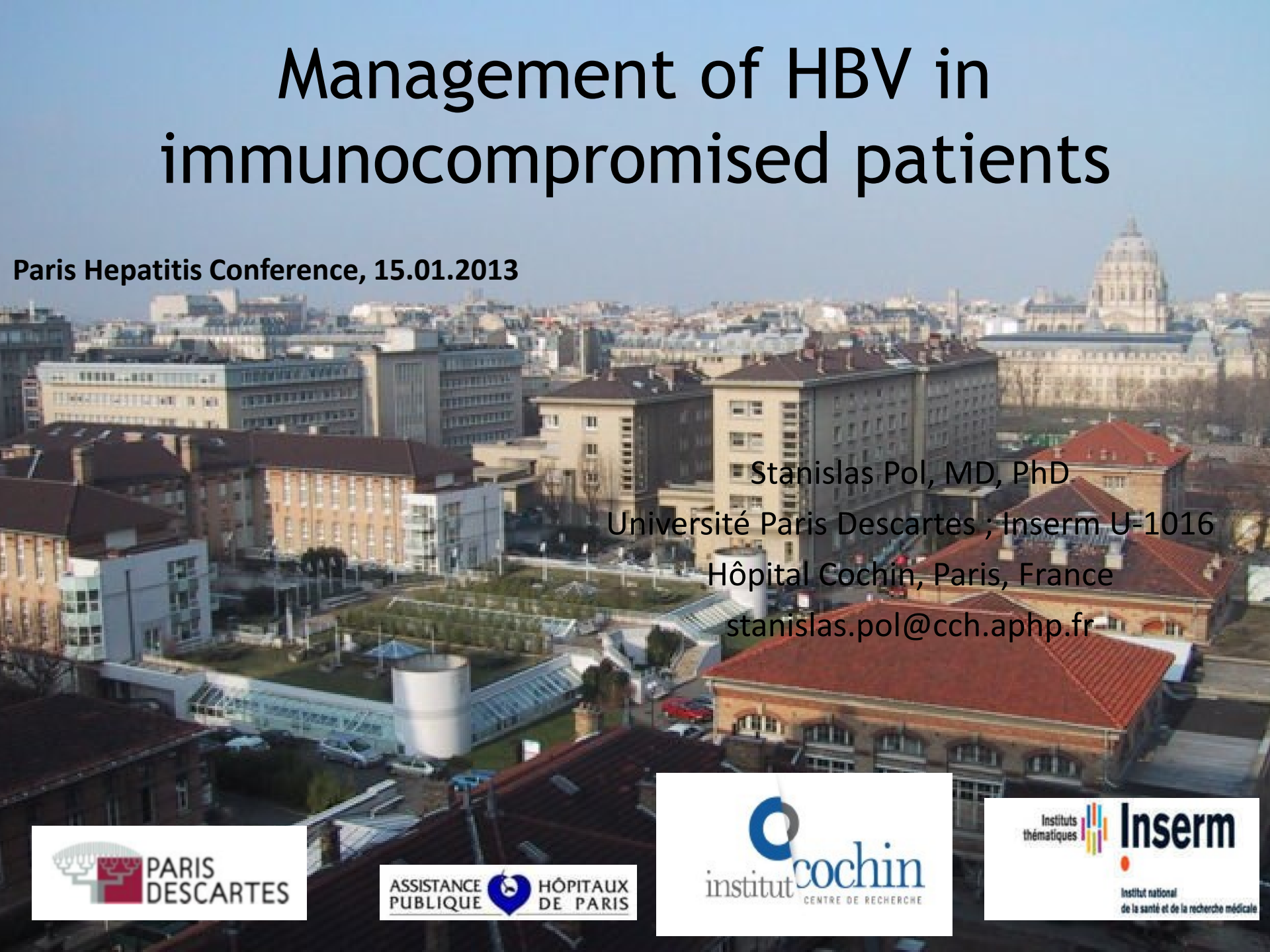
Management of HBV in immunocompromised patients

Paris Hepatitis Conference, 15.01.2013



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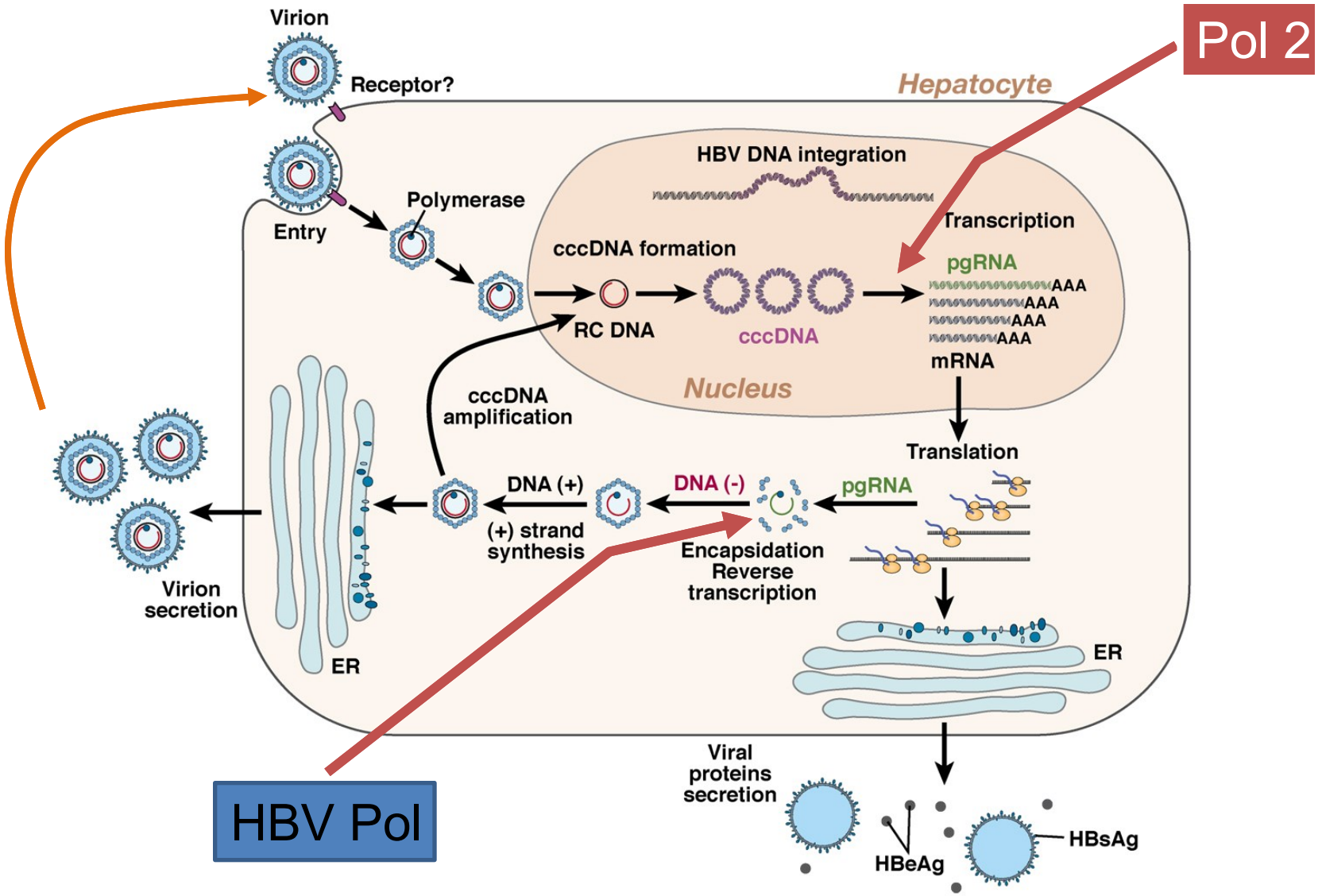
HBV in immune compromised patients

- Pathobiology of HBV infection
- Consequences of immune deficiency on HBV infection
- Therapeutic implications

HBV in immune compromised patients

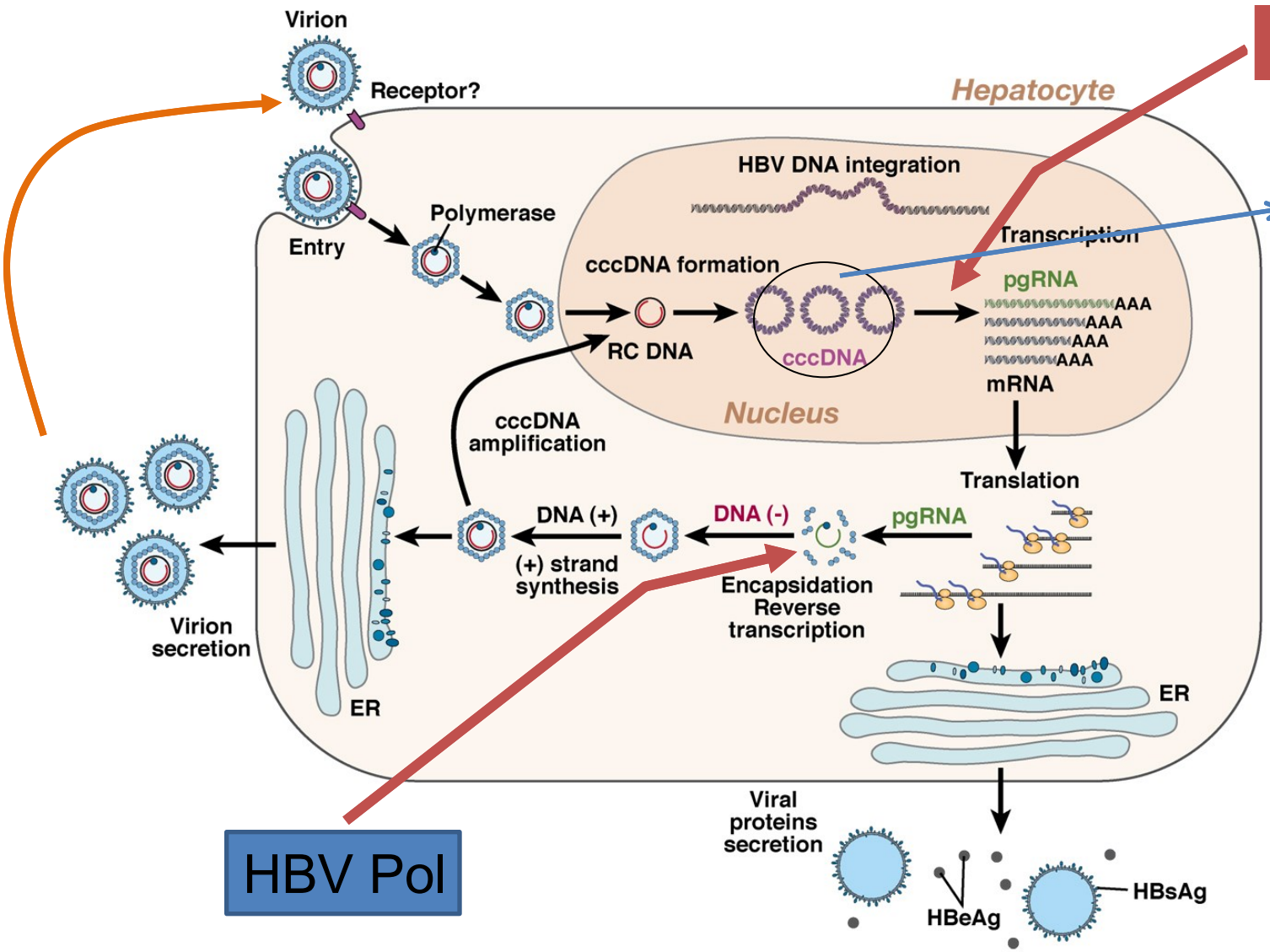
- Pathobiology of HBV infection
  - Replication cycle: cccDNA/HBV integration
  - Immune-mediated pathobiology
- Consequences of immune deficiency on HBV infection
- Therapeutic implications

HBV Replication Cycle



Zoulim F Gastroenterology 2009

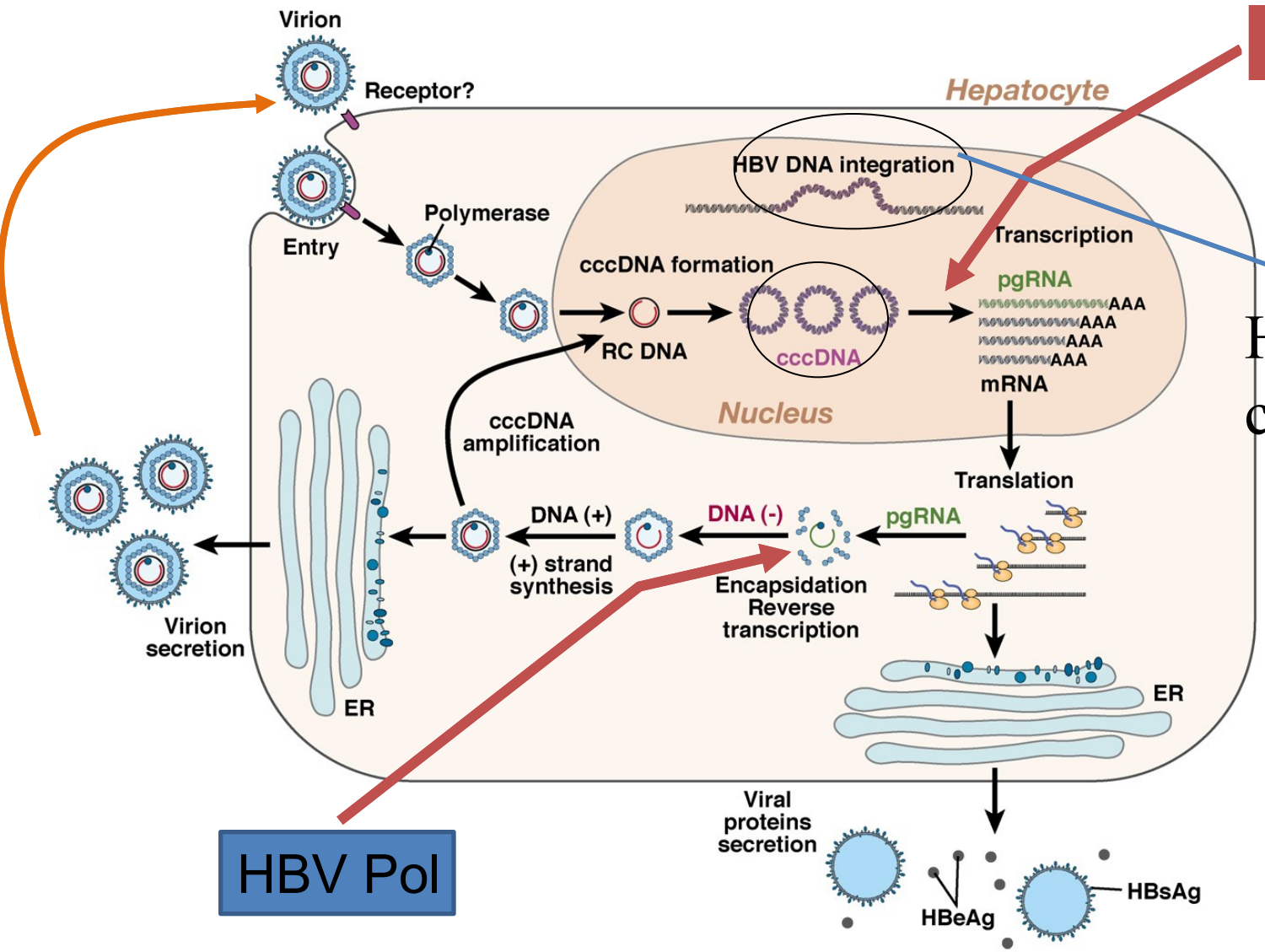
HBV Replication Cycle



Reactivation

Zoulim F Gastroenterology 2009

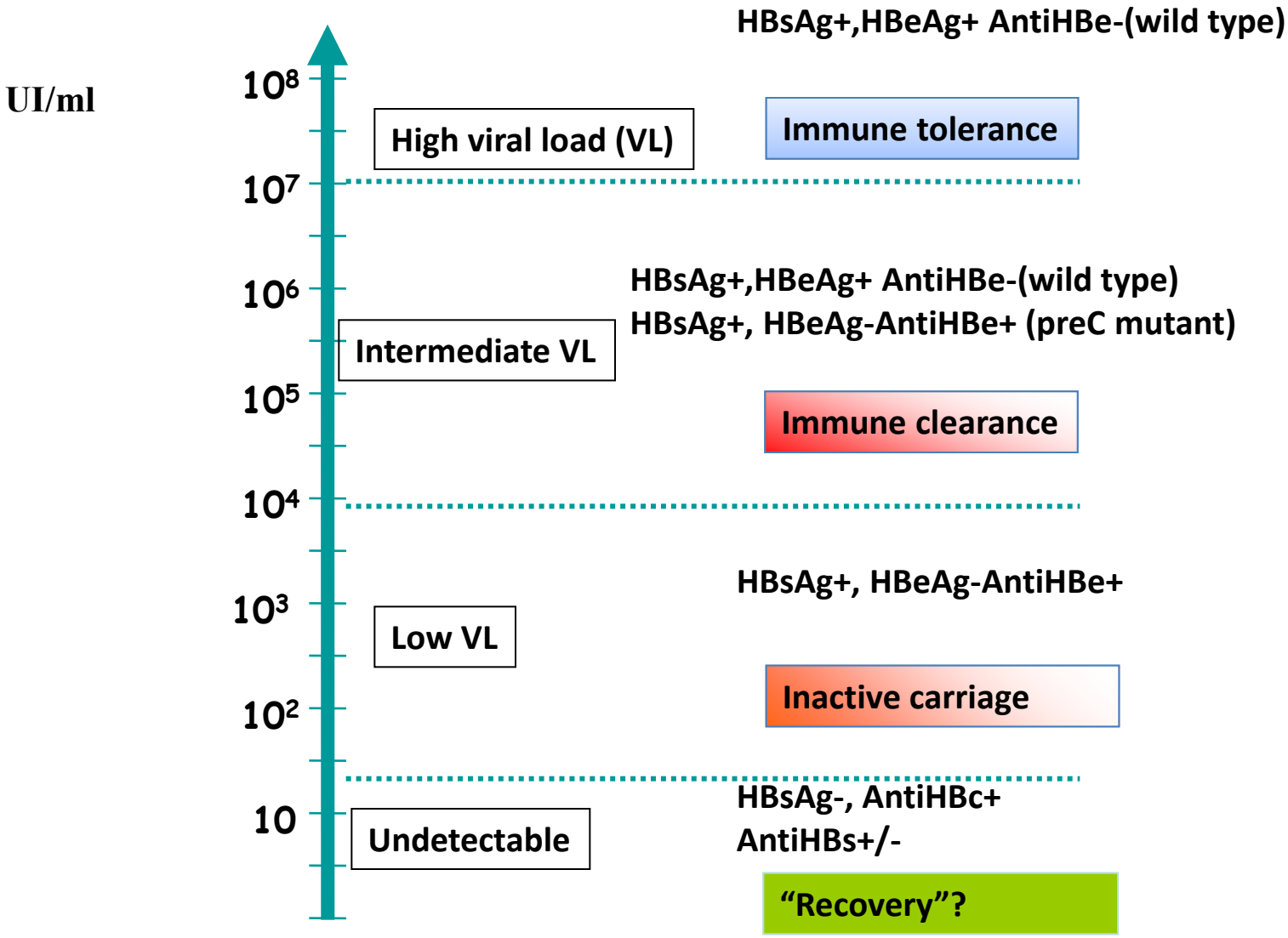
HBV Replication Cycle



Hepatocellular carcinoma

Zoulim F Gastroenterology 2009

Natural history of HBV infection



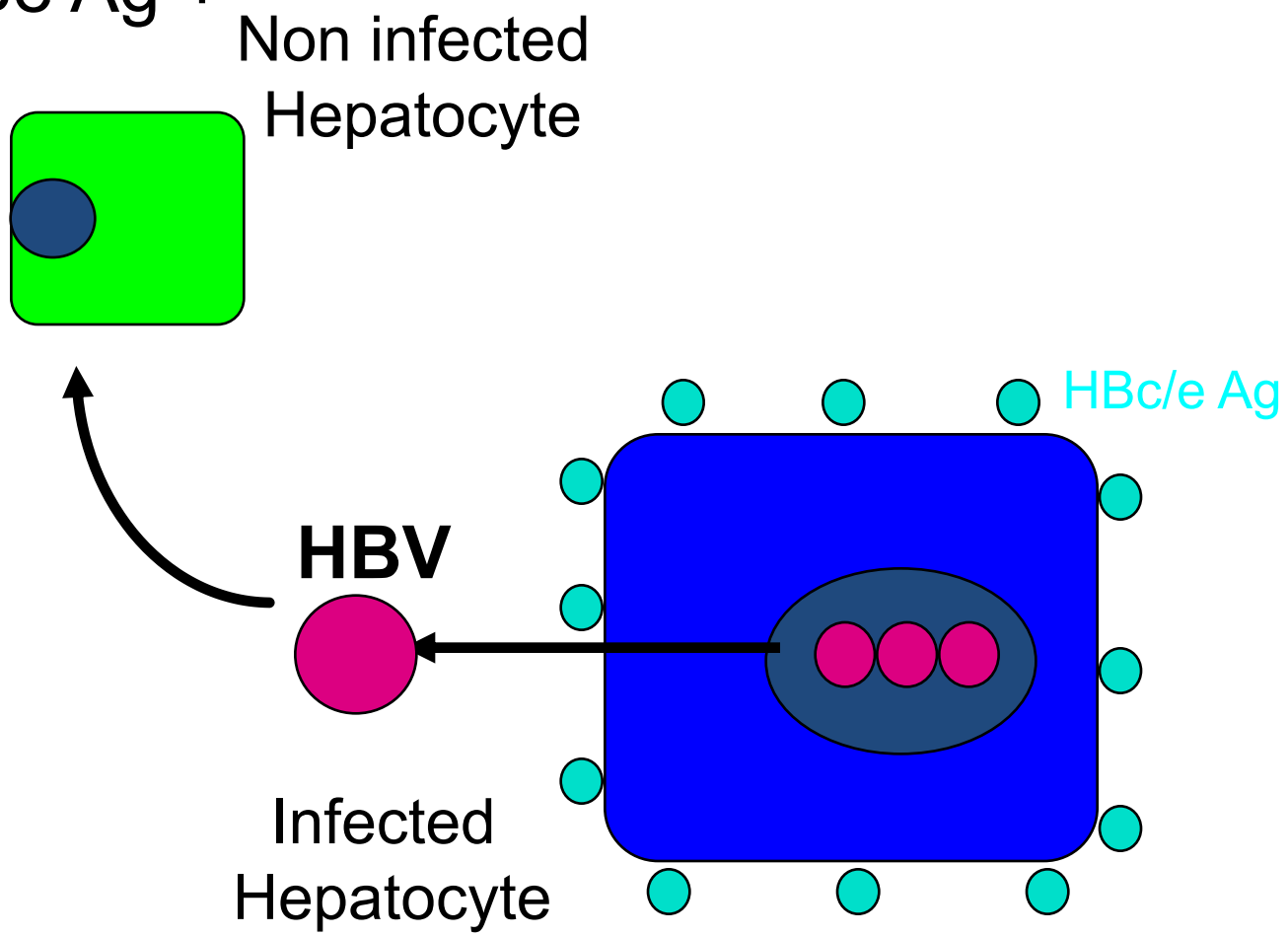
Yim et al. Hepatology 2006

Natural history of HBV infection

Immune tolerance

Normal ALT

HBe Ag +

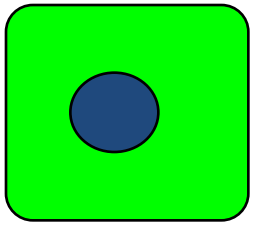


Natural history of HBV infection

Inactive carriage

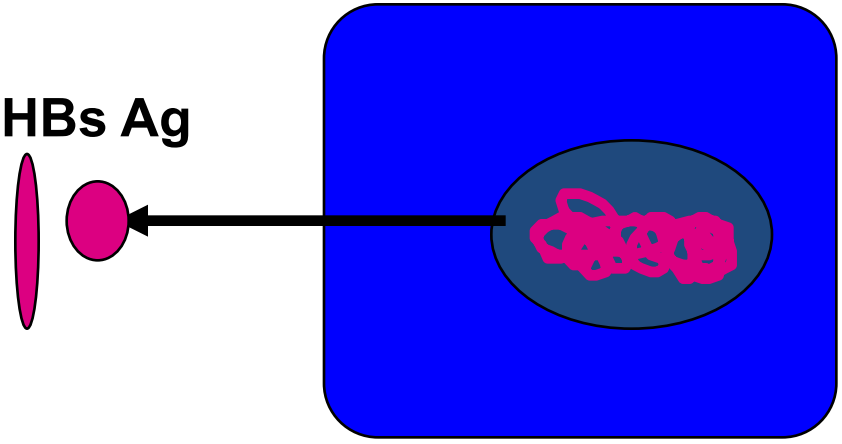
AntiHBeAc+

Normal ALT



Non infected Hepatocyte

HBs Ag



Infected Hepatocyte

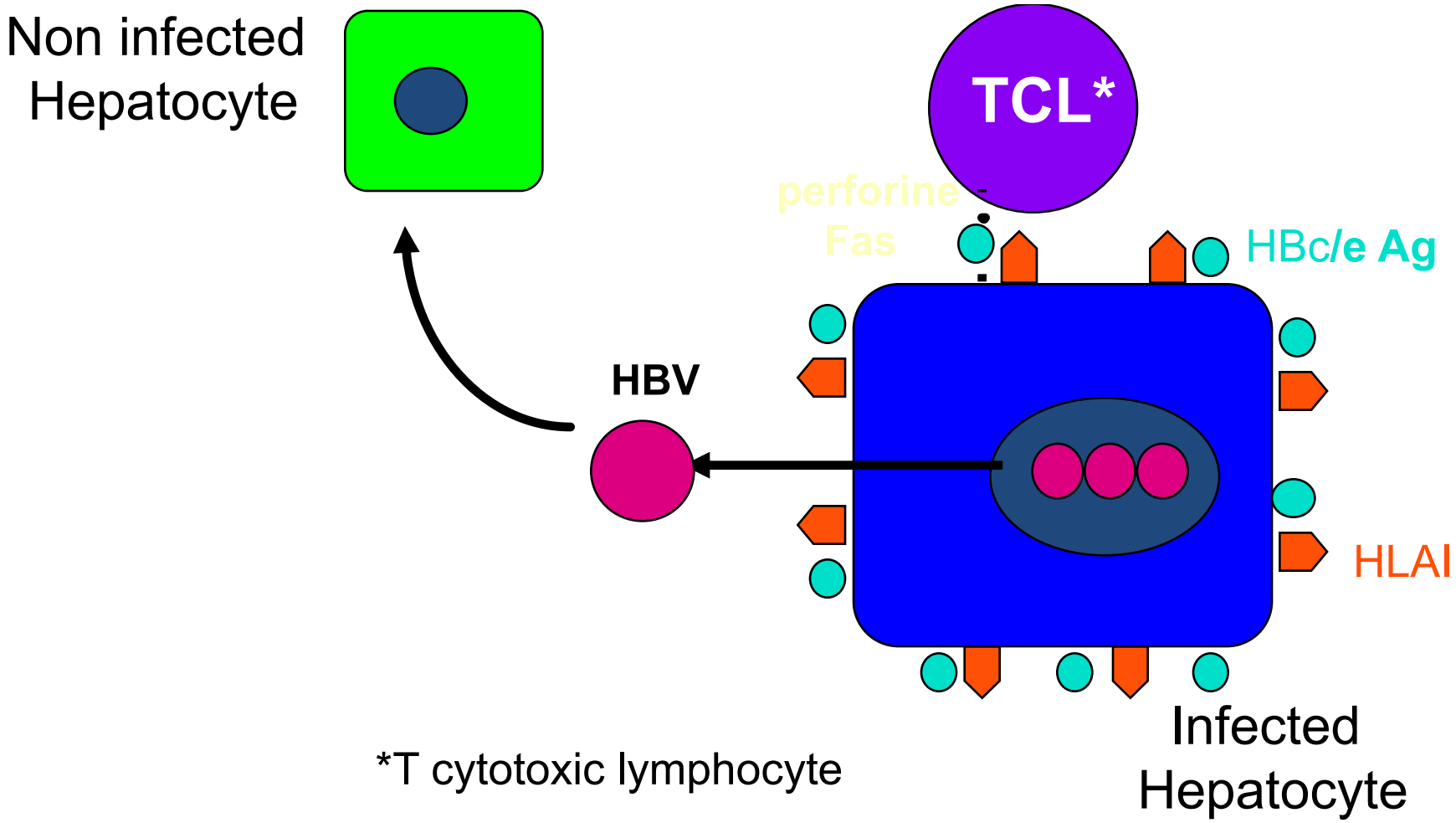
Lok et al. Gastroenterology 2001; 120:1828-53

Natural history of HBV infection

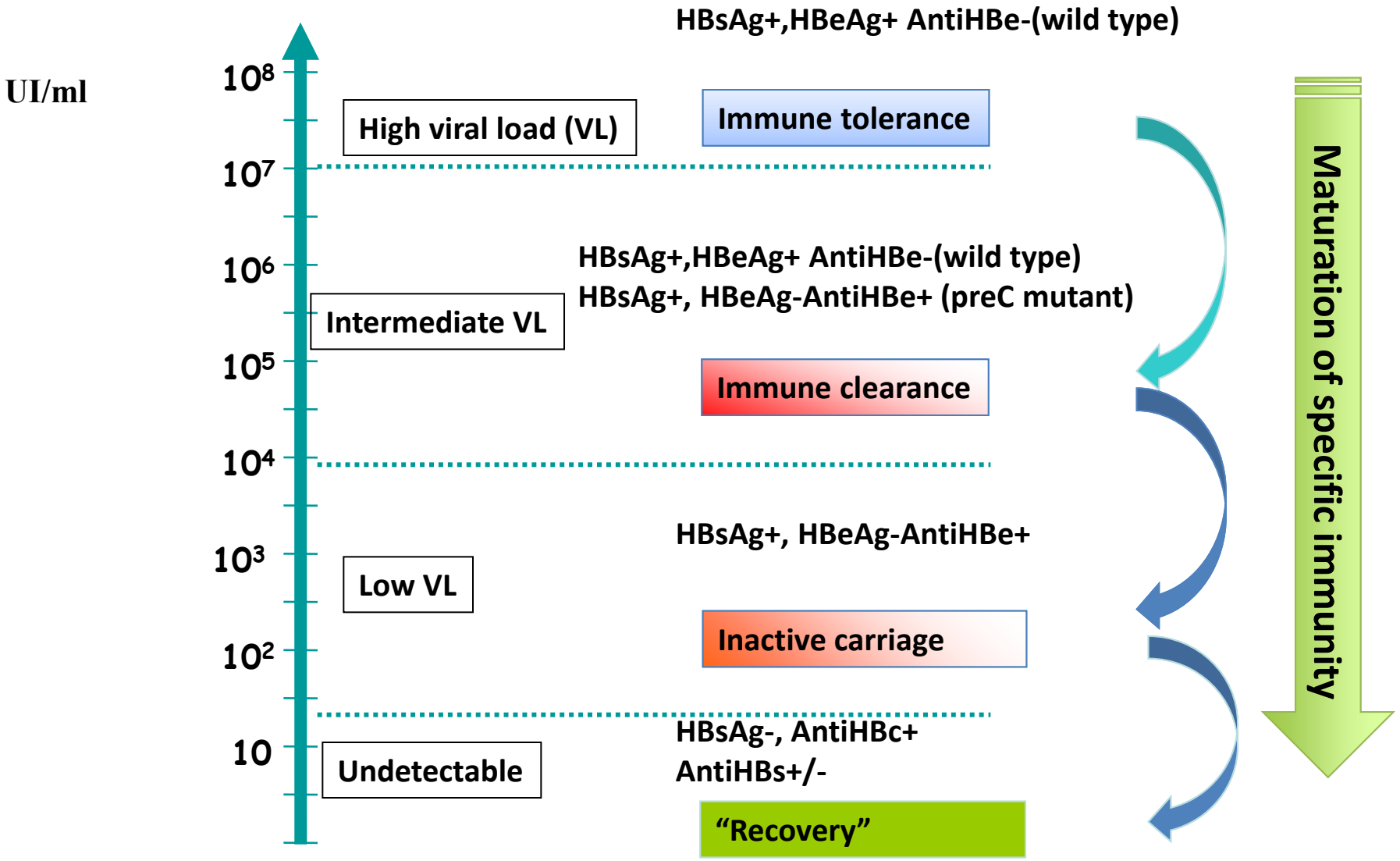
Immune clearance :chronic hepatitis

Abnormal ALT/Necro-inflammation

Fibrosis/cirrhosis



Natural history of HBV infection



Yim et al. Hepatology 2006

HBV in immune compromised patients

- Pathobiology of HBV infection

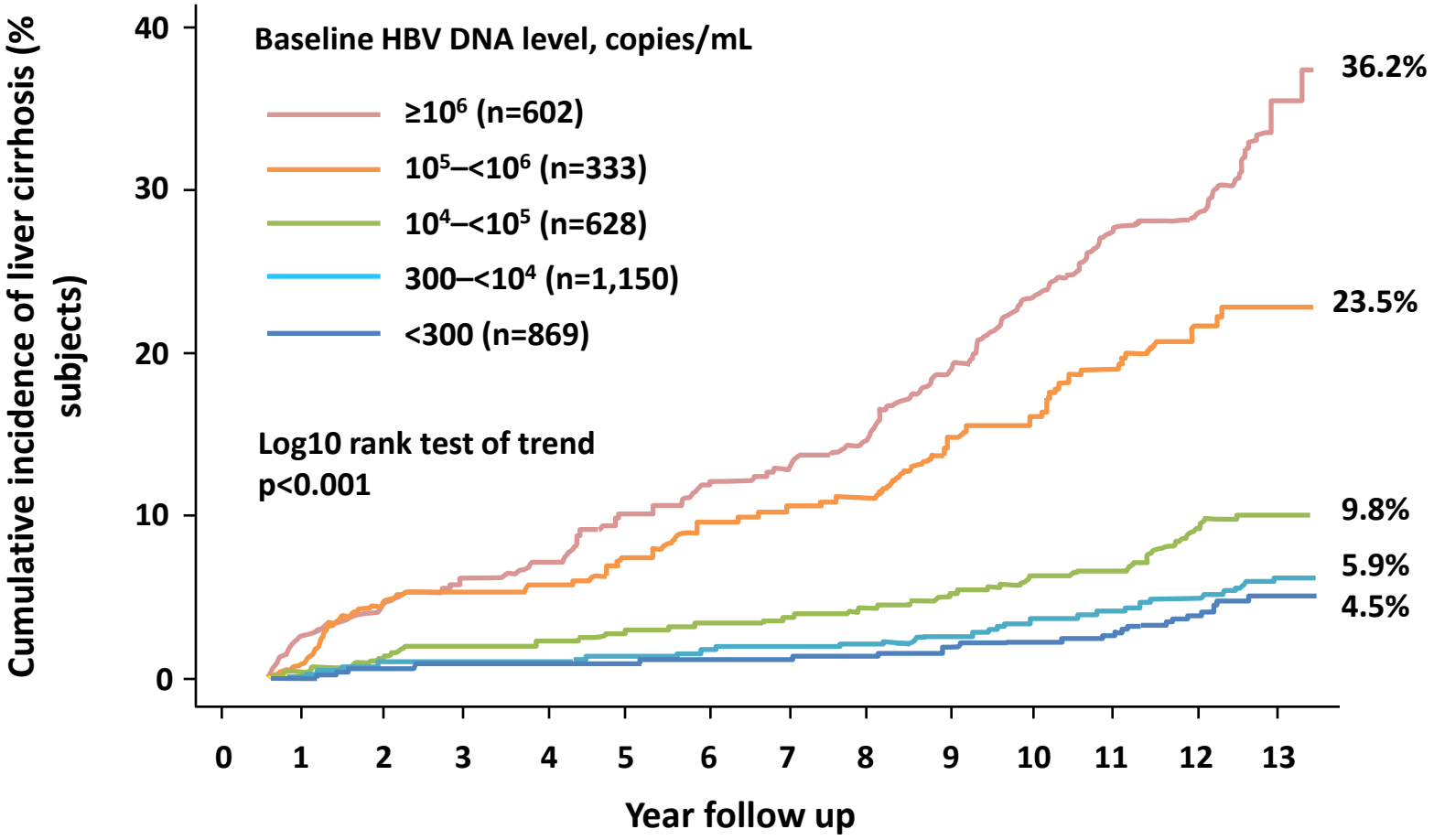
- Consequences of immune deficiency on HBV infection:
  - Increase in viral replication/reactivation
  - Decrease in spontaneous reduction of HBV replication
  - Harmful liver impact: cirrhosis/HCC

- Therapeutic implications

High baseline viral load is associated with increased incidence of cirrhosis

REVEAL study: Cumulative incidence of liver cirrhosis

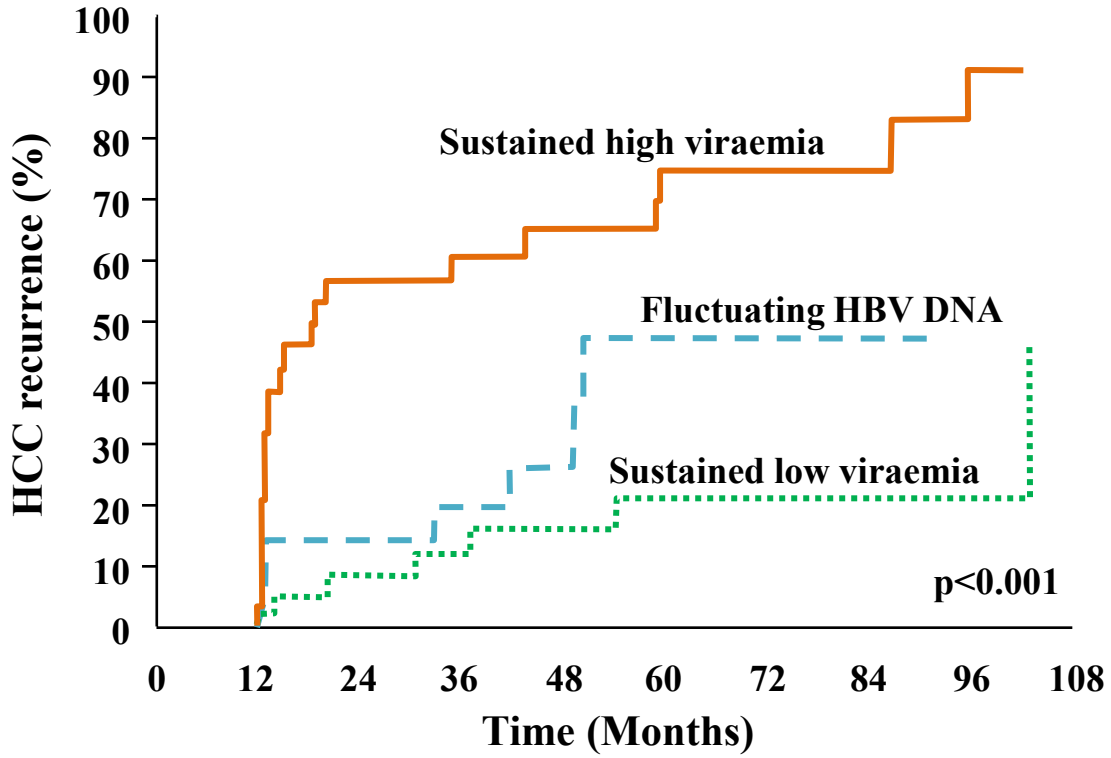
All subjects (N=3,582)



Iloeje UH et al. Gastroenterology 2006;130:678–86.

Recurrence of HCC is significantly lower in patients with sustained low HBV DNA

Recurrence of hepatocellular carcinoma (HCC) in the 115 patients surviving >1 year without recurrence after resection



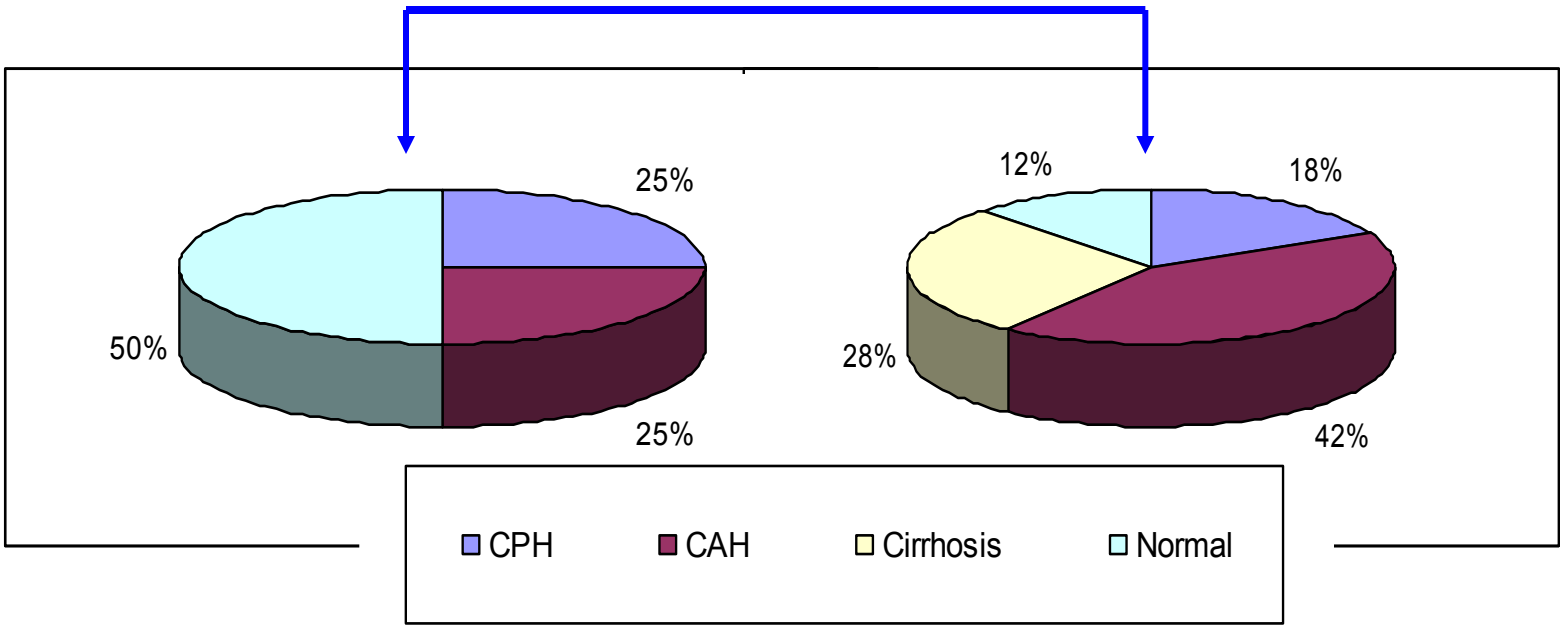
There is a significantly low recurrence of HCC in the sustained low viraemia group than the other groups (log-rank test, p<0.001)

An HJ, et al. J Gastroenterol Hepatol 2010;25:1876–82.

HBV in renal transplantation

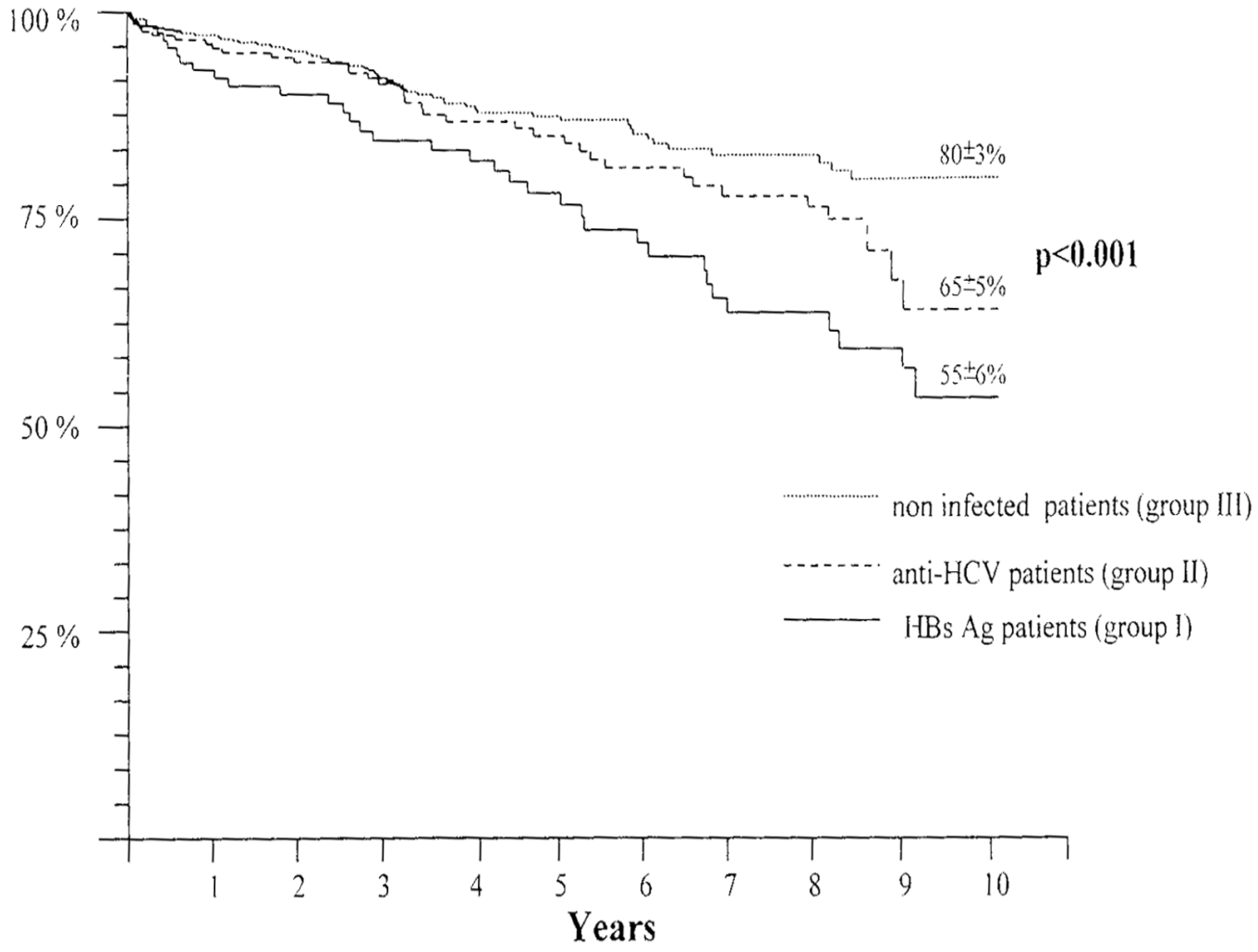
Frequent pathological deterioration: increased prevalence of cirrhosis and hepatocellular carcinoma

mean interval: 66 months (n = 131)



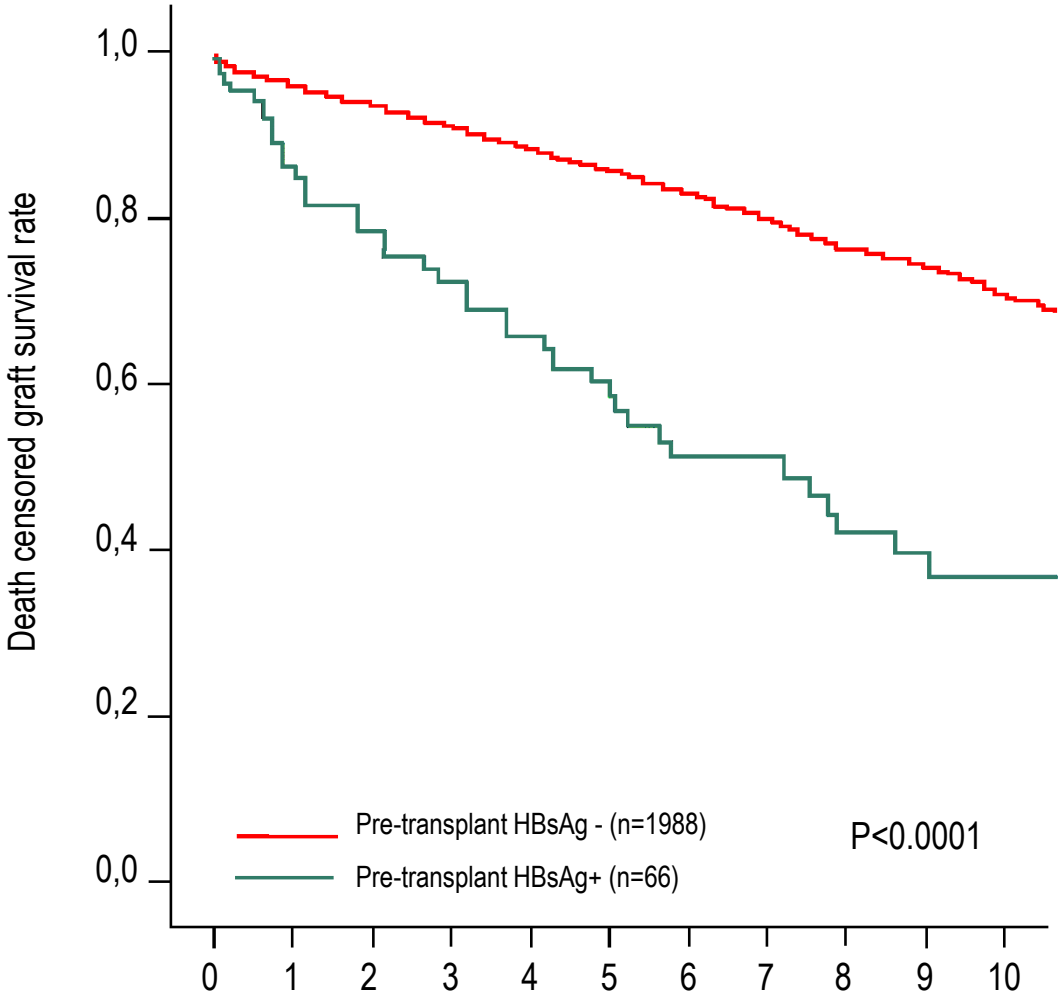
Fornairon et al. Transplantation 1996

Survival according to HCV and HBV status in renal transplantation



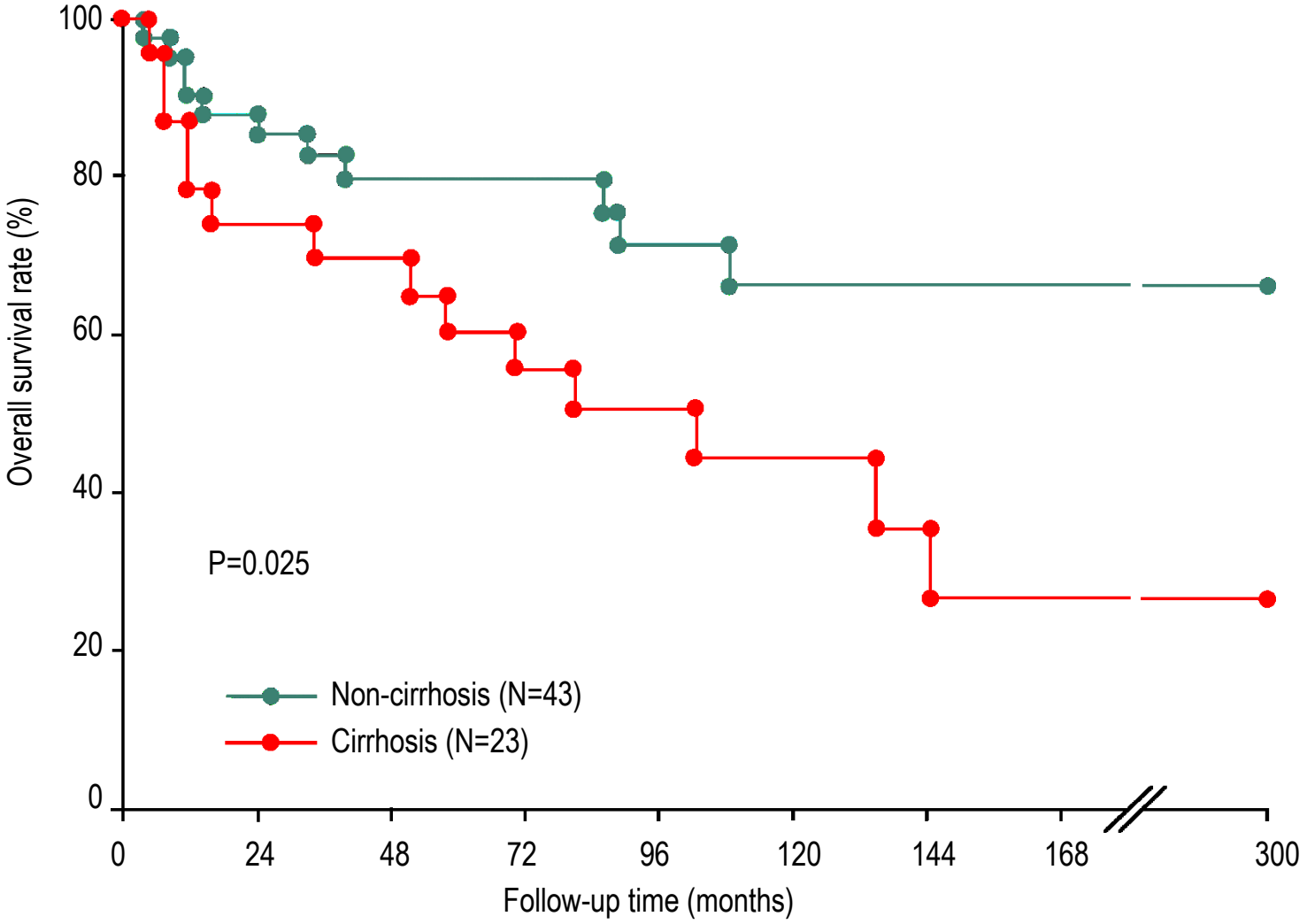
Mathurin et al. Hepatology 1999

Impact of HBV on allograft survival



Ahn HJ, 2007

HBV-cirrhosis and survival in kidney transplantation

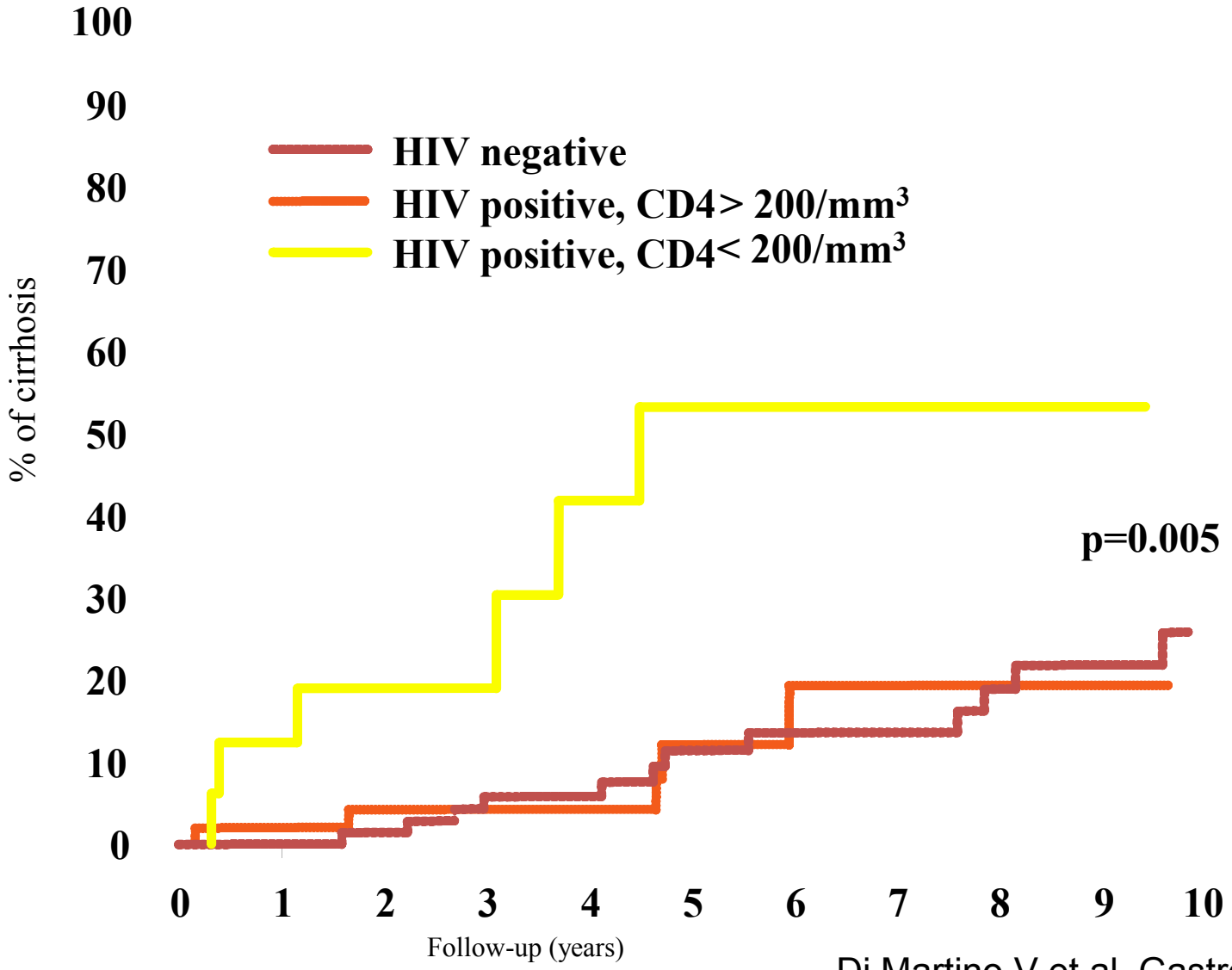


Non-cirrhosis	43	35	24	23	17	13	10	9	1
Cirrhosis	23	17	15	12	9	6	3	2	0

Fan WC, 2006

HIV & HVB co-infection

Immune deficiency has a negative impact



Di Martino V et al. Gastroenterology 2002

HIV & HVB co-infection

EpiB Germivic study

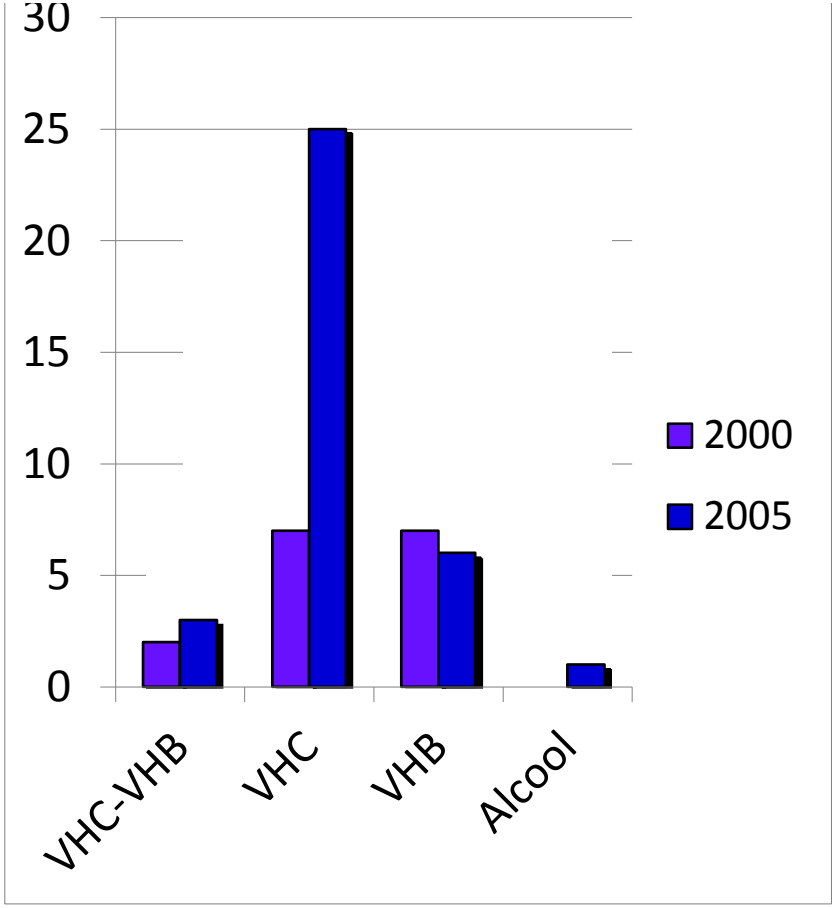
	HIV-positive patients (n = 246)	HIV-negative patients (n = 205)	p*
First HBV DNA (mean ± SD, log_{10} IU/ml)	3.9 ± 2.6	4.8 ± 2.5	0.002
First HBe Ag positive, n/N (%) **	70/151 (46.4%)	59/180 (32.8%)	0.01
First ALT (x normal value, mean ± SD)	2.1 ± 3.2	1.9 ± 3.0	0.09
First METAVIR Fibrosis score **** (mean ± SD)	2.0 ± 1.3	2.1 ± 1.2	0.84
HBV treatment received during the entire medical history, (n, %)	228 (92.7%)	117 (57.1%)	<0.0001
Mean time spent on anti-HBV therapy (mean ± SD, months) (n)**	80 ± 53 (n=243)	35 ± 43 (n=166)	<0.0001
On HBV monotherapy	56 ± 45 (n=217)	33 ± 37 (n=101)	0.0002
On HBV combined therapy	40 ± 26 (n=176)	34 ± 26 (n=64)	0.12
On tenofovir	43 ± 25 (n=180)	16± 15 (n=14)	0.0002
On lamivudine/emtricitabine	81 ± 48 (n=220)	55 ± 38 (n=78)	<0.0001
On adefovir	26 ± 23 (n=23)	34 ± 21 (n=68)	0.06
On entecavir	13 ± 6 (n=5)	13 ± 9 (n=28)	0.65
Last HBV DNA < 2,000 IU/ml (n/N, %)	206/238 (86.6%)	157/202 (77.7%)	0.02
Last HBV DNA below LOQ (n/N, %)	169/238 (71.0%)	89/202 (44.1%)	<0.0001
HBe Ag loss (n/N, %) ***	39/108 (36.1%)	28/63 (44.4%)	0.36
HBe seroconversion (n/N, %) ***	9/108 (8.3%)	10/63 (15.9%)	0.21
HBs Ag loss (n/N, %)	19/189 (10.1%)	3/155 (1.9%)	0.002
HBs seroconversion (n/N, %)	12/160 (7.5%)	2/127 (1.6%)	0.02
Last Fibrosis score (mean ± SD)	1.9 ± 1.4	1.4 ± 1.1	0.002
Last clinical presentation			0.02
Cirrhosis, n (%)	34 (14.4%)	12 (6.4%)	
Hepatocellular carcinoma, n (%)	3 (1.3%)	2 (1.1%)	

Piroth et al. J Hepatol 2008

HIV & HVB co-infection
Liver related mortality

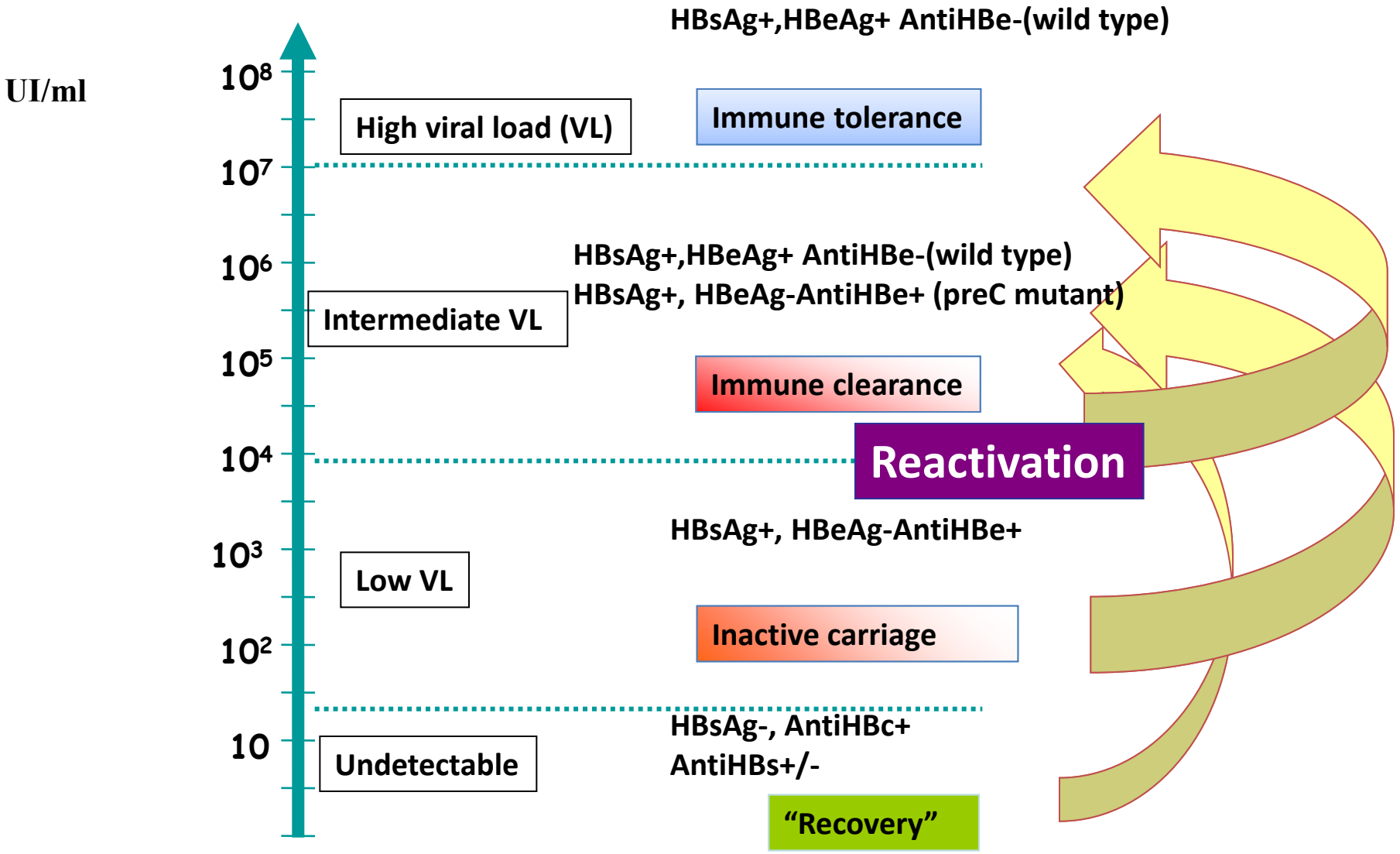
	n	%
Cirrhosis decompensation	91	66
Hepatocellular carcinoma	35	25
Other HCV (2 related to IFN Tt)	3	2
HBV reactivation	1	0.7
Others	8	6

Number of deaths related to HCC



Salmon D et al. J Hepatol 2009

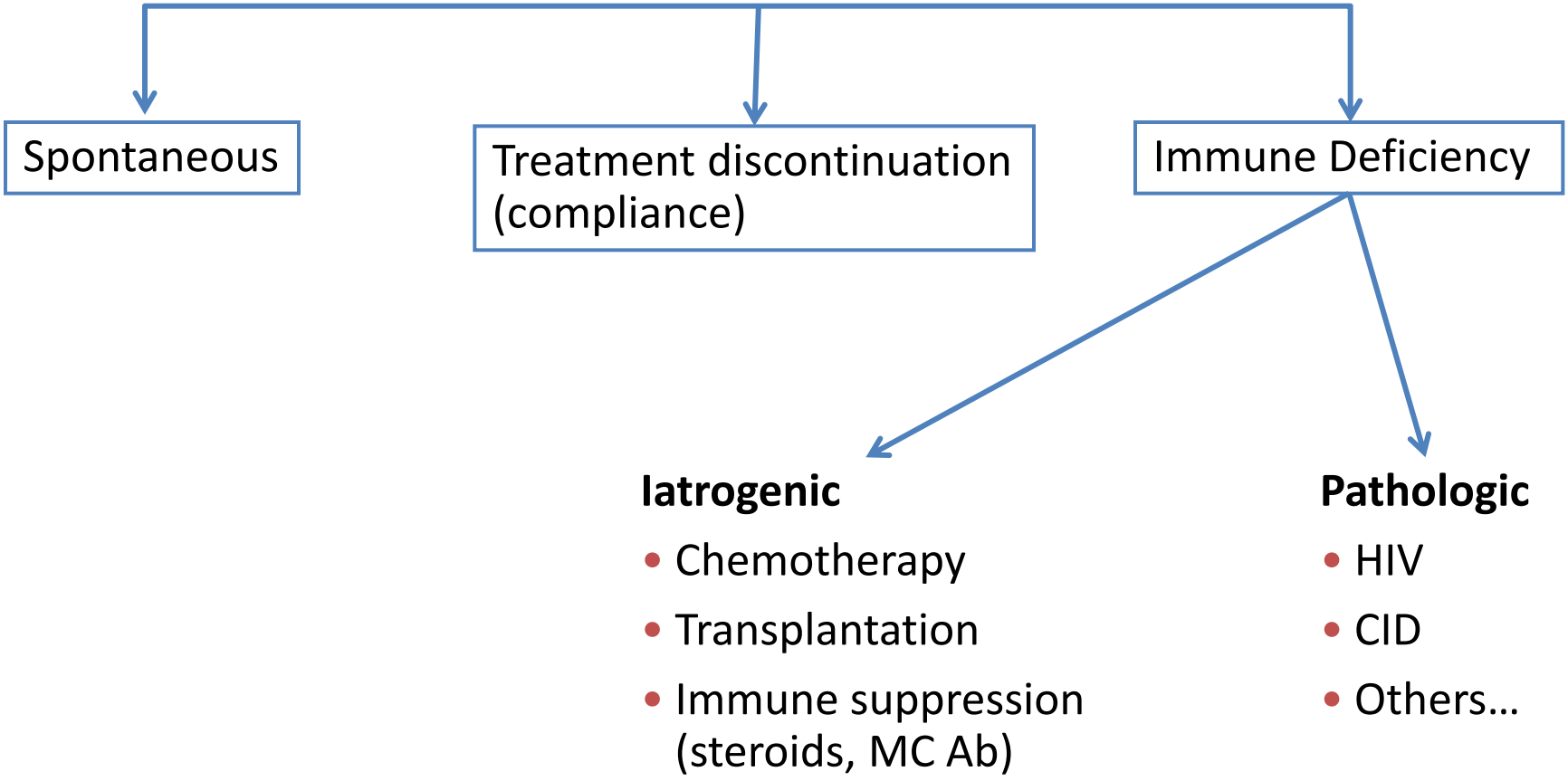
HBV reactivation



> 1 log HBV DNA or re-appearance of HBsAg/HBV DNA

Yim et al. Hepatology 2006

HBV reactivation

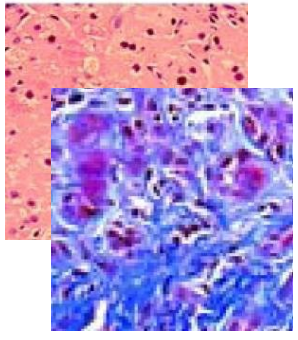


HBV reactivation

Immune deficiency

High HBV replication

Acute Hepatitis

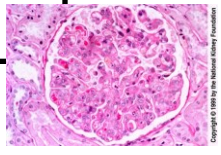


Fulminant Hepatitis

Fibrosing cholestatic Hepatitis

Chronic Hepatitis

Extra-hepatic impact of HBV



Risk factors of reactivation

Factors	HBsAg positive	HBsAg negative
Host-related	• Lymphoma • Hematologic disease • Underlying liver disease/ALT • Young age • Male gender • High BMI	• Hematological malignancy • BMT
Virus-related	• High viral load • HBeAg+	• AntiHBc+ • AntiHBs decline ?
Treatment-related	• High doses of chemotherapy, 2nd line, anthracyclines • Corticosteroids	• Rituximab

Risk factors of reactivation

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Treatment-related	• High doses of chemotherapy, 2nd line, anthracyclines • Corticosteroids	• Rituximab

Any modification of the immune status of a HBsAg carrier requires a pre-emptive therapy

Prevalence of HBV reactivation in HBs Ag+

	Prevalence	Extremes
Reactivations	46 % (193 / 424)	24 – 88 %
Hepatitis	33 % (159 / 476)	24 – 88 %
Hepatic decompensation	13 % (21 / 162)	5 – 33 %
Liver-related mortality	5 % (27 / 494)	0 – 33 %

Loomba et al. Ann Intern Med 2008

Prevalence of HBV reactivation in HBsAg-/Ac antiHBs +/Ac antiHBc +

References	Prevalence	
Lok AK et al. Gastroenterology 1991	5 %	2 / 33
Huy CK et al. Gastroenterology 2006	5 %	1 / 21

HBV in immune compromised patients

- Pathobiology of HBV infection
- Consequences of immune deficiency on HBV infection:
  - Increase in viral replication/reactivation
  - Decrease in spontaneous reduction of HBV replication
  - Harmful liver impact: cirrhosis/HCC
  - Risk of immune restoration after discontinuation of immune suppression
- Therapeutic implications

HBV reactivation and Immune restoration

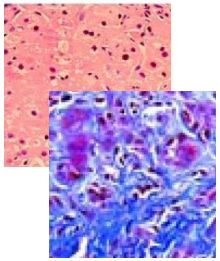
Discontinuation of immune deficiency)

Immune deficiency

Immune restoration

High HBV replication

Acute Hepatitis

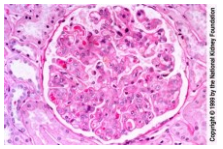


Fulminant Hepatitis

Fibrosing cholestatic Hepatitis

Chronic Hepatitis

Extra-hepatic impact of HBV



HBV reactivation and Immune restoration

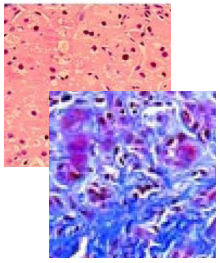
Discontinuation of immune deficiency)

Immune deficiency

Immune restoration

High HBV replication

Acute Hepatitis

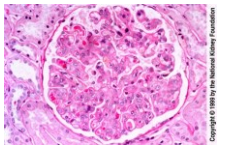


Fulminant Hepatitis

Fibrosing cholestatic Hepatitis

Chronic Hepatitis

Extra-hepatic impact of HBV



HBV in immune compromised patients

- Pathobiology of HBV infection
- Consequences of immune deficiency on HBV infection:
  - Increase in viral replication/reactivation
  - Decrease in spontaneousreduction of HBV replication
  - Harmful liver impact: cirrhosis/HCC
  - Risk of immune restoration after discontinuation of immune suppression
  - « Collateral damage »
- Therapeutic implications

HBV reactivation and Immune restoration

Discontinuation of immune deficiency)

Immune deficiency

Immune restoration

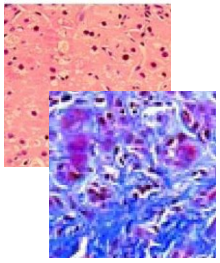
High HBV replication

«Collateral damage*»

Acute Hepatitis

Fulminant Hepatitis

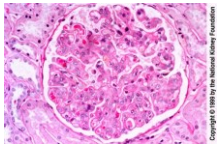
Discontinuation or delay of specific therapies



Fibrosing cholestatic Hepatitis

Chronic Hepatitis

Extra-hepatic impact of HBV



*related to the severity of the liver disease

HBV in immune compromised patients

- Pathobiology of HBV infection
- Consequences of immune deficiency on HBV infection
- Therapeutic implications:
  - Antiviral treatment of all immune compromised patients
  - Pre-emptive therapy

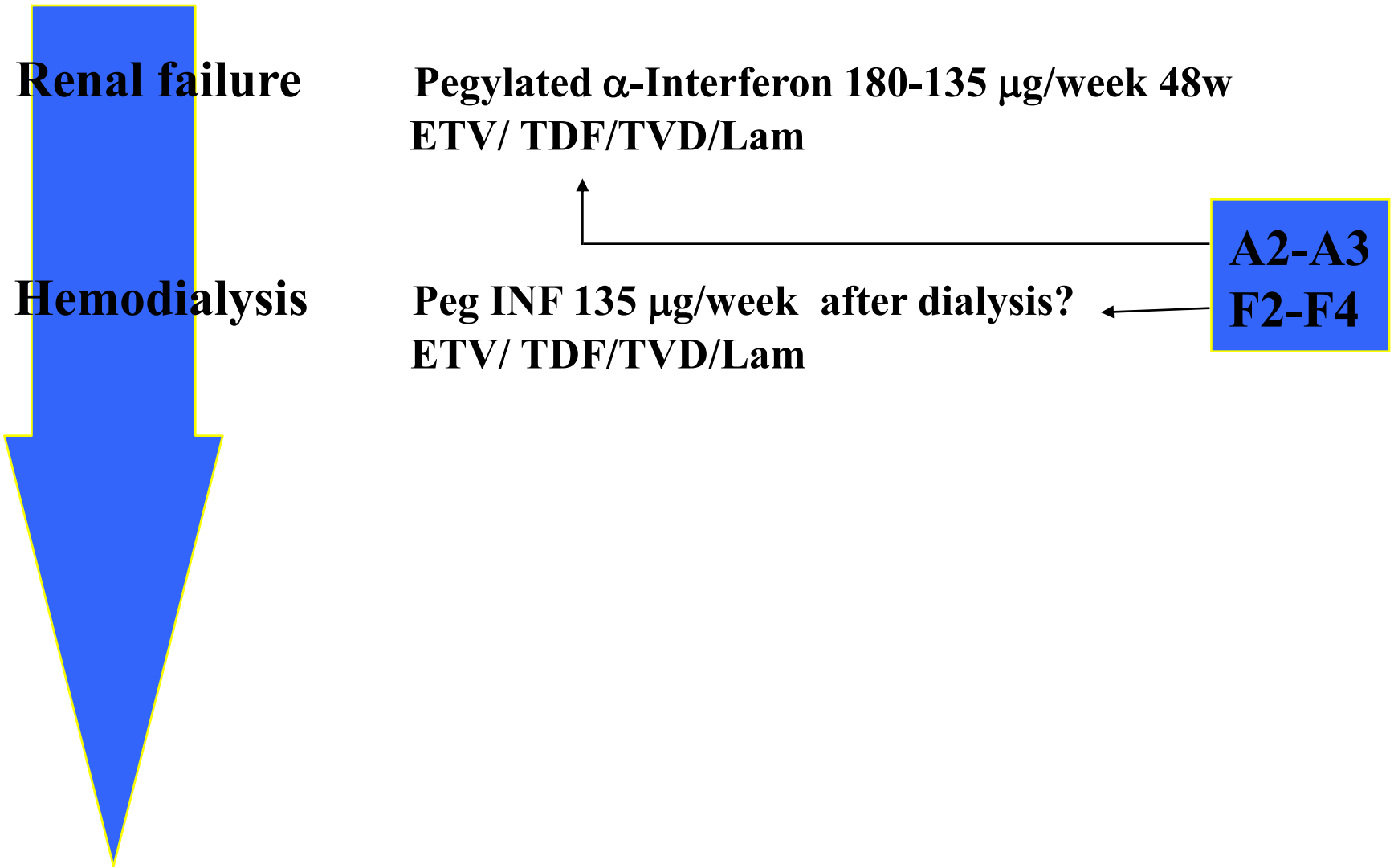
Treatment guidelines of HBV

"**Entecavir and tenofovir are potent HBV inhibitors** and they have a high barrier to resistance. Thus they can be confidently used as first-line monotherapies (A1)."[1]

F>1
& HBV DNA> 2000 UI/mL or ALT >N

EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol 2012

Therapeutical options in HBV-infected patients with renal disorders



Therapeutical options in HBV-infected patients with renal disorders

Renal function	Treatment	Liver biopsy
Renal failure	**Pegylated α-Interferon 180-135 µg/week 48w** **ETV/ TDF/TVD/Lam**	**A2-A3** **F2-F4**
Hemodialysis	**Peg INF 135 µg/week after dialysis?** **ETV/ TDF/TVD/Lam**	
	Pre-emptive ttt by Nuc. Analogues	
Kidney Tx	**All kidney recipients should be treated by Nucs* whatever the underlying liver status**	

*Every HBsAg positive patient who undergoes renal transplantation and receives immunosuppressive agents should receive anti-HBV prophylaxis with a NA. The need for antiviral prophylaxis or treatment should be constantly and frequently evaluated for all HBV positive renal transplant patients.

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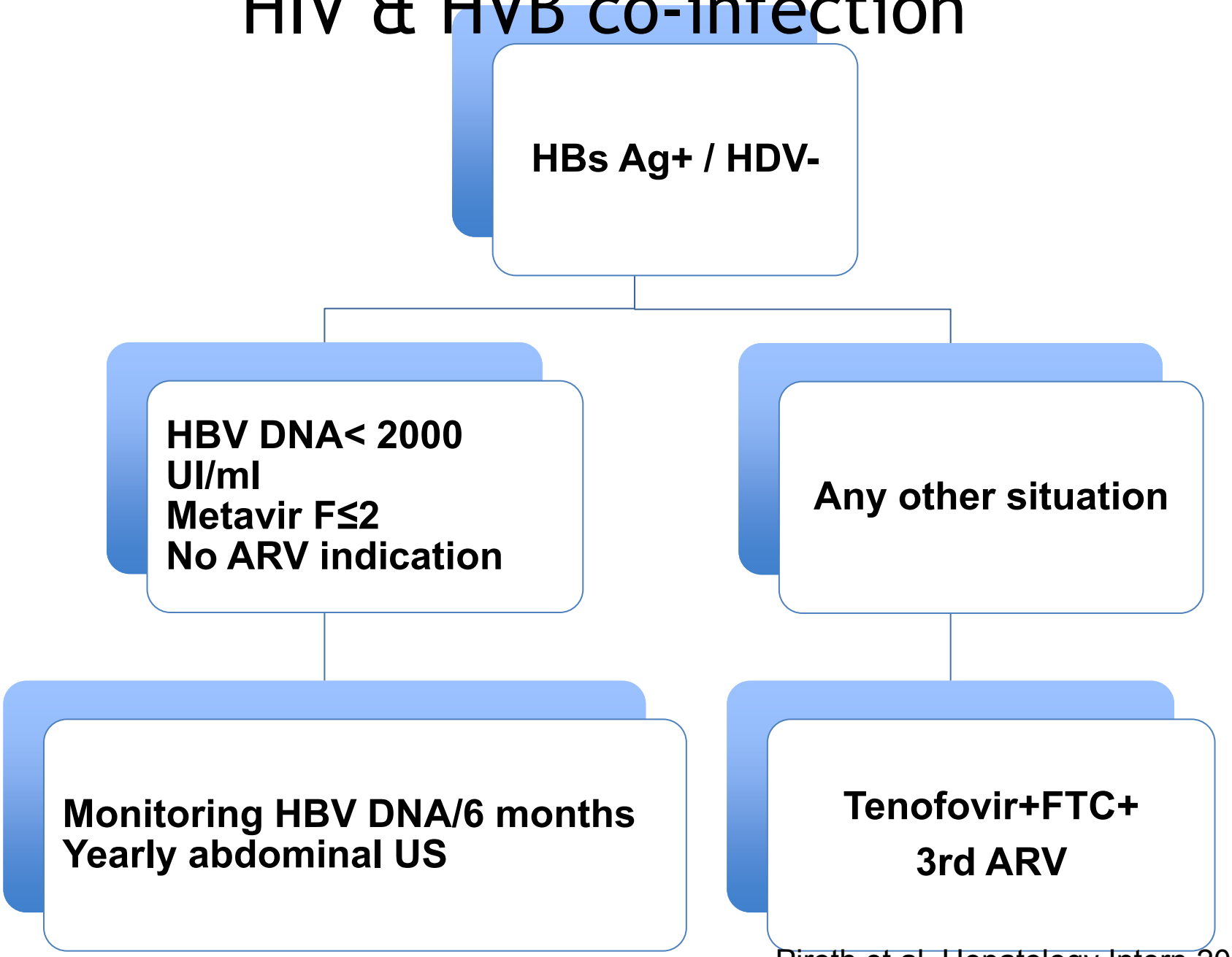
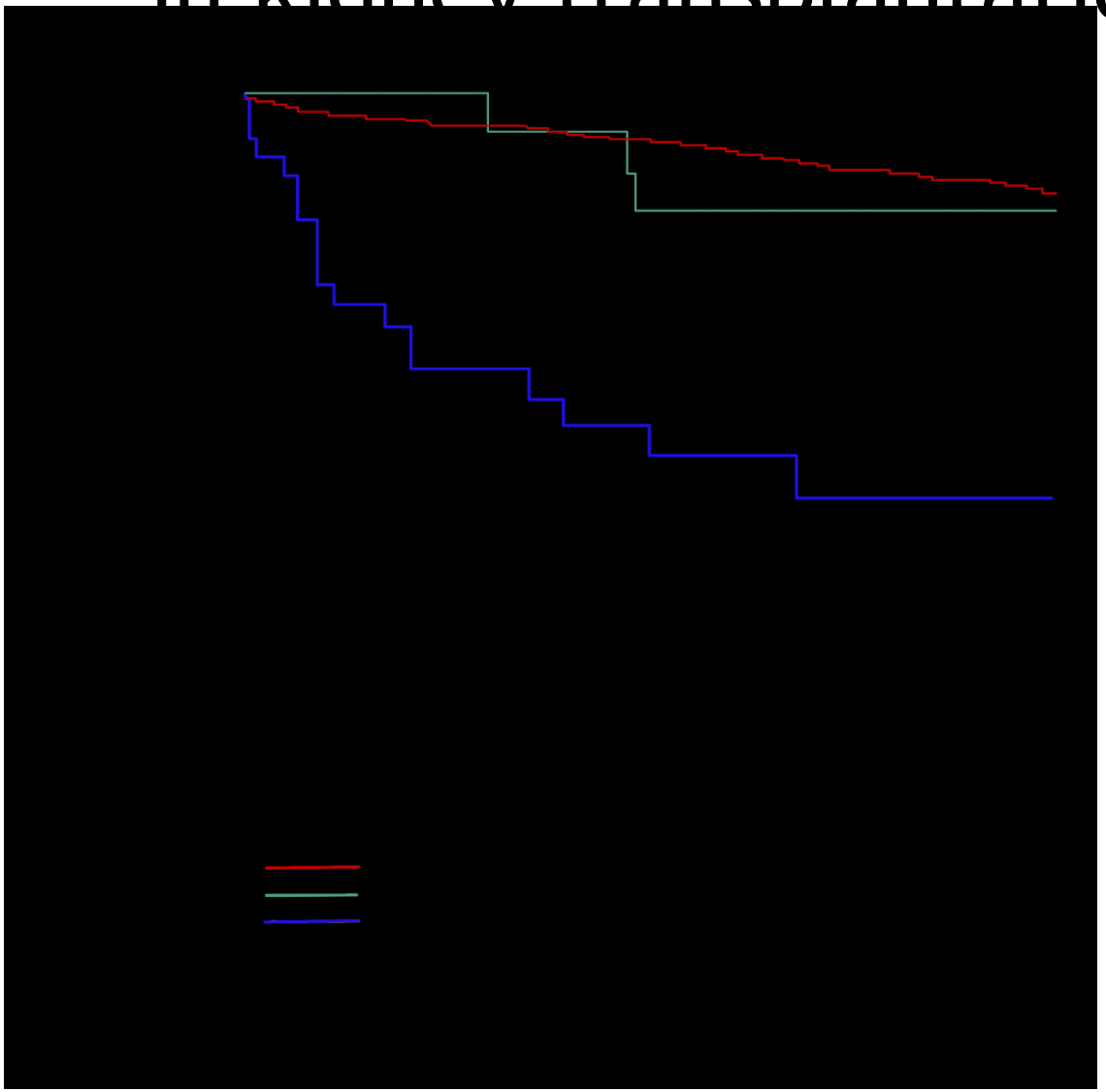
HIV & HVB co-infection



Piroth et al. Hepatology Intern 2011

Benefits related to viral suppression in kidney transplantation



Ahn HJ et al., 2007

Benefits of HBV treatment in immune compromised patients

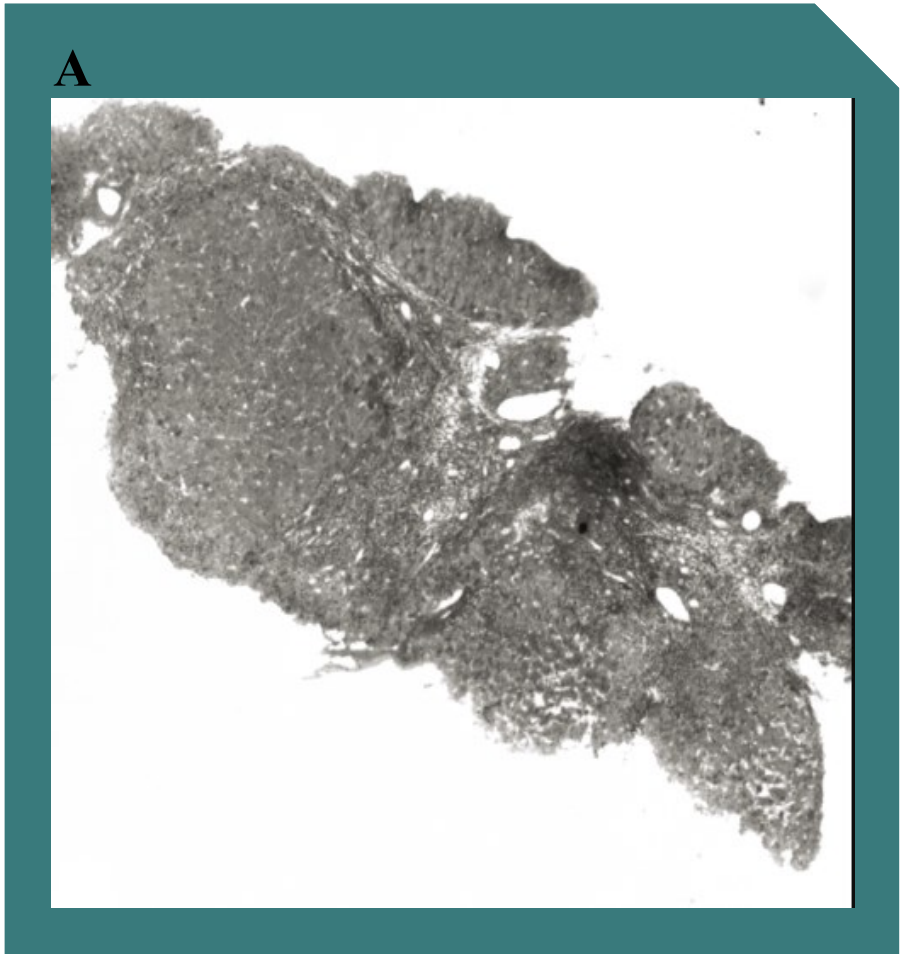
Survival of HBsAg+ kidney recipients with or without Nucs

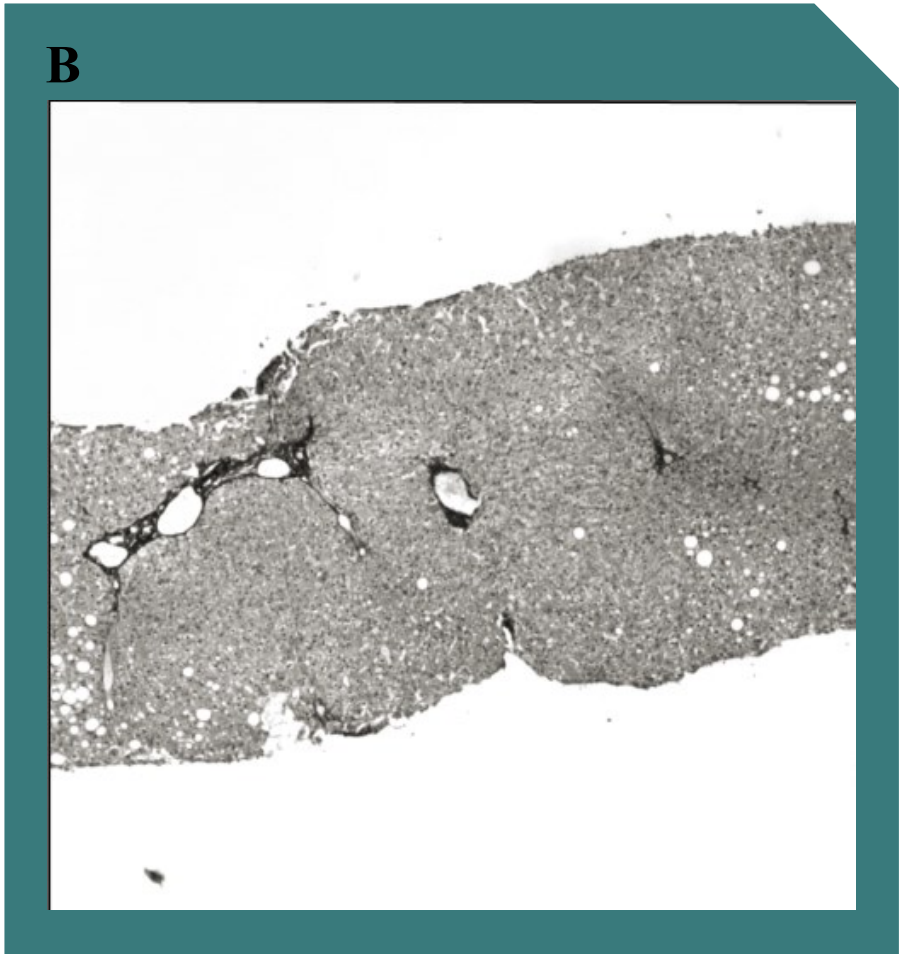
	Mathurin 1997	Ahn 2010	Cosconea* 2012
% 5-year survival	62	61	100
% 10-year survival	36	36.6	97.6

*97% undetectable HBV DNA but persistent risk of HCC, even in noncirrhotic patients

Cosconea et al. J Hepatol 2012

HBV-cirrhosis reversal





Mallet V et al. Antiviral Therapy 2007

HBV therapy in immune compromised patients

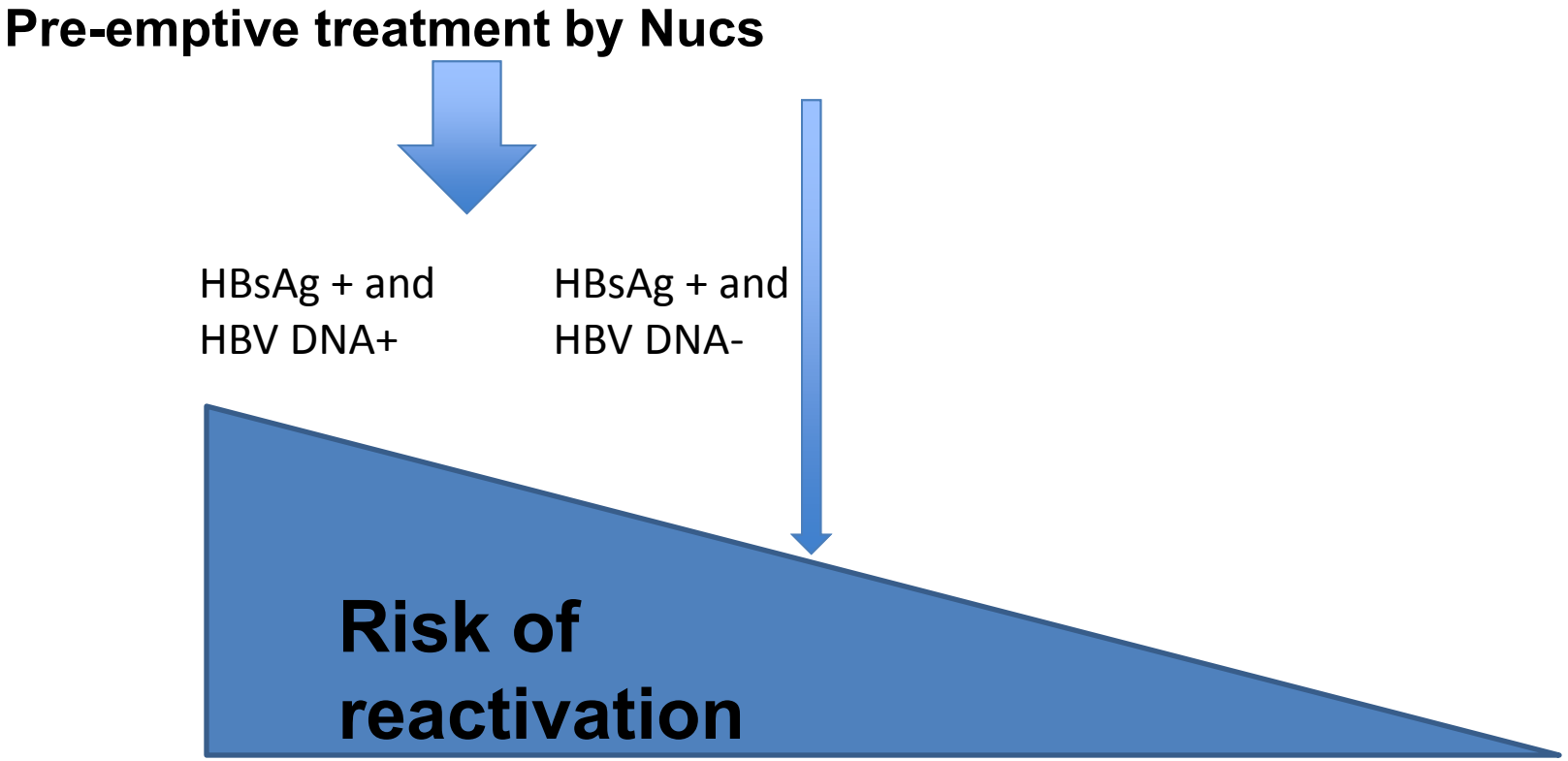
- Pathobiology of HBV infection
- Consequences of immune deficiency on HBV infection
- Therapeutic implications:
  - Antiviral treatment of all immune compromised patients
  - Pre-emptive therapy

Management of HBV during chemotherapy or immunosuppression

- Reactivation of HBV replication common during immunosuppression/chemotherapy (20% to 50%)
- Prophylactic antiviral therapy recommended in HBV carriers at onset of cancer chemotherapy or immunosuppressive therapy
  - If baseline HBV DNA < 2000 IU/mL, continue treatment for 6 mos after discontinuation
  - If baseline HBV DNA > 2000 IU/mL, continue treatment until they reach treatment endpoints for hepatitis B
- Tenofovir or entecavir preferred if treatment for > 12 mos

Lok AS, et al. Hepatology. 2009;50:661-662.

Pre-emptive treatment and EASL recommandations



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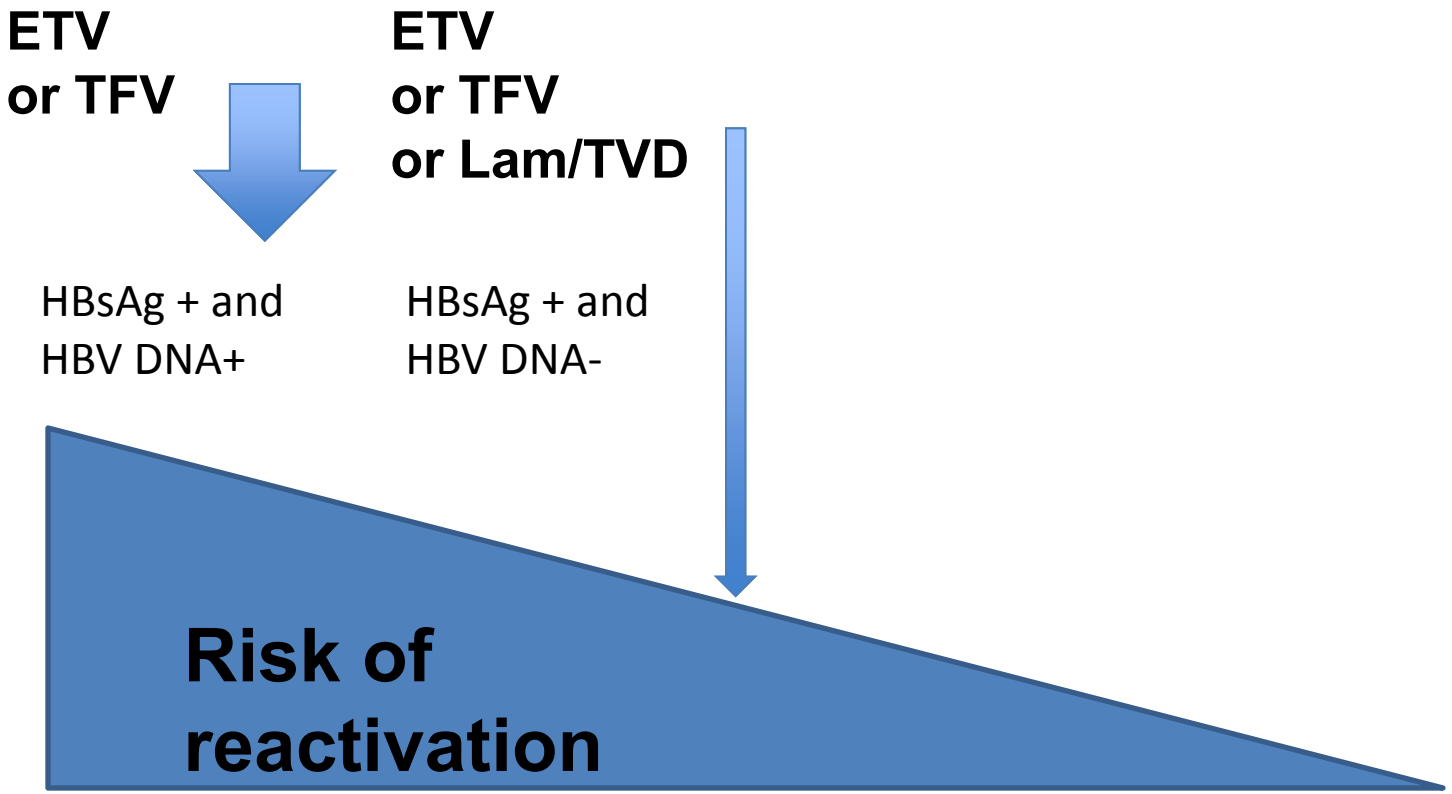
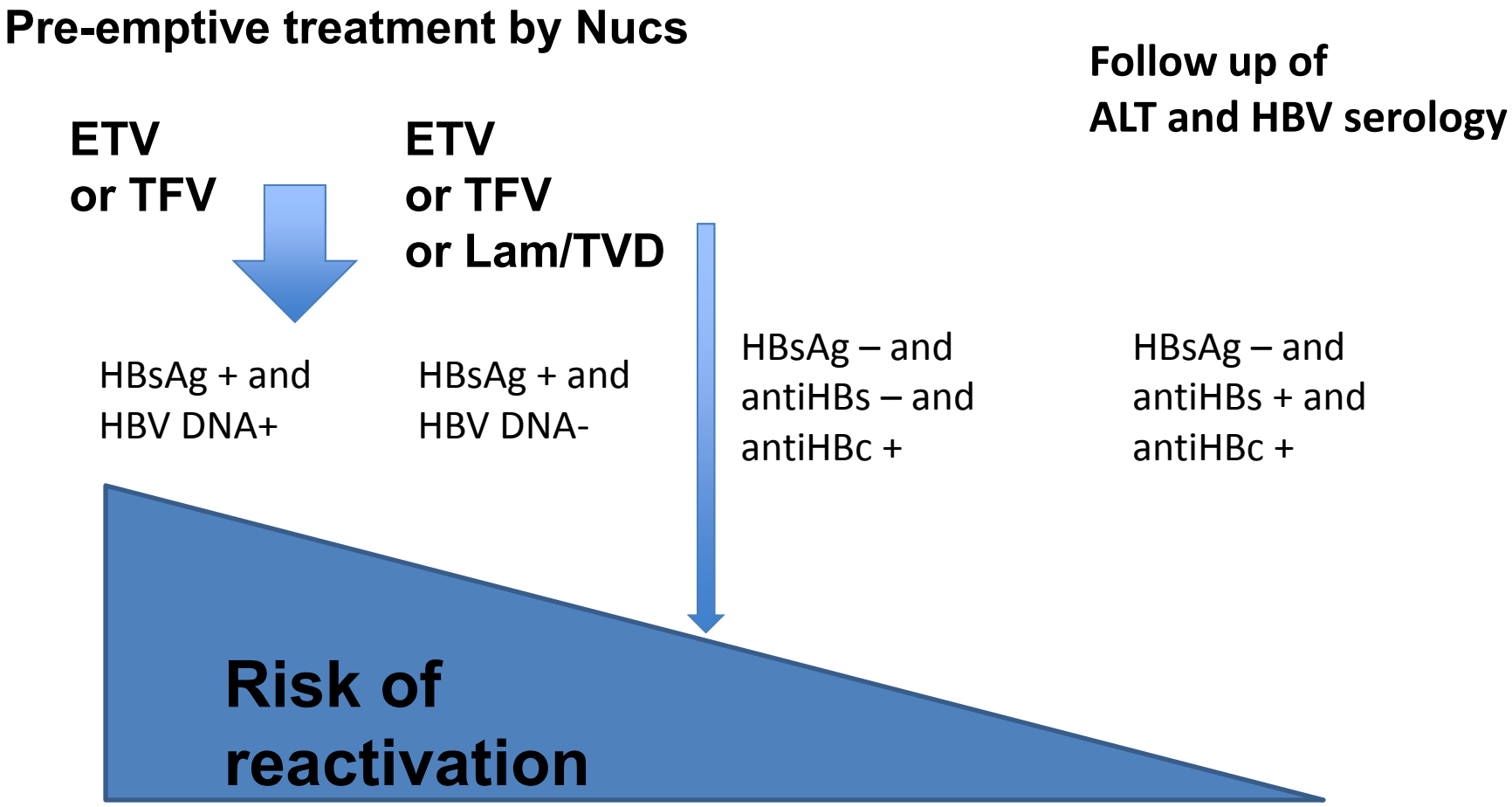
Pre-emptive treatment and EASL recommandations

Pre-emptive treatment by Nucs



EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol 2012

Pre-emptive treatment and EASL recommandations



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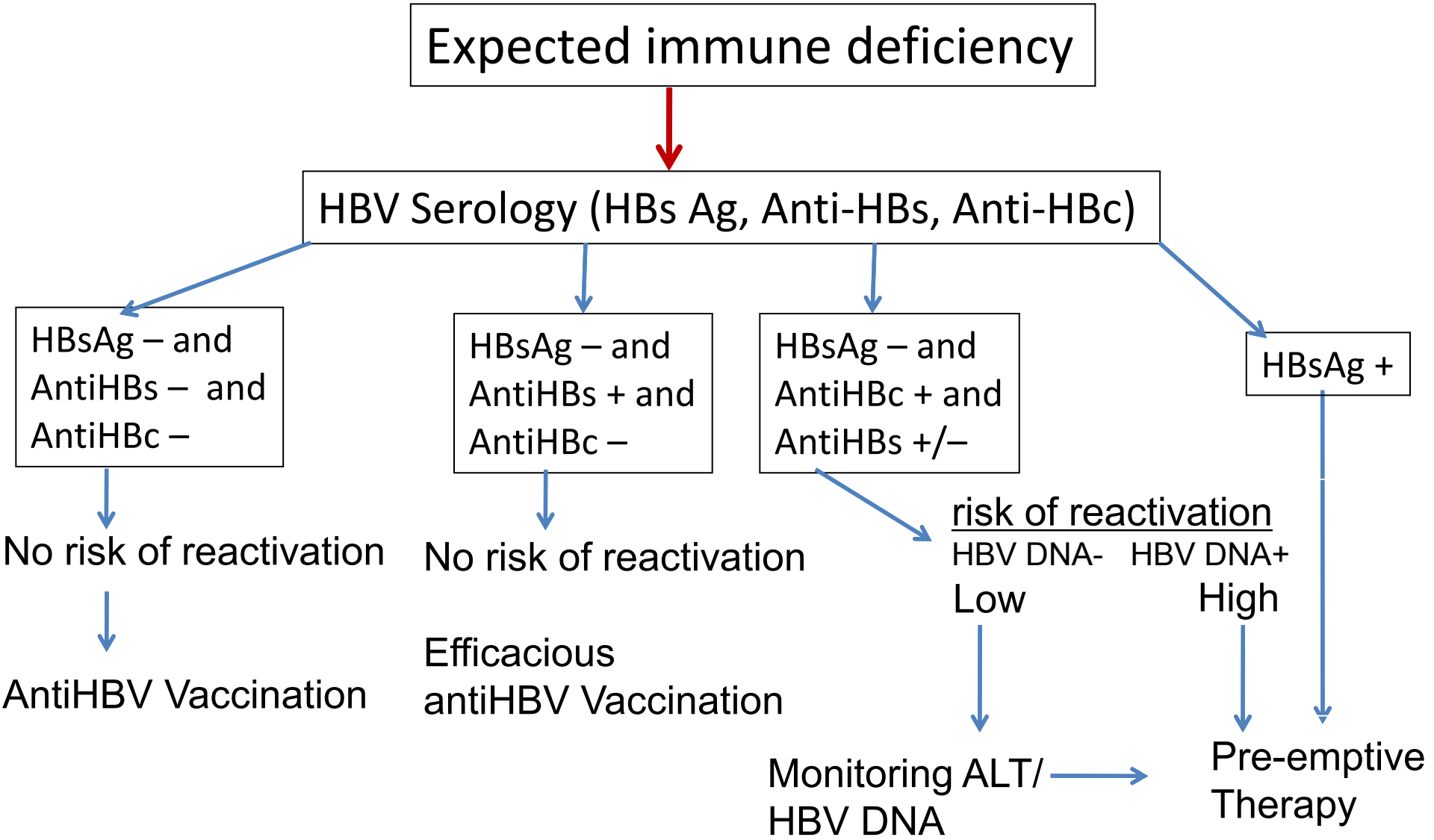
HBV and recommandations of pre-emptive treatment



Benefits of pre-emptive therapy of reactivation

Meta-analysis: 11 studies; 220 treated and 400 controls

	ARR (prophylaxis/control)	↓ Incidence
↓ HBV reactivation	-0.46 (-0.61 to -0.31)	87 %
↓Specific mortality	-0.03 (0.07 to 0.00)	70 %
↓Chemotherapy discontinuation or delay	-0.33 (-0.33 to -0.15)	92 %
Overall mortality	NS	

Martyak LA et al, Liver International 2007

Pre-emptive therapy
Risks associated with reactivation

Tumoral risk in chemotherapies

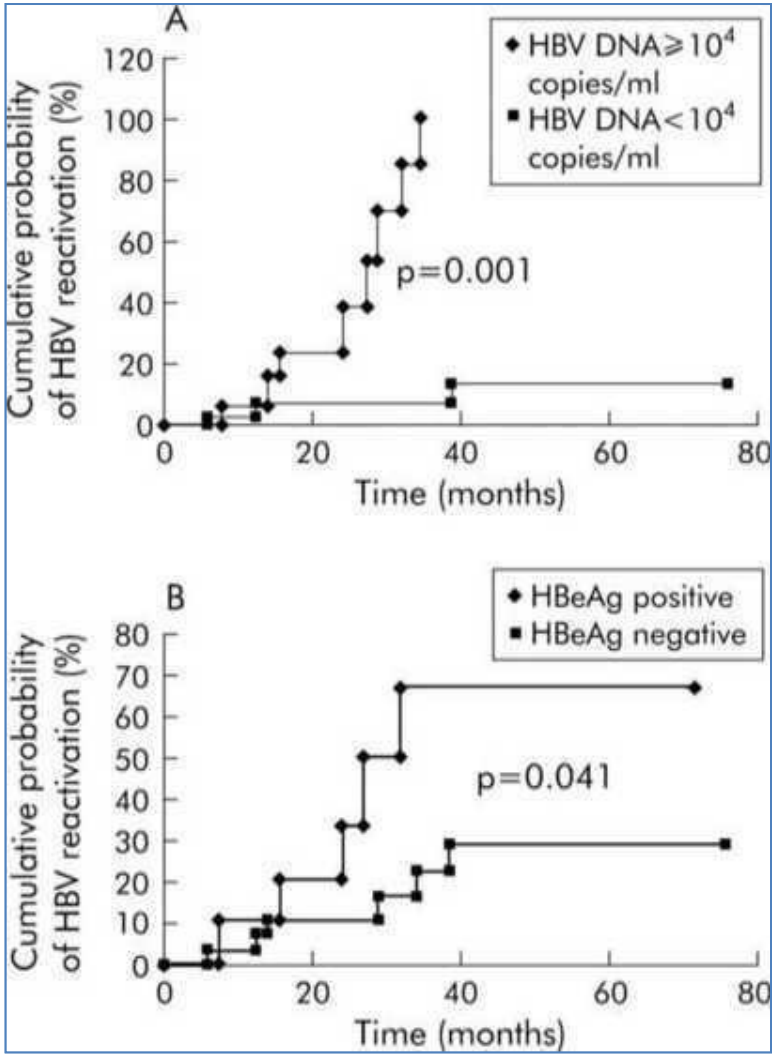
	Number of studies	Lamivudine	Controls
Chemotherapy discontinuation	6	17 %* (27 / 156)	39 % (127 / 322)
Tumor-related deaths	4	26 %* (11 / 42)	35 % (15 / 43)
All deaths	8	18 %* (21 / 118)	36 % (57 / 157)

* : p <0.05 vs. controls

Loomba et al. Ann Intern Med 2008

Reactivation after discontinuation of pre-emptive therapy

- 25.7 months follow-up after lamivudine discontinuation
- % reactivations = 23.9% (11/46)
  - During therapy = 0%
  - 3 months after = 0%
  - 6 months after = 2%
  - 12 months after = 13%
  - 24 months after = 16%
  - 36 months after = 33%



Hui C-K et al., Gut 2005

HBV in immune compromised patients In practice