

# **Kinetics of hepatitis B surface antigen specific immune responses in acute and chronic hepatitis B**

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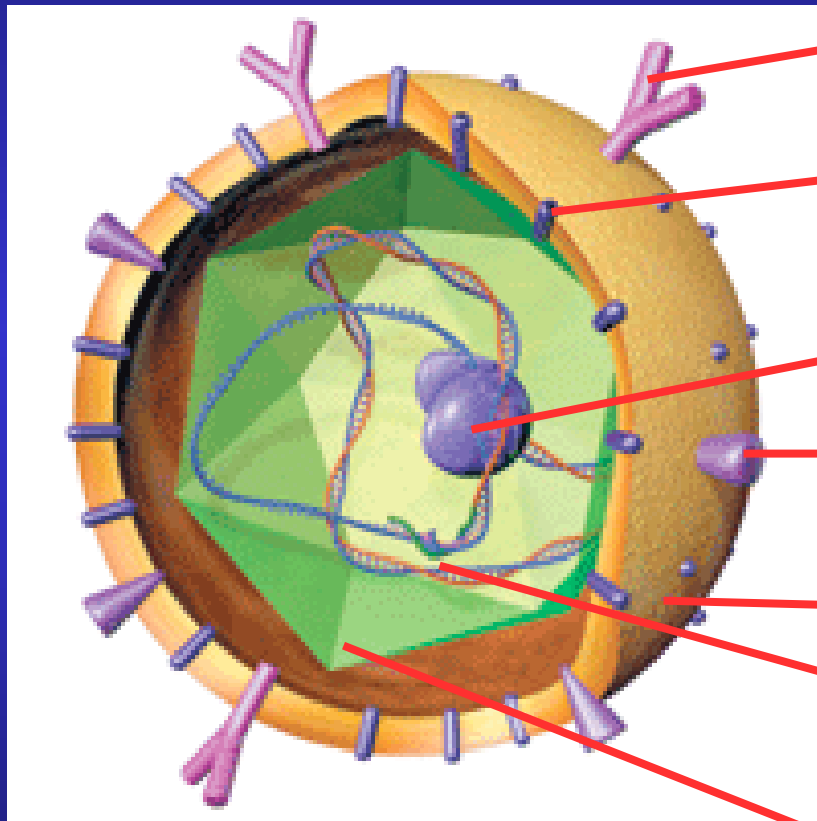
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# Overview

1. The HBV and its envelope
2. HBV immunopathogenesis
3. Envelope specific antibody production
4. Envelope specific T cells in *acute* hepatitis
5. Envelope specific T cells in *chronic* hepatitis B
6. Summary and Conclusion

# The Hepatitis B Virus (HBV)



**large HBs antigen**

(preS1/2 + sHBs)

**major HBs antigen**

(sHBs)

**polymerase**

**middle HBs antigen**

(preS2 + sHBs)

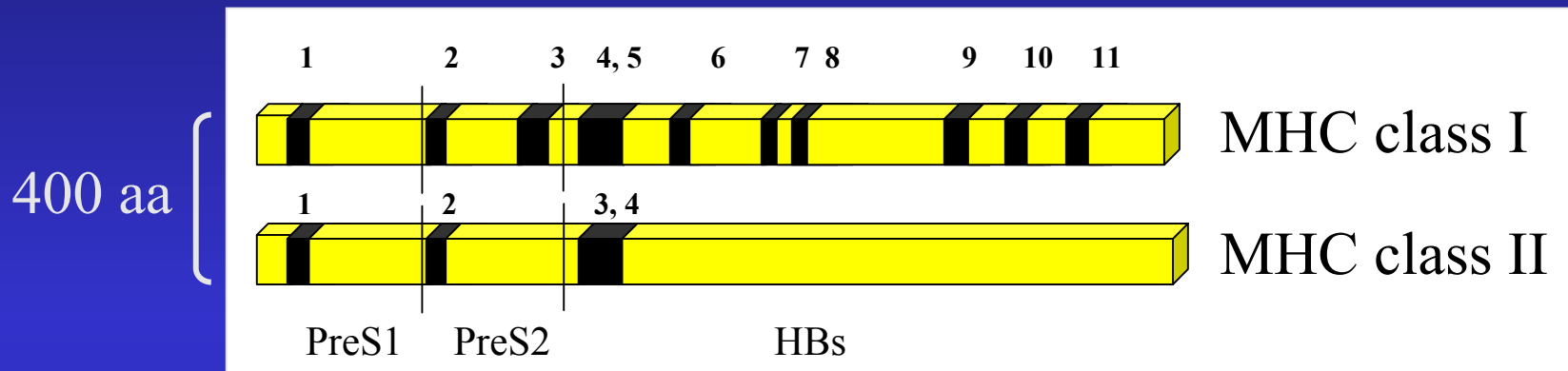
**lipid layer**

**dsDNA genome**

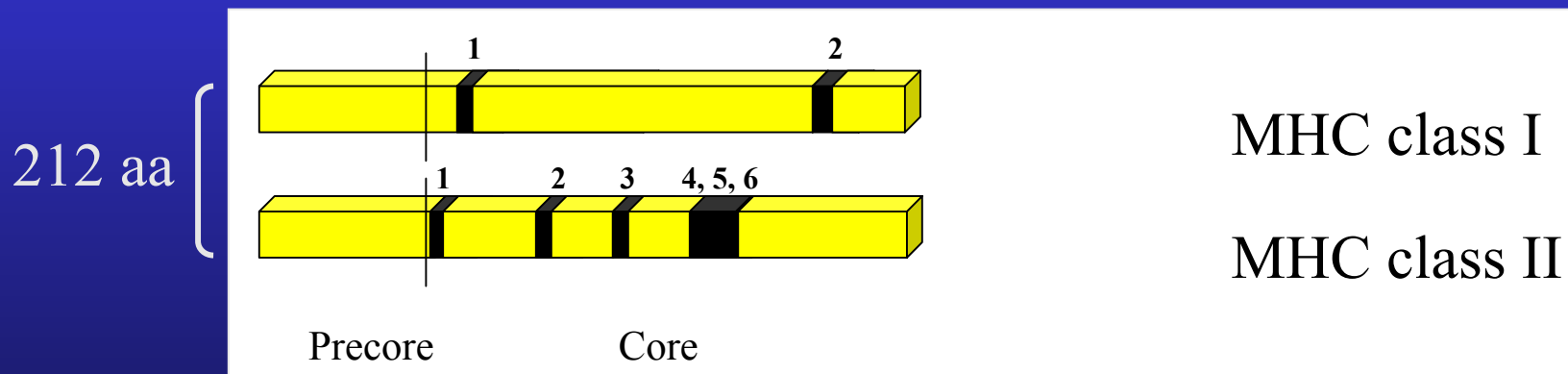
**nucleocapsid antigen**

# CTL and Th cell epitopes

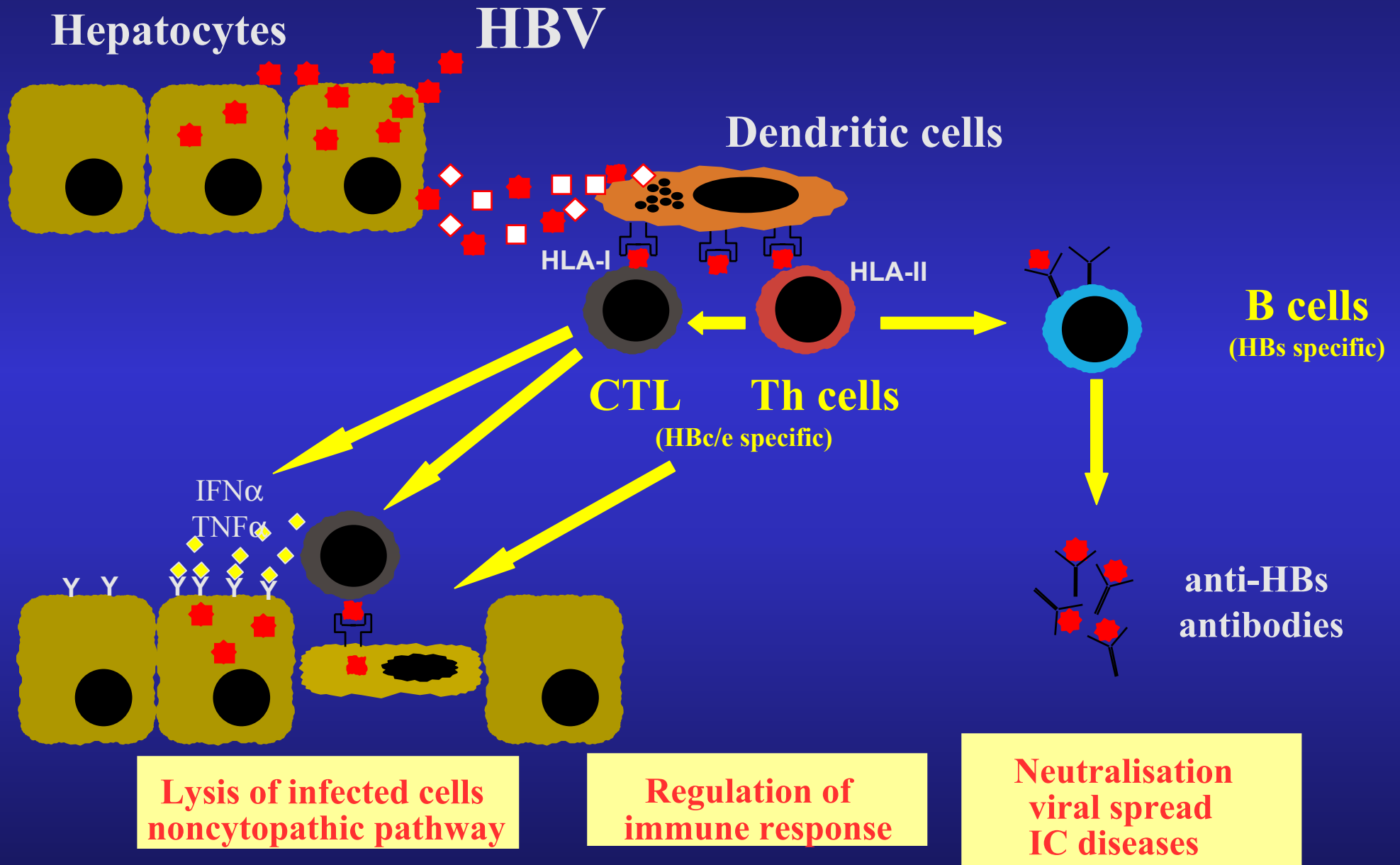
## HBV envelope protein



## HBV nucleocapsid protein



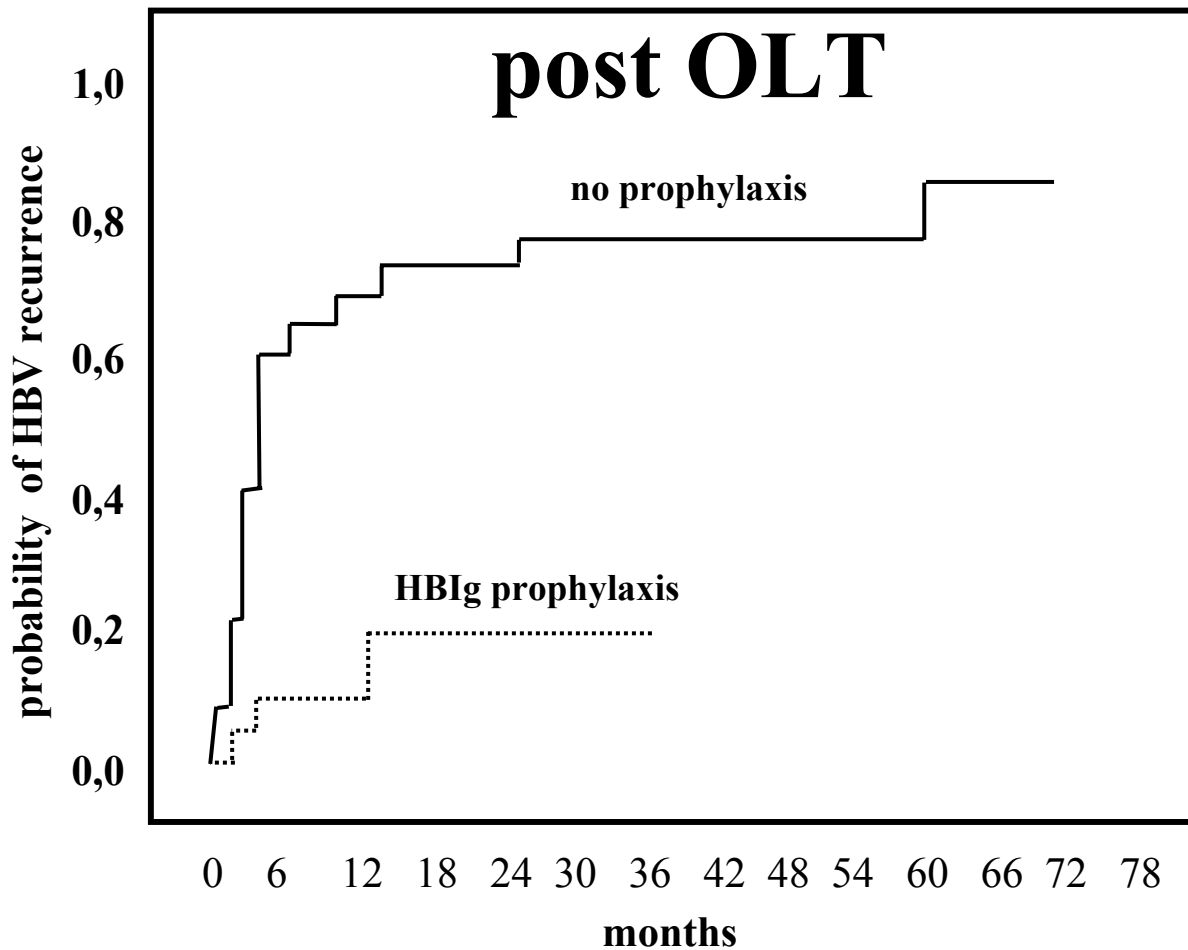
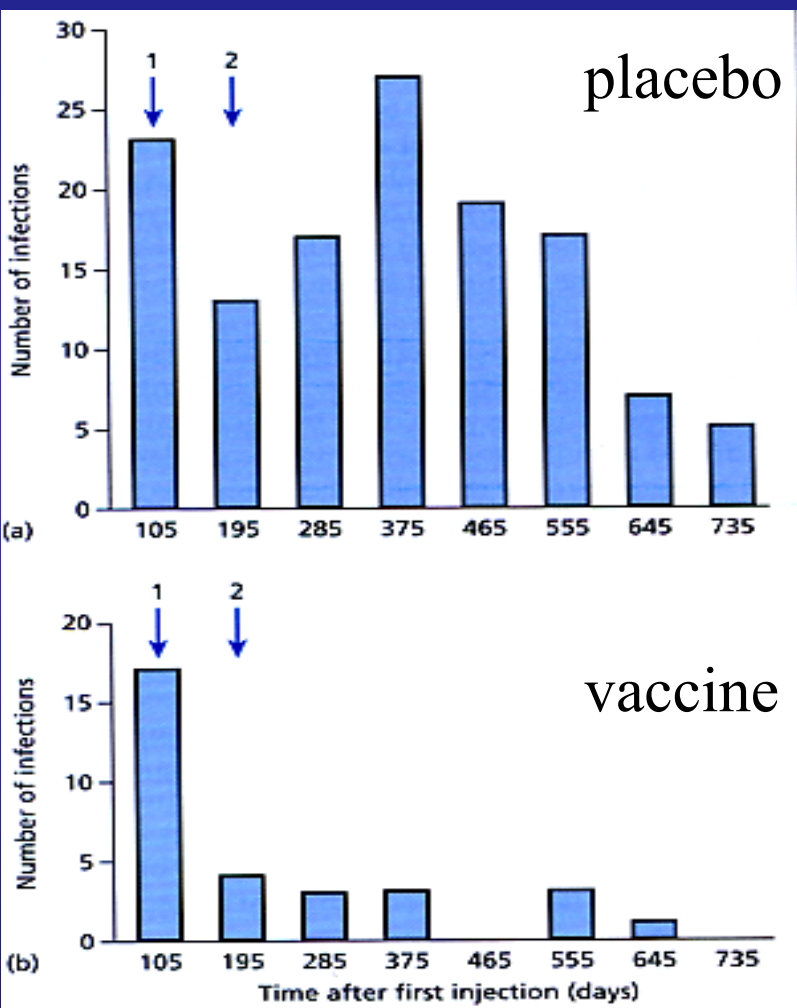
# Pathogenesis of HBV infection



# Anti-HBs abs: virus neutralisation

active (HBs) vaccination

passive (HBIG) vaccination

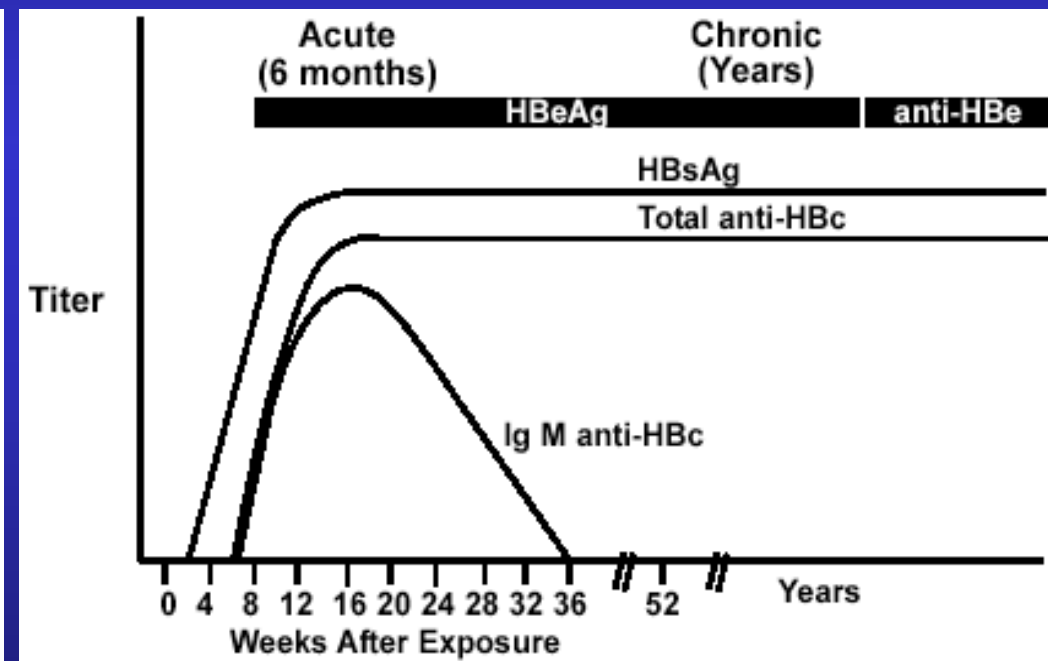
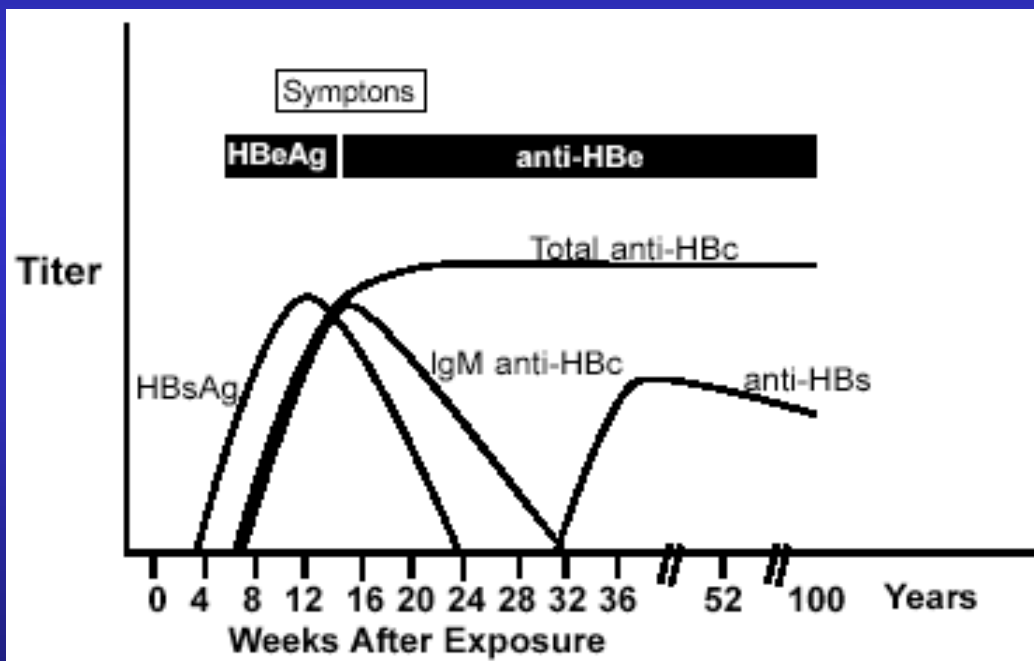


# Anti-HBs antibody response:

selflimited

vs.

chronic infection



# Anti-HBs/preS<sub>1/2</sub> in HBV infection

- 5-10% positivity for **anti-HBs antibodies** in chronic hepatitis B (Mishra,1992)  
-> super-/co-infection with different HBV subtypes or mutants  
(i.e. HBsAg subtype **ad** or **ay** and anti-HBs subtype **-ay** or **-ad**)

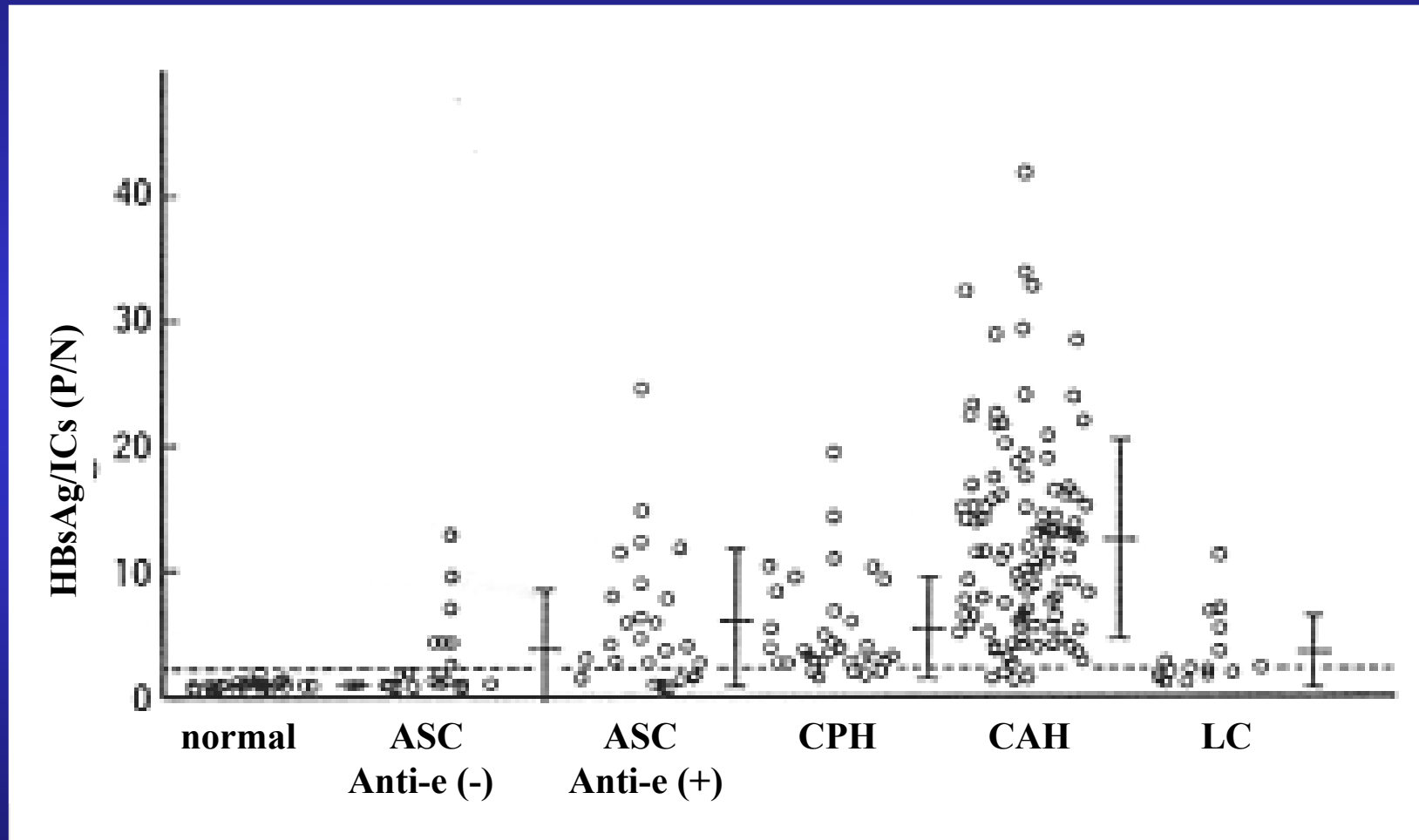
(Tabor, J Immunol 1977; Wang, J Gastro 1999)

- seropositivity of **anti-preS antibodies** in acute (45%) and in chronic hepatitis B (14%) correlate with preS-antigenemia and viremia  
-> indicator of HBe seroconversion

(Budkowski, 1992)

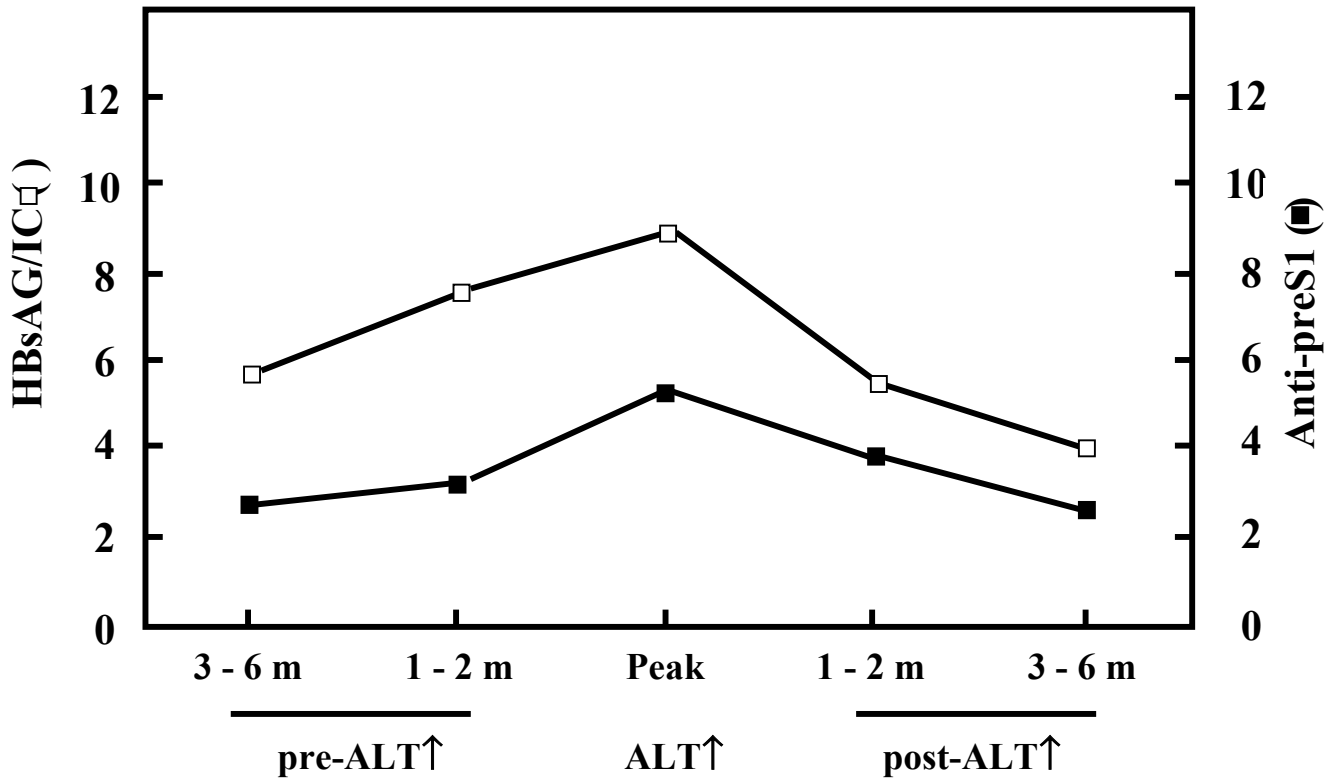


# Anti-envelope ICs in *chronic* hepatitis B

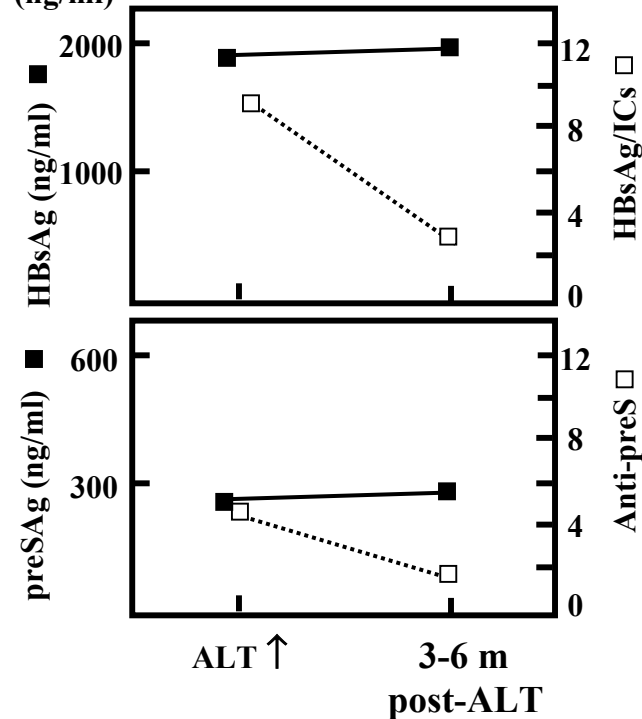


# Anti-HBVenV in *chronic* hepatitis B

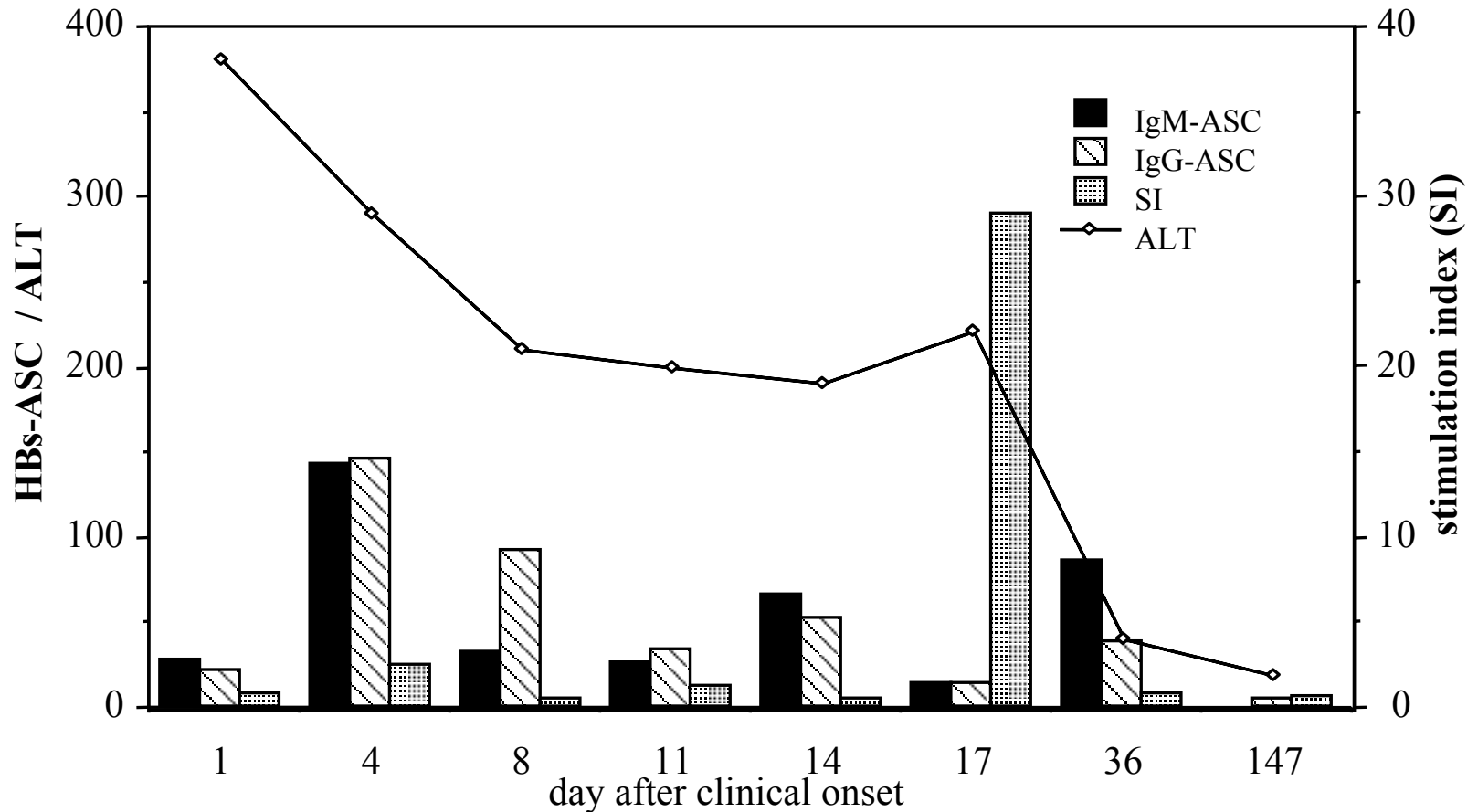
ALT (U/l) 45 ± 30      104 ± 70      415 ± 214      98 ± 88      38 ± 38



HBV DNA 672 ± 1828      16 ± 320  
(pg/ml)  
HBcAg 26.4 ± 23.6      0.9 ± 1.7  
(ng/ml)

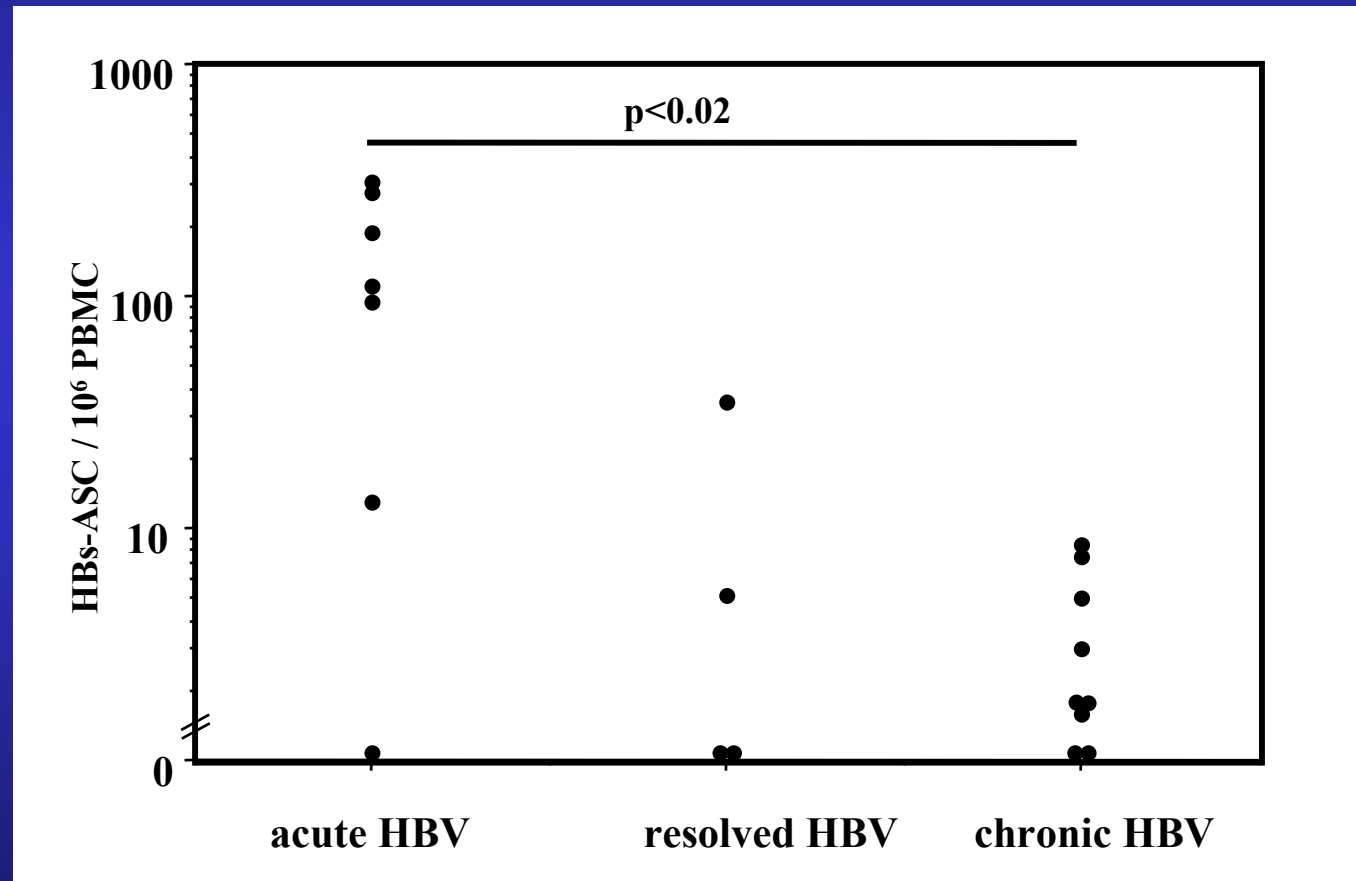


# HBs specific B / Th cells in *acute* hepatitis B

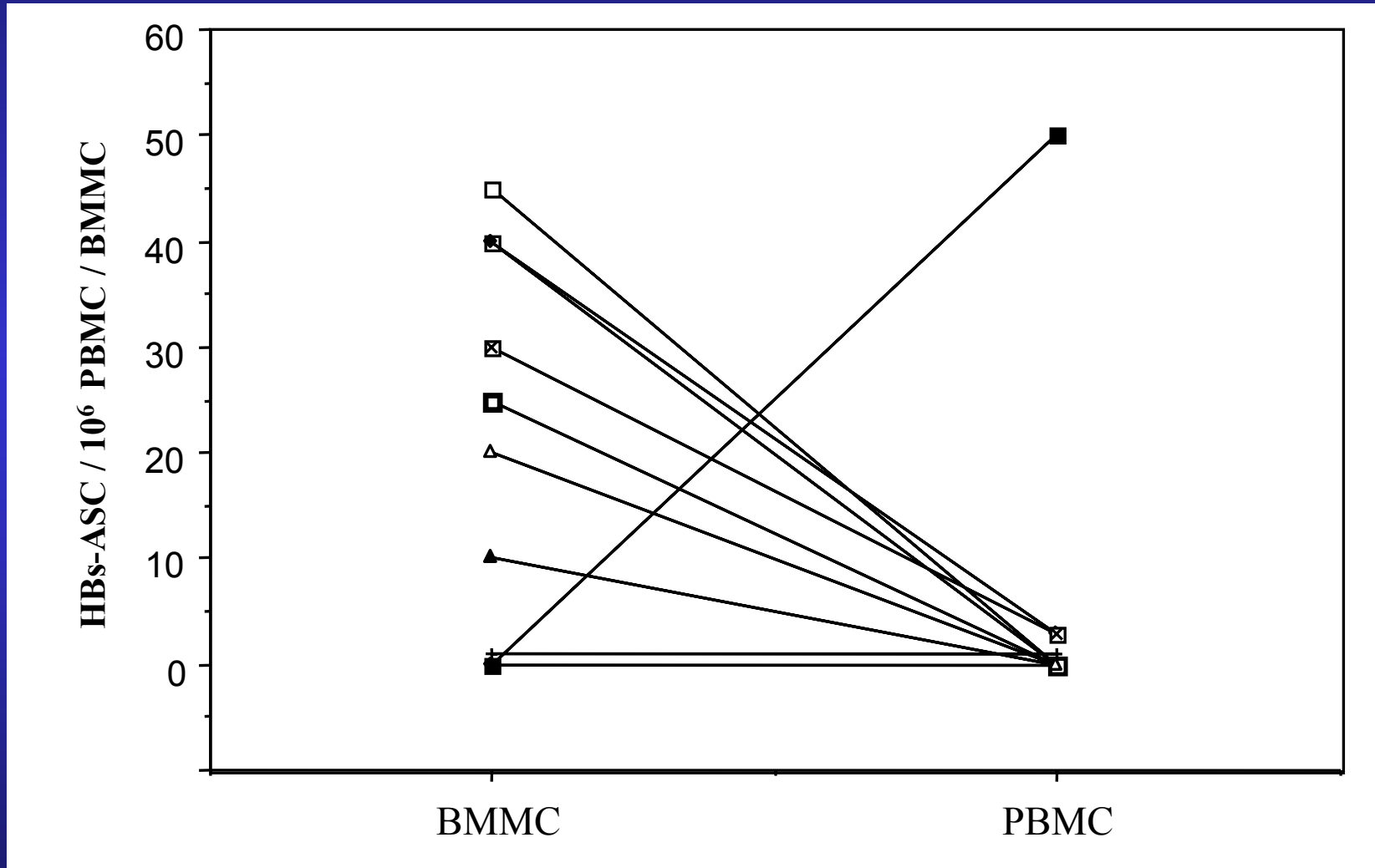


<b>HBsAg</b>	+	+	+	+	+	-
<b>HBV-DNA</b>		+		+		- (PCR -)
<b>anti-HBs</b>	-	-	-	-	-	70 U/l

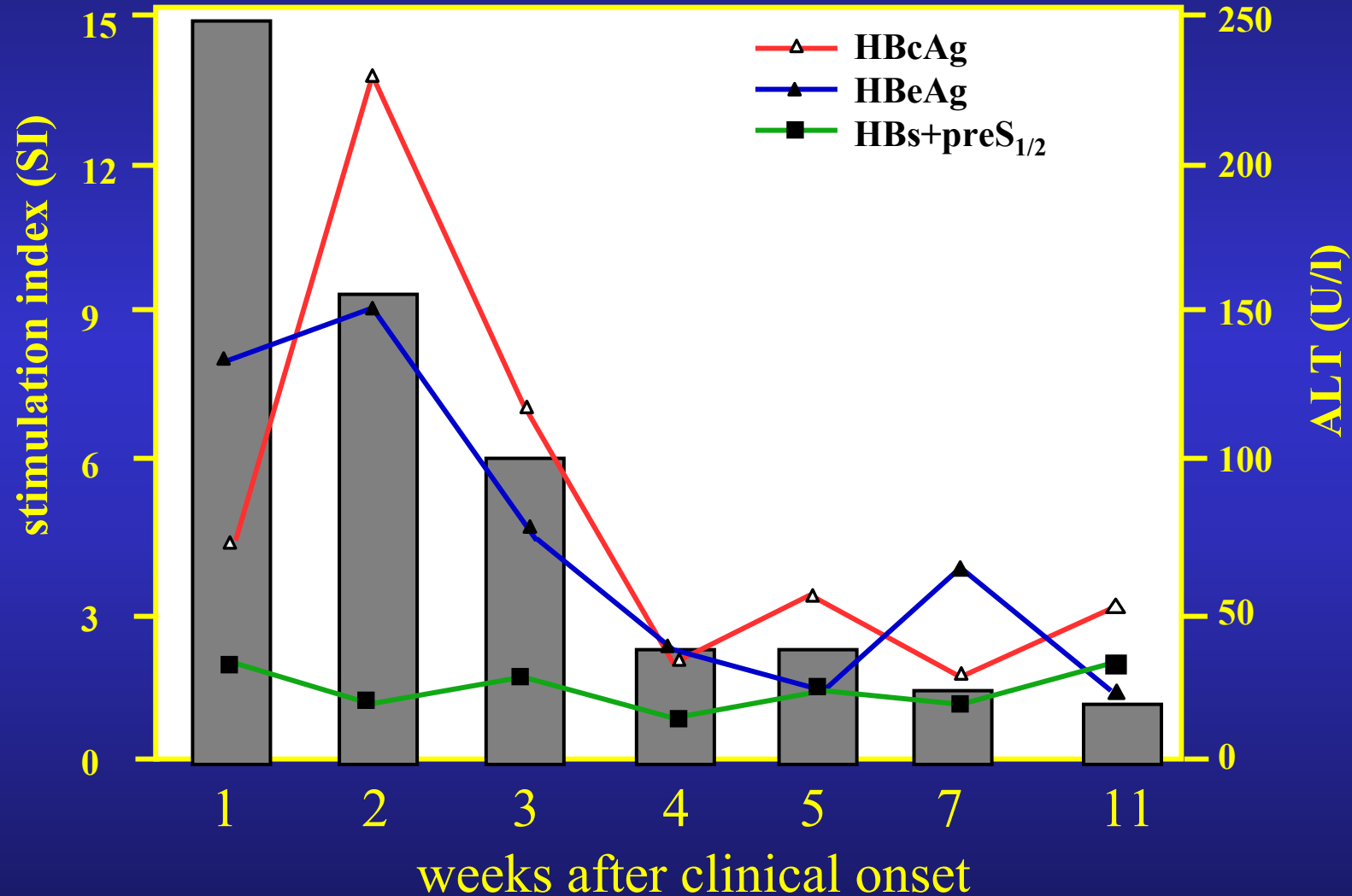
# HBs specific B cells in acute and chronic HBV infection



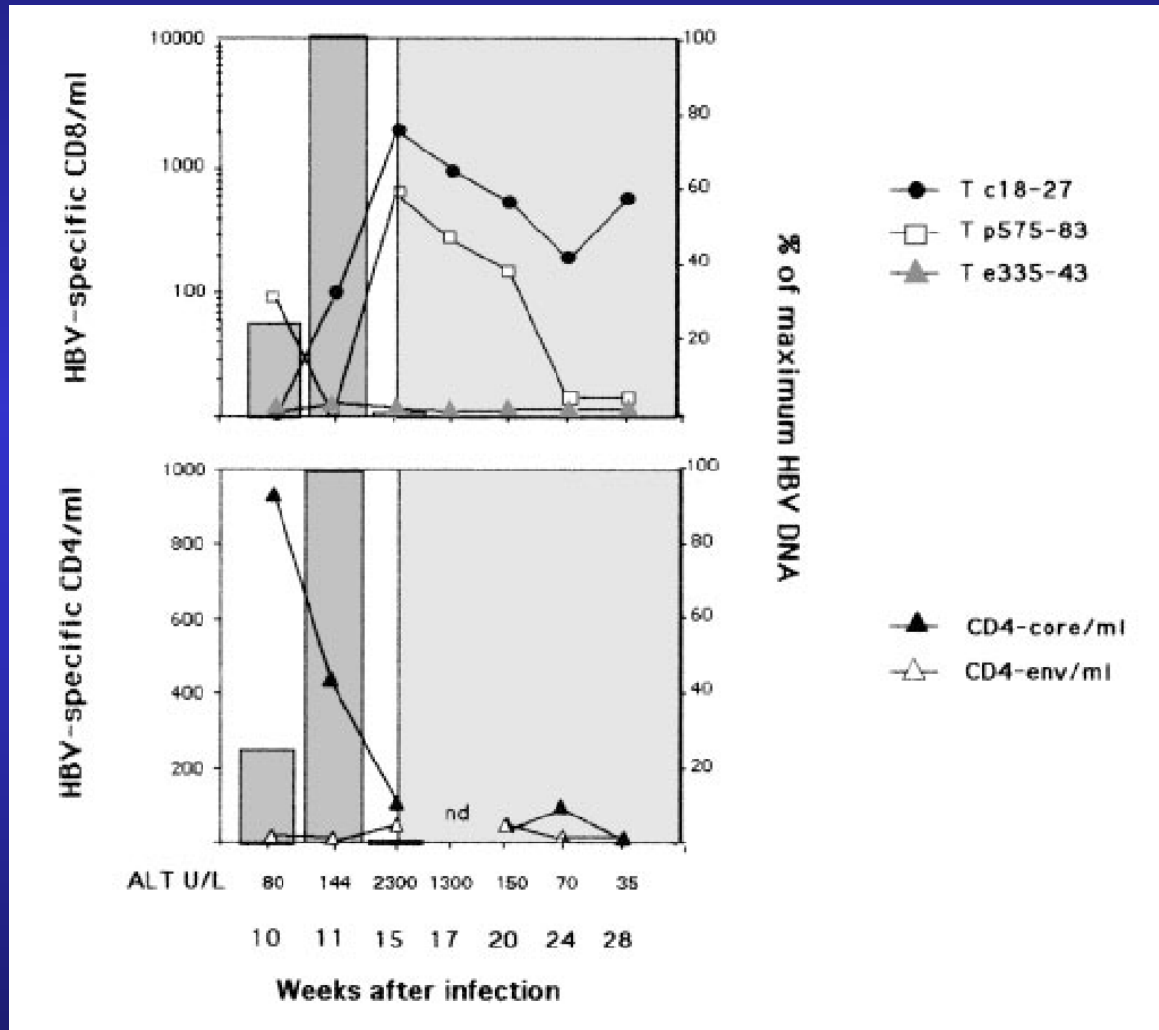
# Enrichment of HBs specific B cells in bone marrow



# HBV specific Th cells in acute hepatitis B

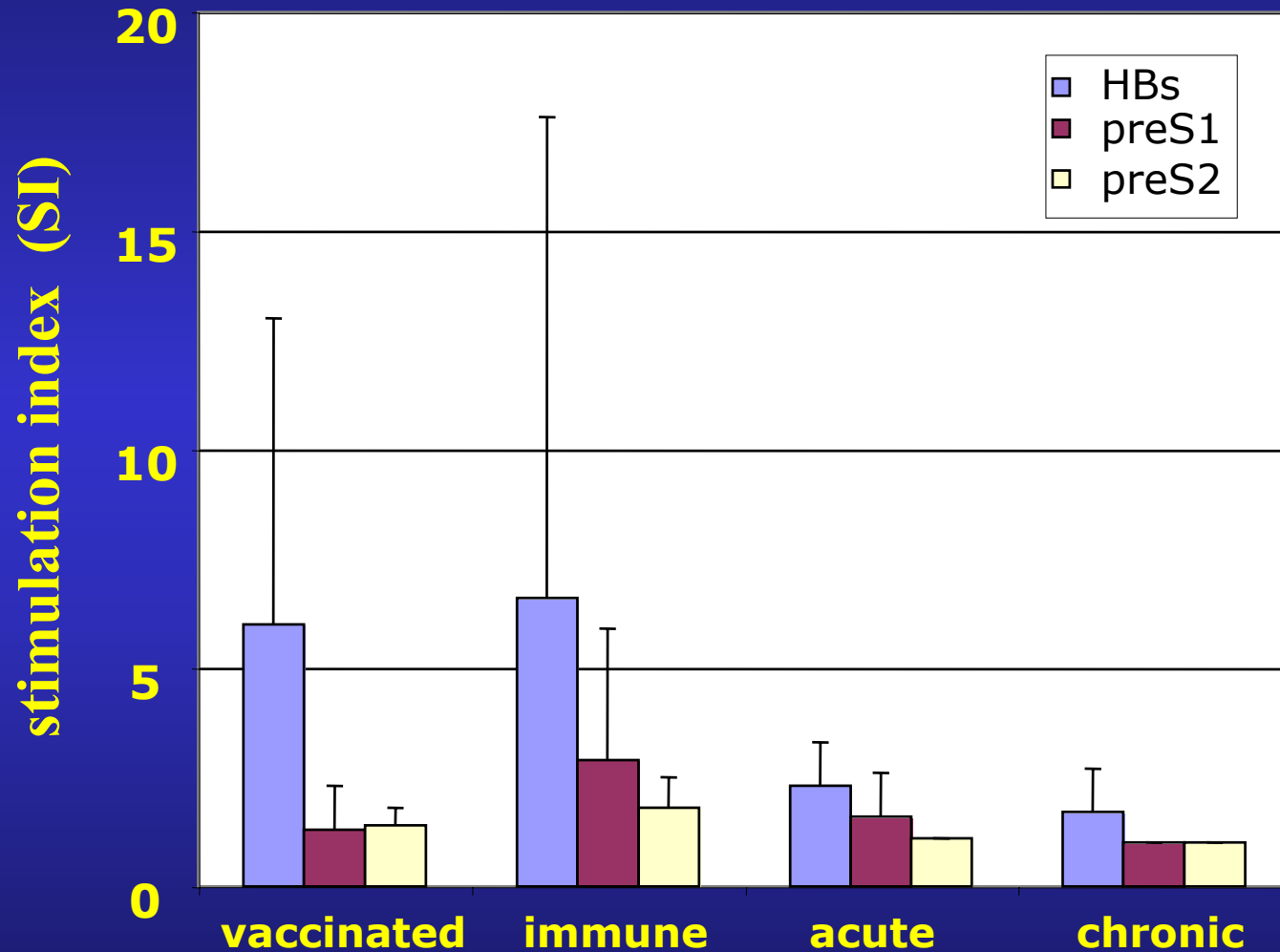


# Correlation of HBc specific CTL and Th cells with HBV clearance in acute infection



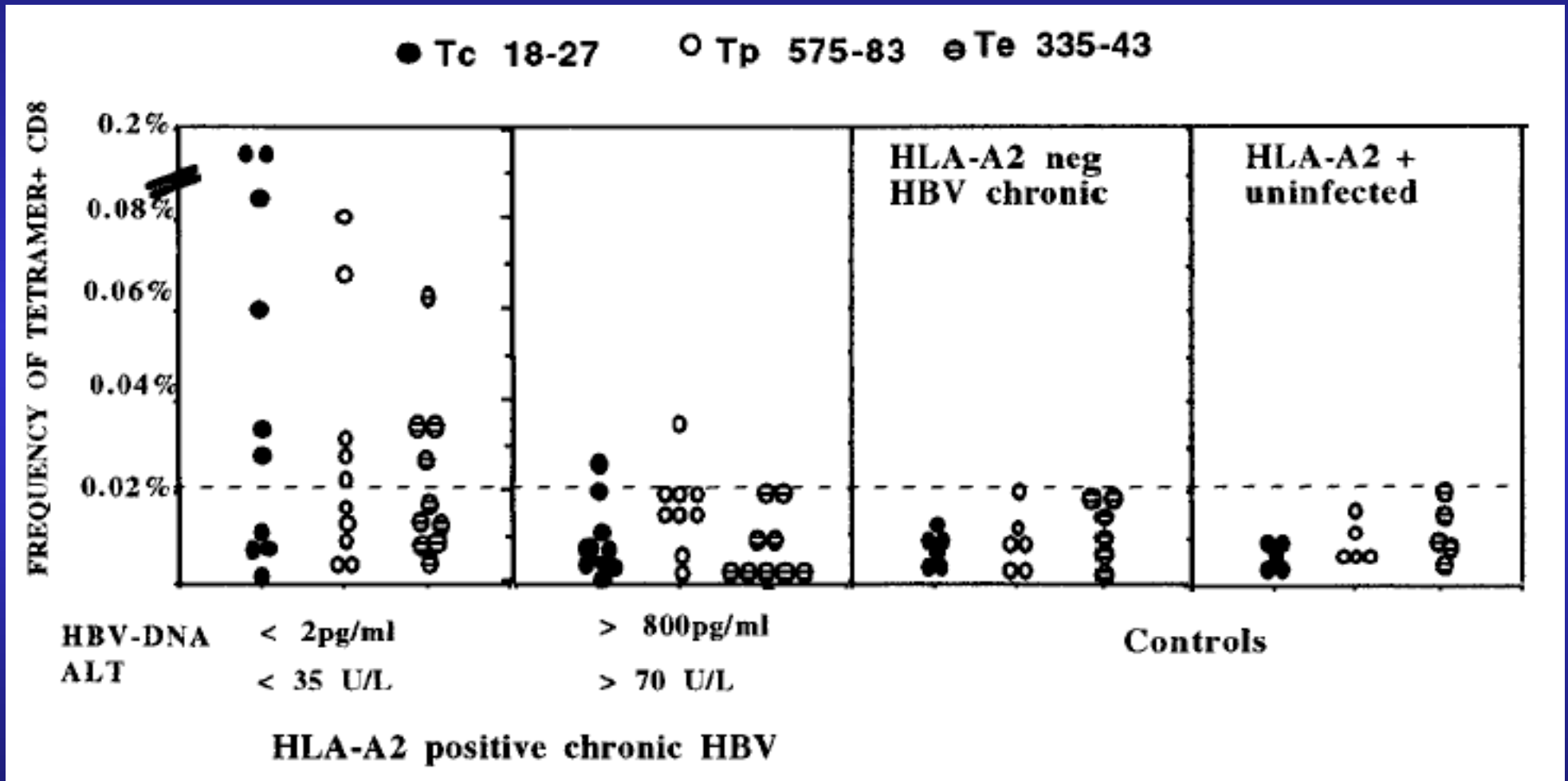
Webster G. et al., Hepatology 2000; (also Maini M. et al., Gastroenterology 1999)

# Envelope specific Th cells in chronic hepatitis B

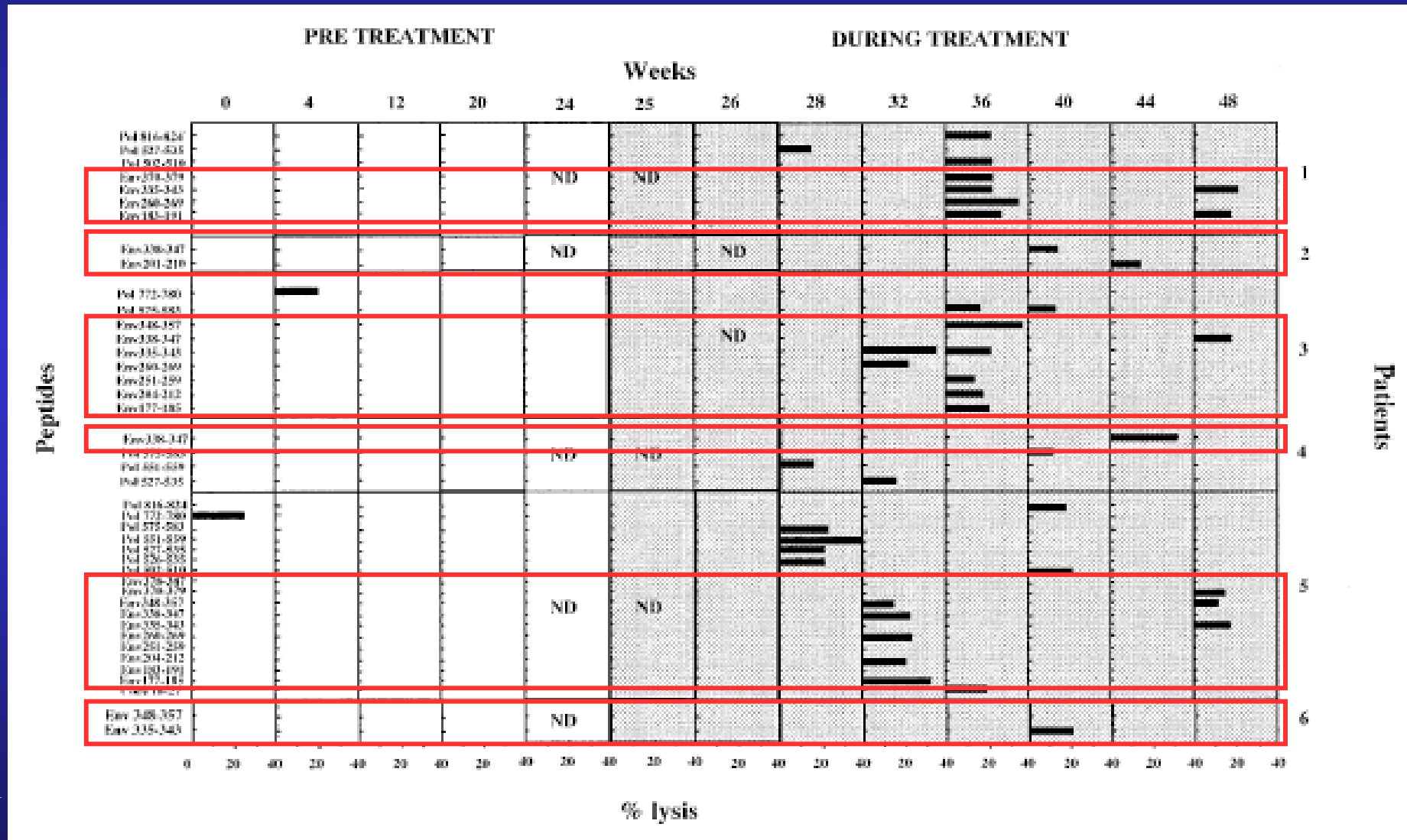




# HBV specific CTL in *chronic* hepatitis B



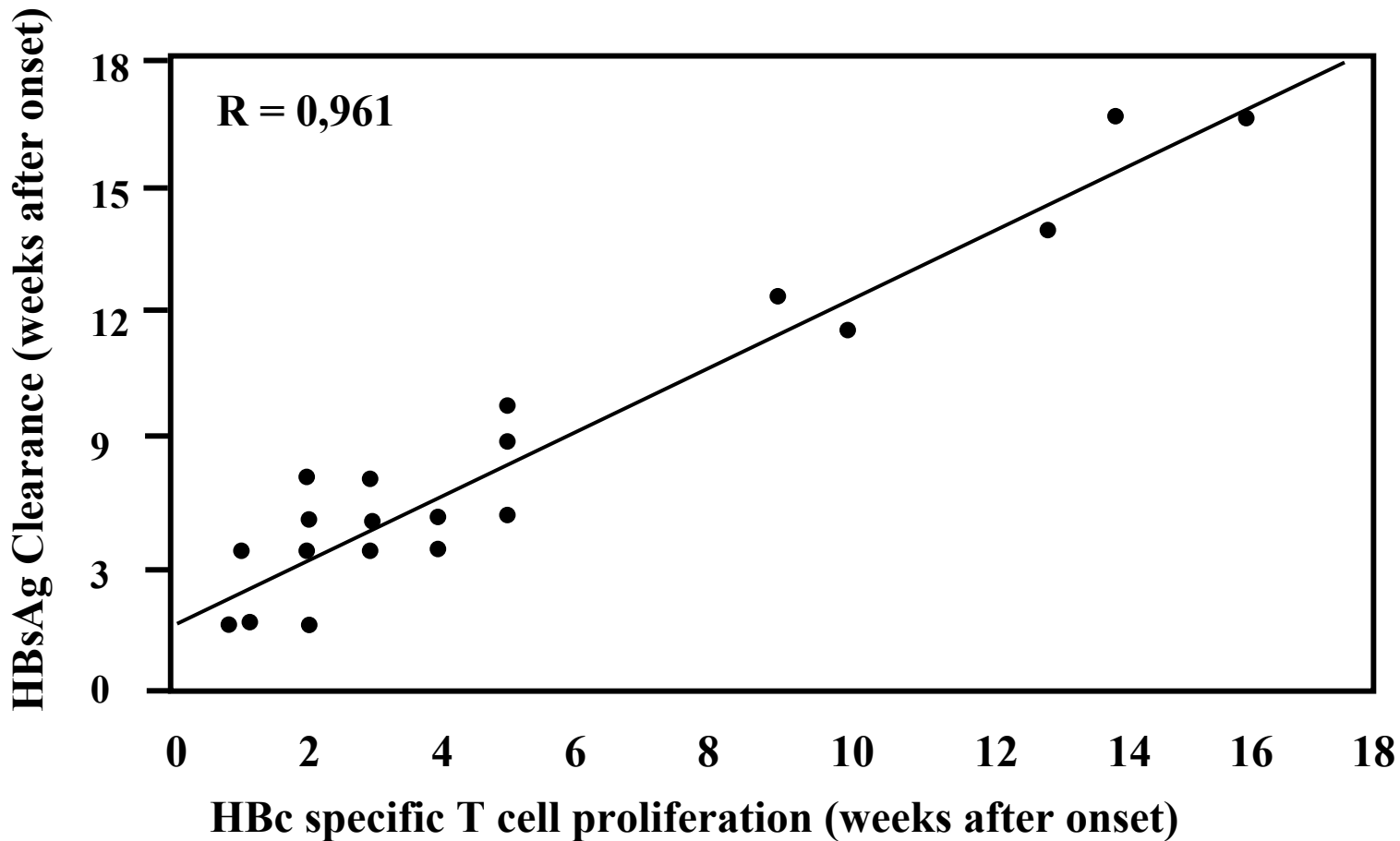
# HBV specific CTL during treatment with lamivudine



# Summary:

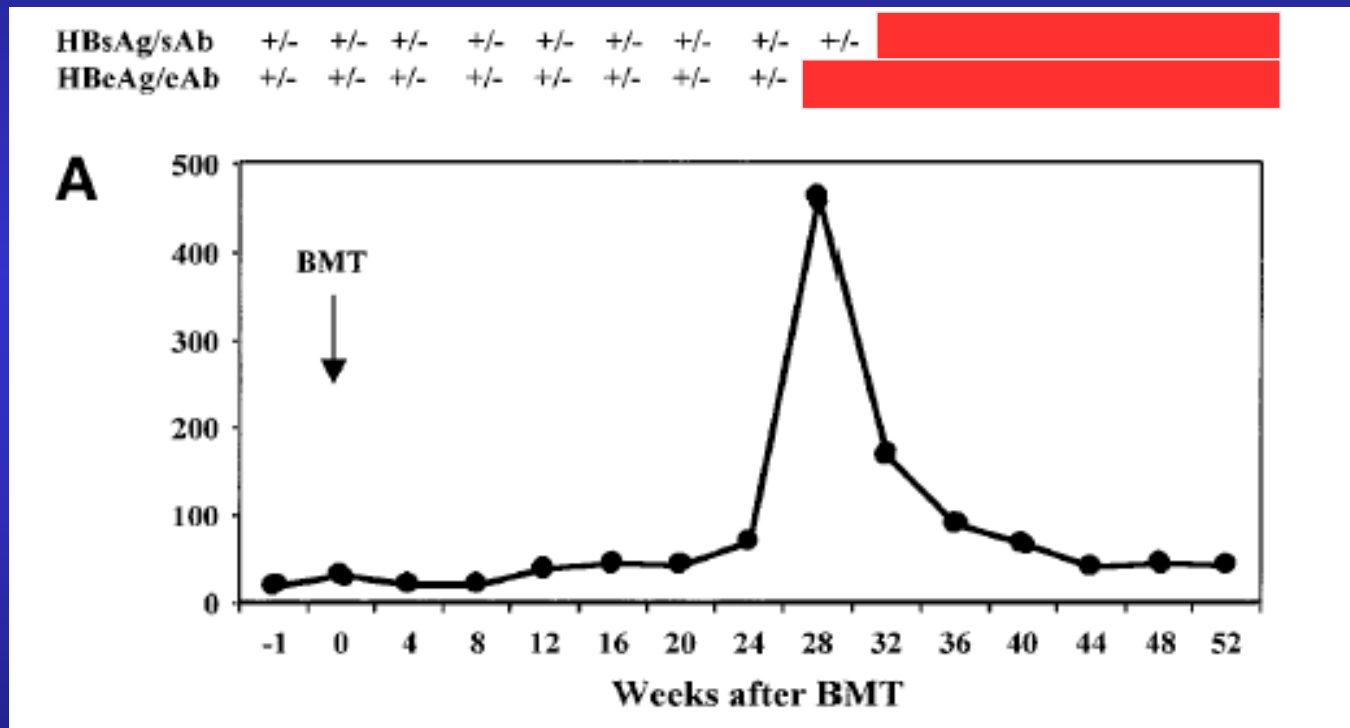
- in *acute* hepatitis B:
  - high frequencies of circulating anti-HBs secreting B cells before HBs seroconversion, migrating to lymphoid organs later on
  - weak envelope specific CTL and Th cell responses during seroconversion
- in *chronic* hepatitis B:
  - correlation of complexed anti-HBs and anti-preS antibodies with inflammatory activity
  - weak envelope specific Th cell activities, no correlation of envelope specific CTL with virus control

# Correlation of HBc specific Th cells with HBV clearance



# HBV clearance is mediated by HBc specific T cells after adoptive transfer

8 patients with chronic HBV and BMT from HLA matched sibling with immunity to HBV (aHBs+, aHBc+)



Lau G et al.,  
Gastroenterol 2002

flare (week 24) in 8/8 recipients, sustained HBsAg seroconversion in 6/8:

weak HBs strong HBc specific T cell activities in recipients (Lau 2002)

no elimination after transfer from HBs vaccinated donors (Lau 1998)

# Conclusion: HBV envelope antigens

- strong B cell antigens in *acute and chronic* HBV infection
  - > virus neutralisation
  - > viral spread ↓, protective immunity
- weak Th cell and CTL antigens in acute and chronic infection
  - > limited role in immune control of HBV replication
  - > core and polymerase specific T cell immunity critical



- suitable as protective vaccine or adjuvant for therapeutic vaccine