

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

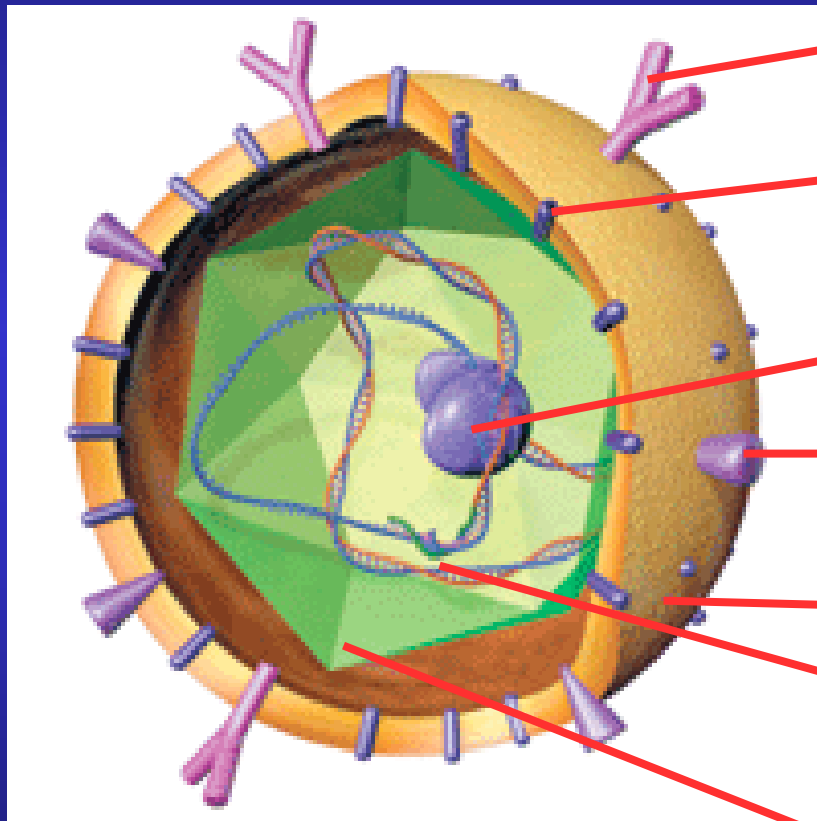
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Overview

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)

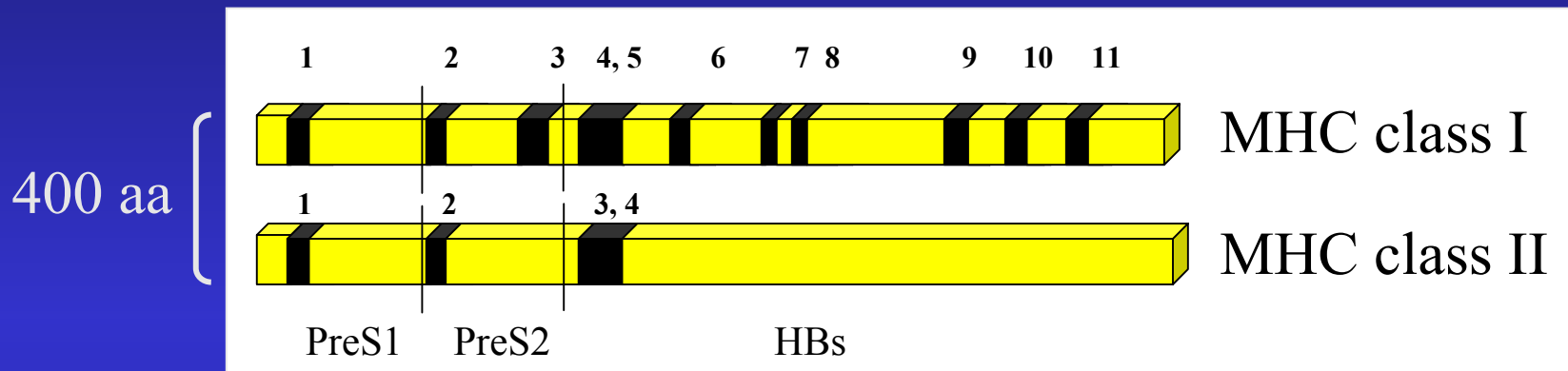
lipid layer

dsDNA genome

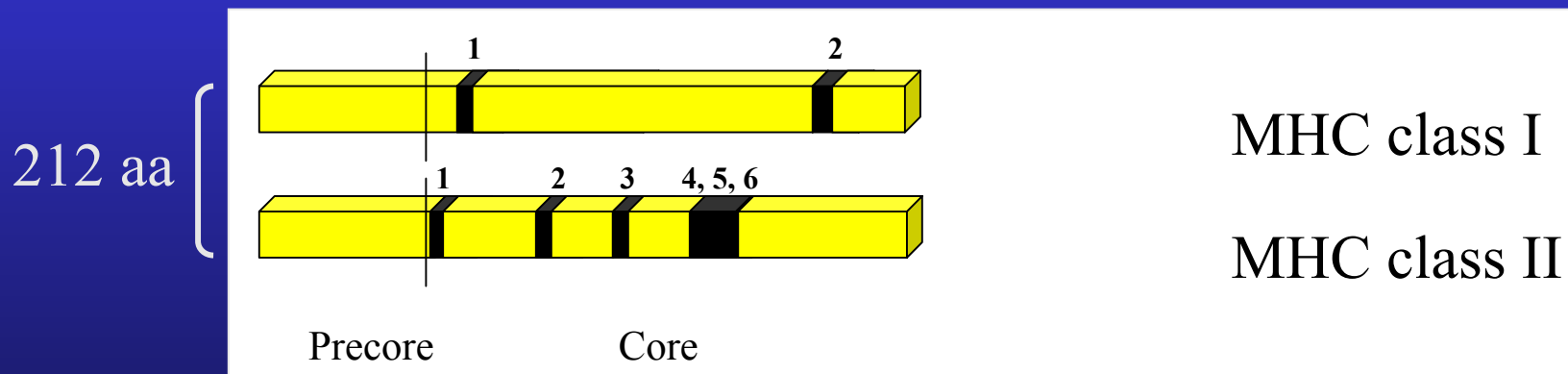
nucleocapsid antigen

CTL and Th cell epitopes

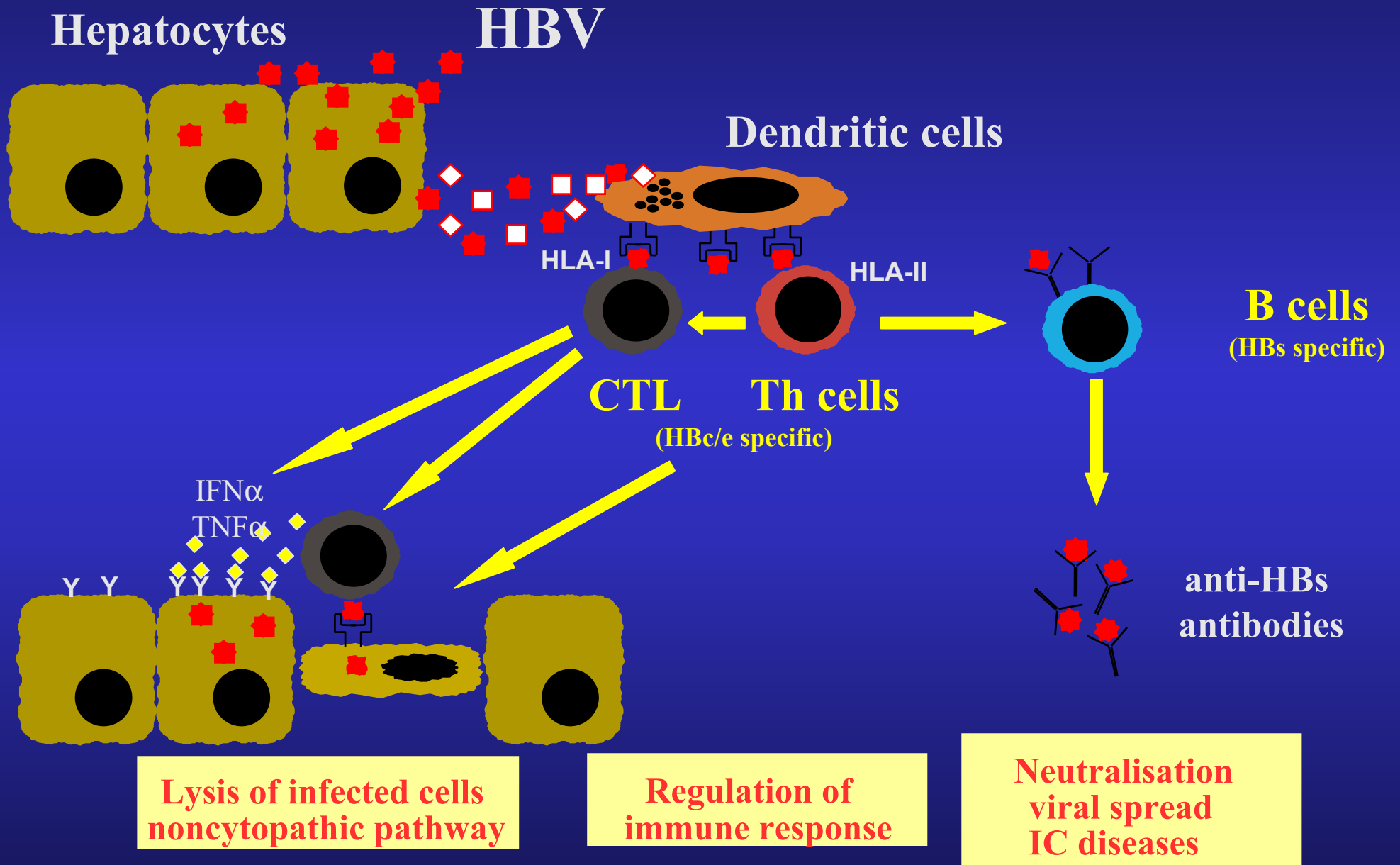
HBV envelope protein



HBV nucleocapsid protein



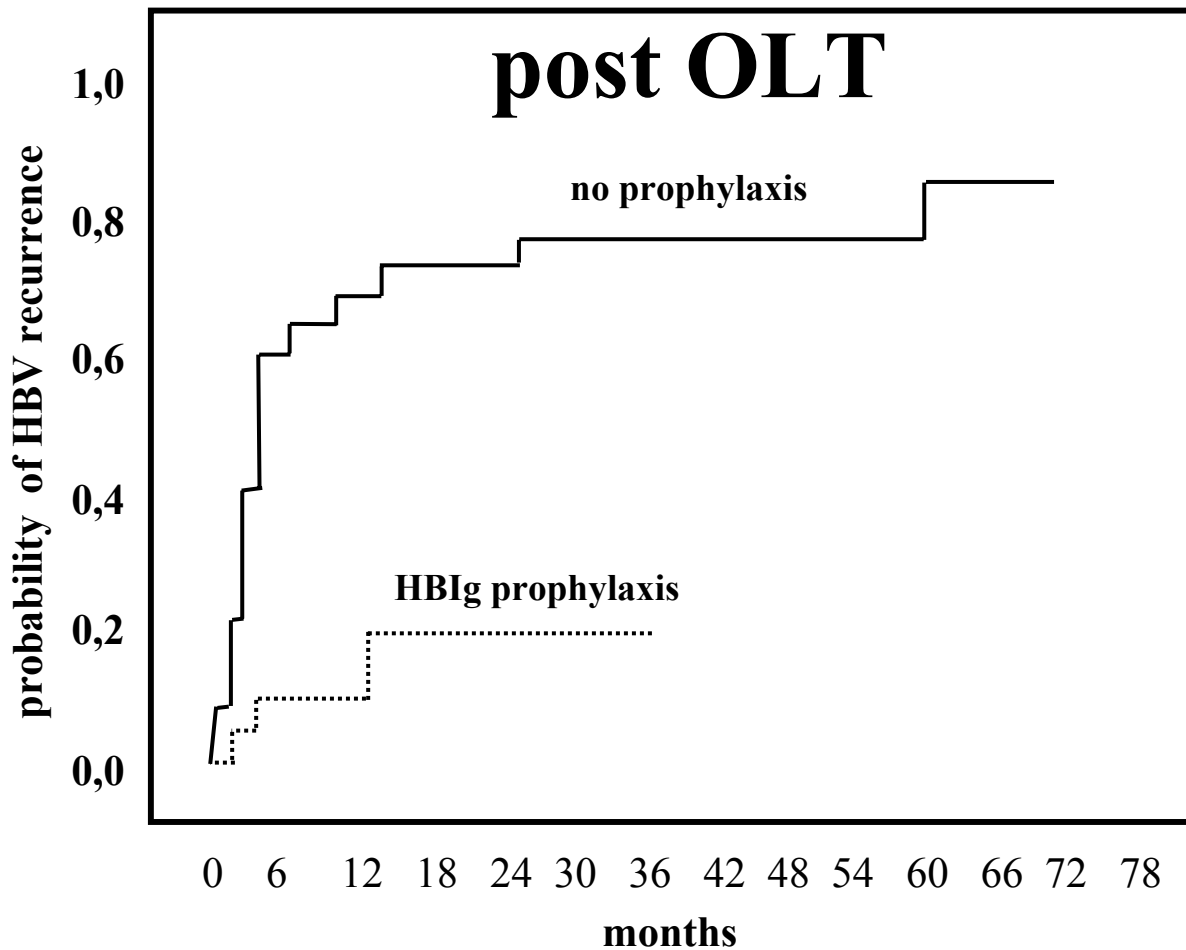
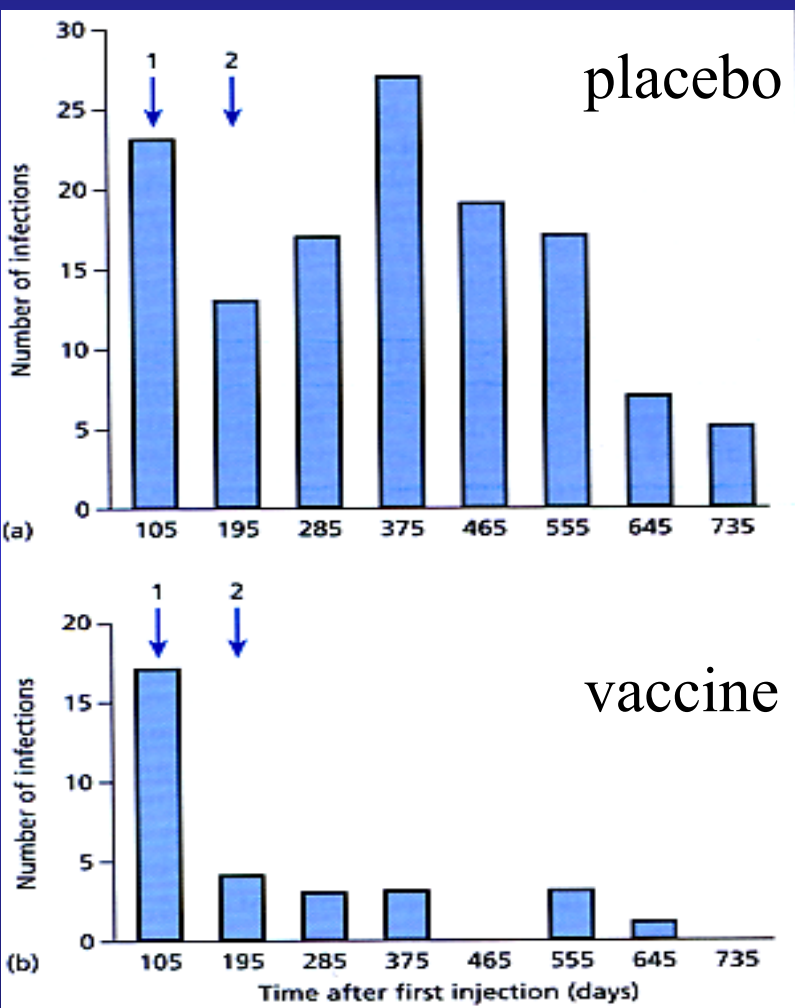
Pathogenesis of HBV infection



Anti-HBs abs: virus neutralisation

active (HBs) vaccination

passive (HBIG) vaccination

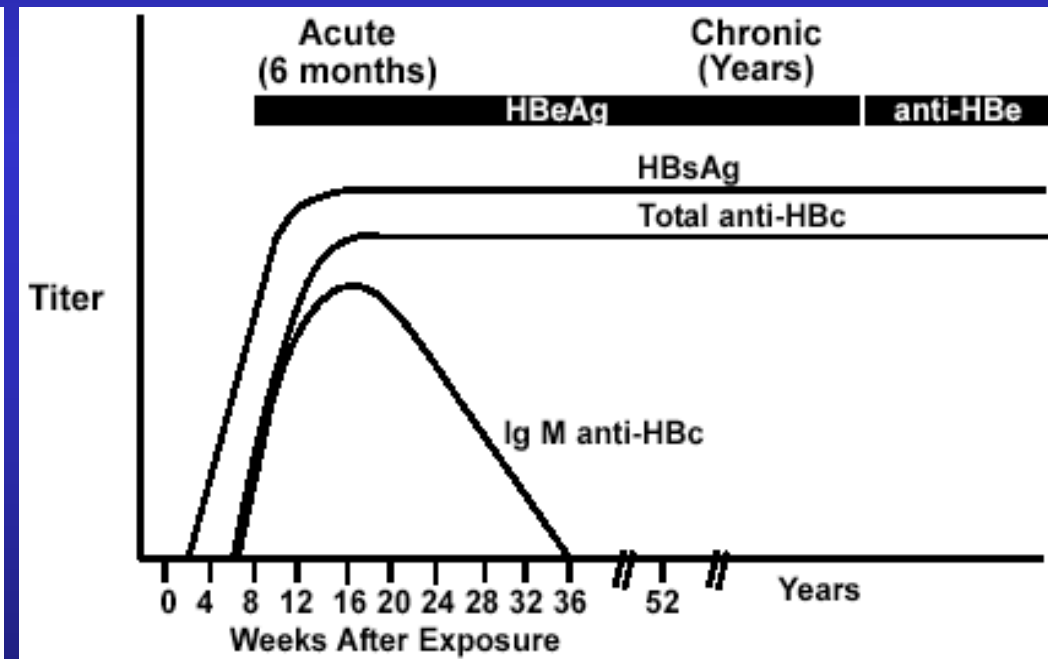
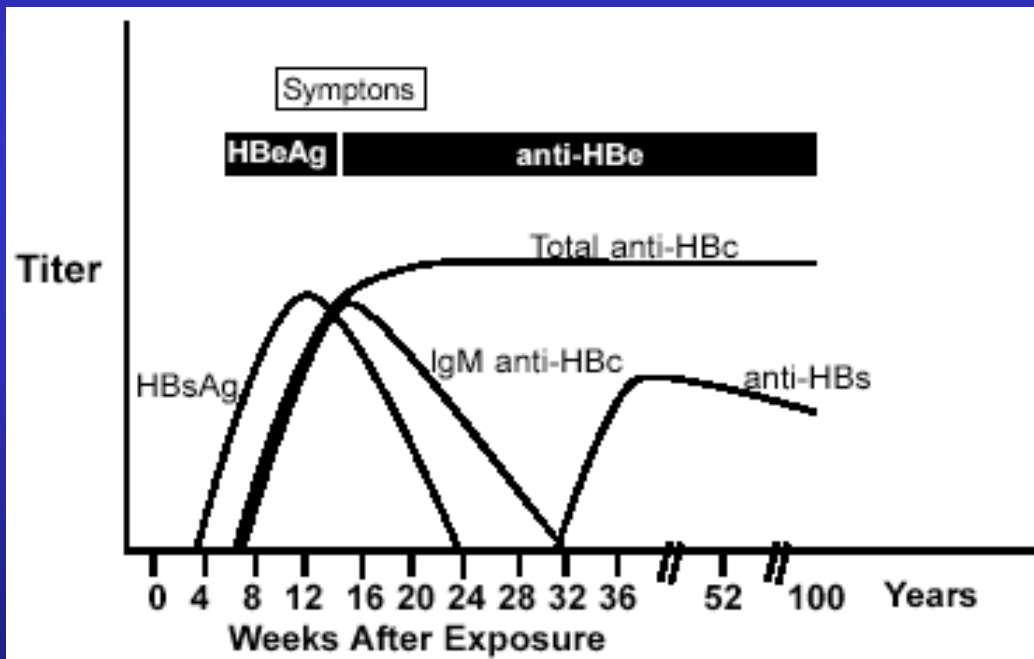


Anti-HBs antibody response:

selflimited

vs.

chronic infection



Anti-HBs/preS_{1/2} in HBV infection

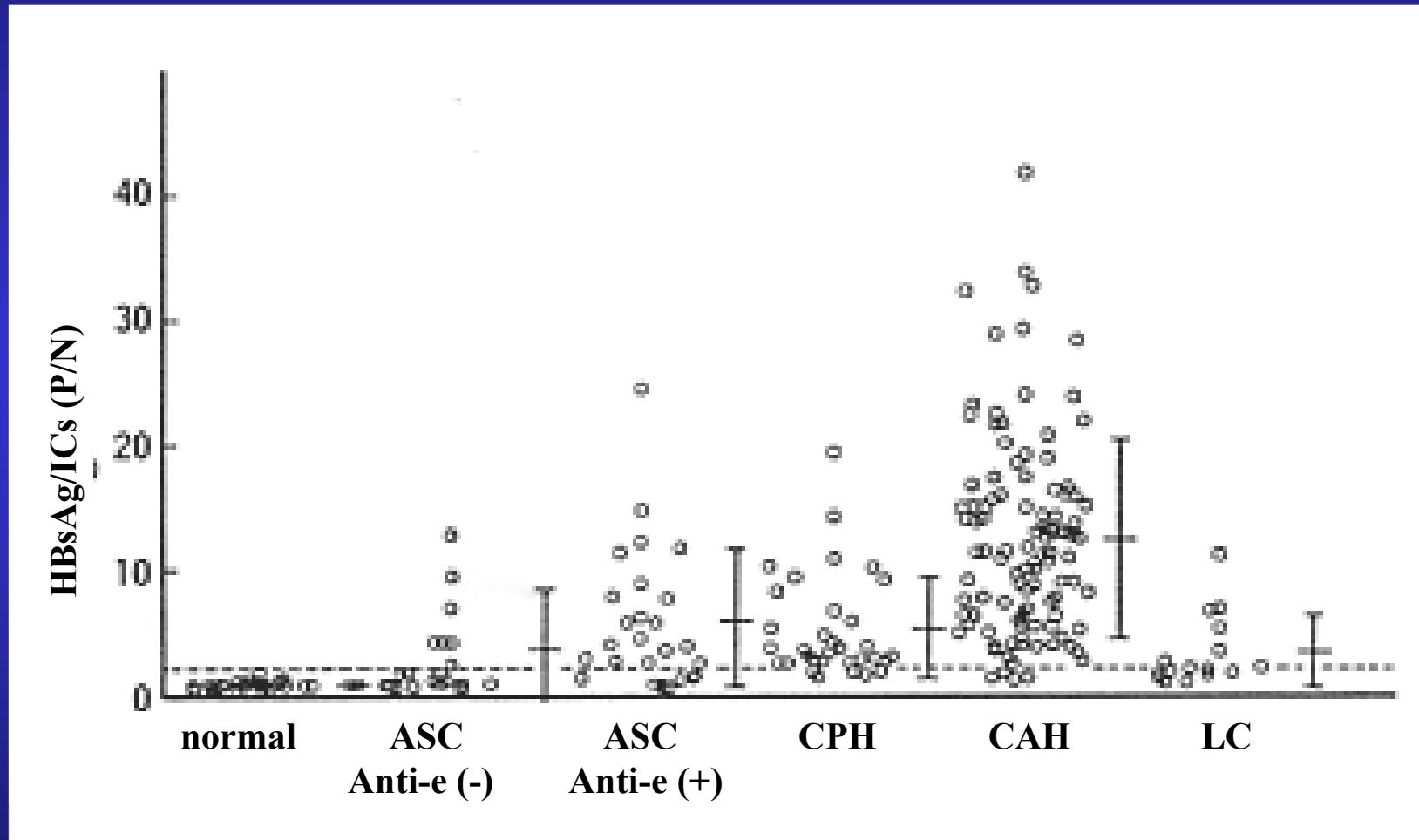
- 5-10% positivity for **anti-HBs antibodies** in chronic hepatitis B (Mishra,1992)
-> super-/co-infection with different HBV subtypes or mutants
(i.e. HBsAg subtype **ad** or **ay** and anti-HBs subtype **-ay** or **-ad**)

(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

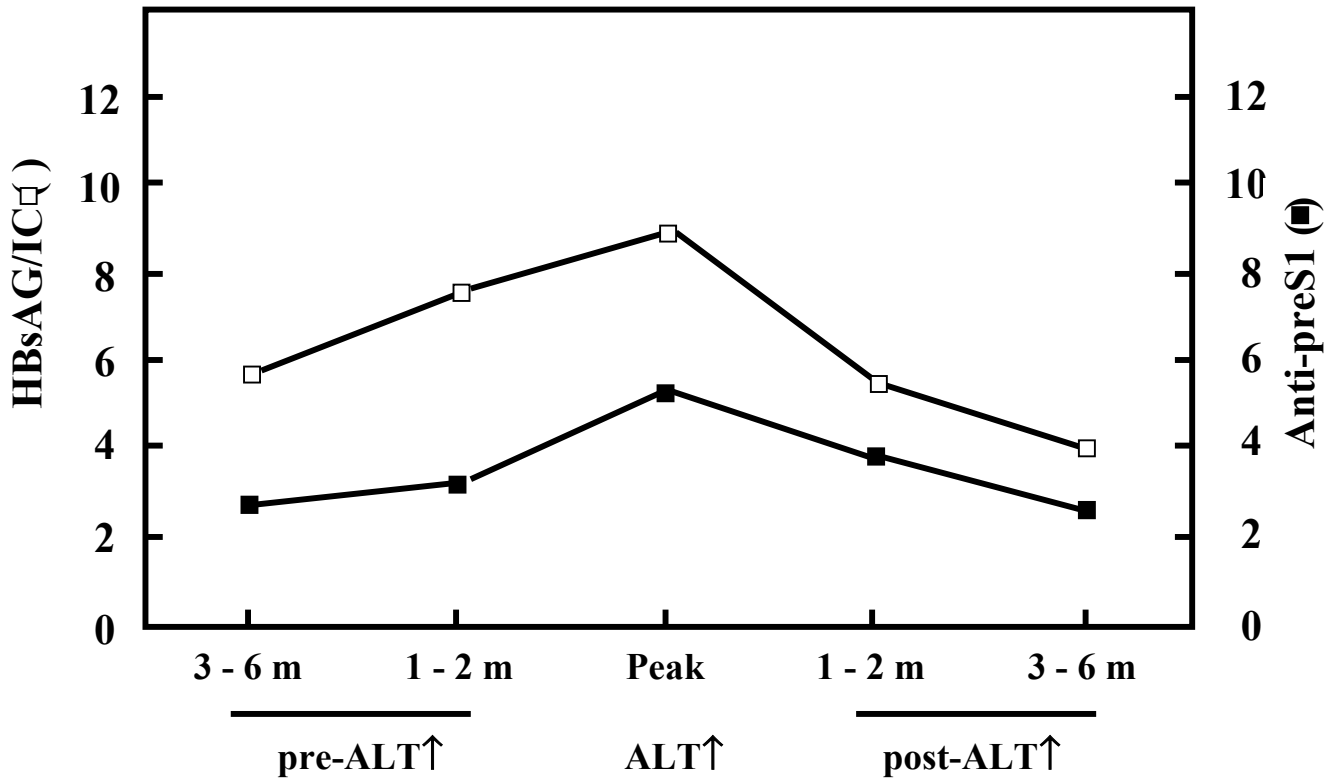
(Budkowski, 1992)

Anti-envelope ICs in *chronic* hepatitis B

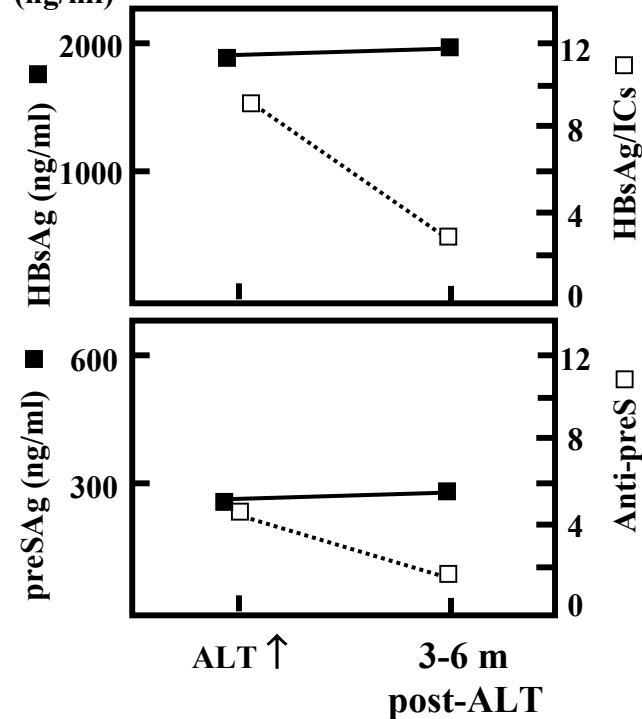


Anti-HBVenV in *chronic* hepatitis B

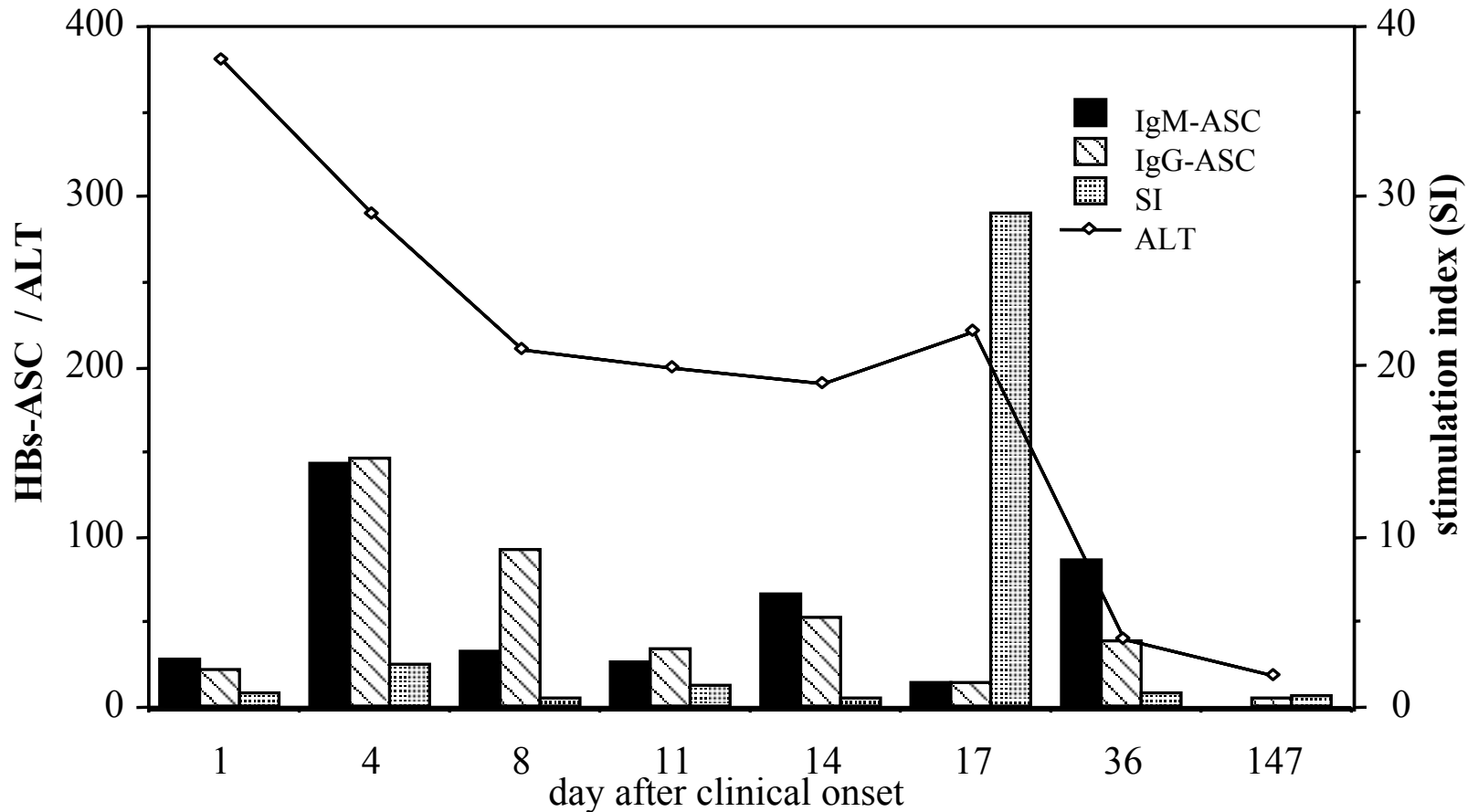
ALT (U/l) 45 ± 30 104 ± 70 415 ± 214 98 ± 88 38 ± 38



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

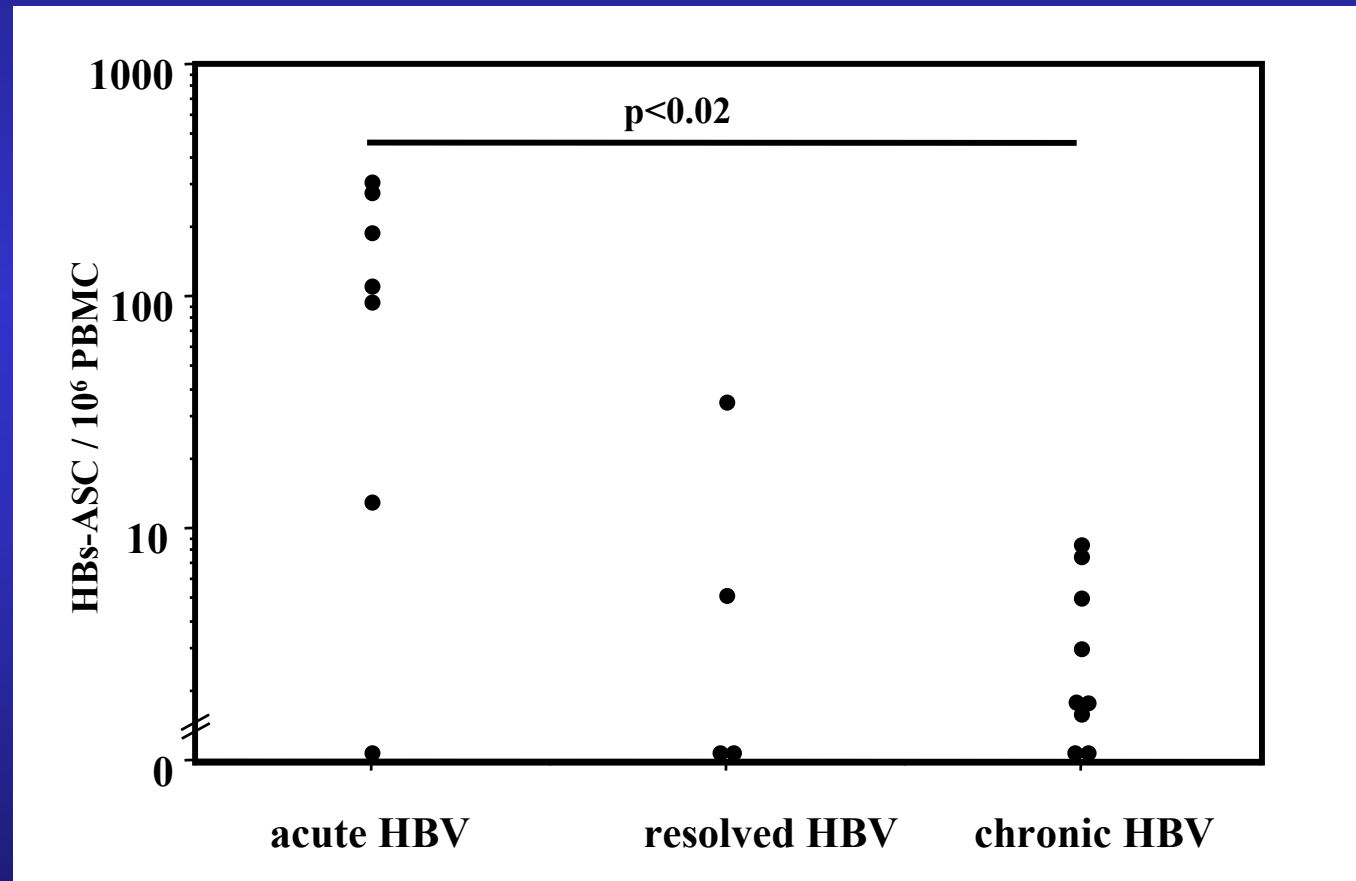


HBs specific B / Th cells in *acute* hepatitis B

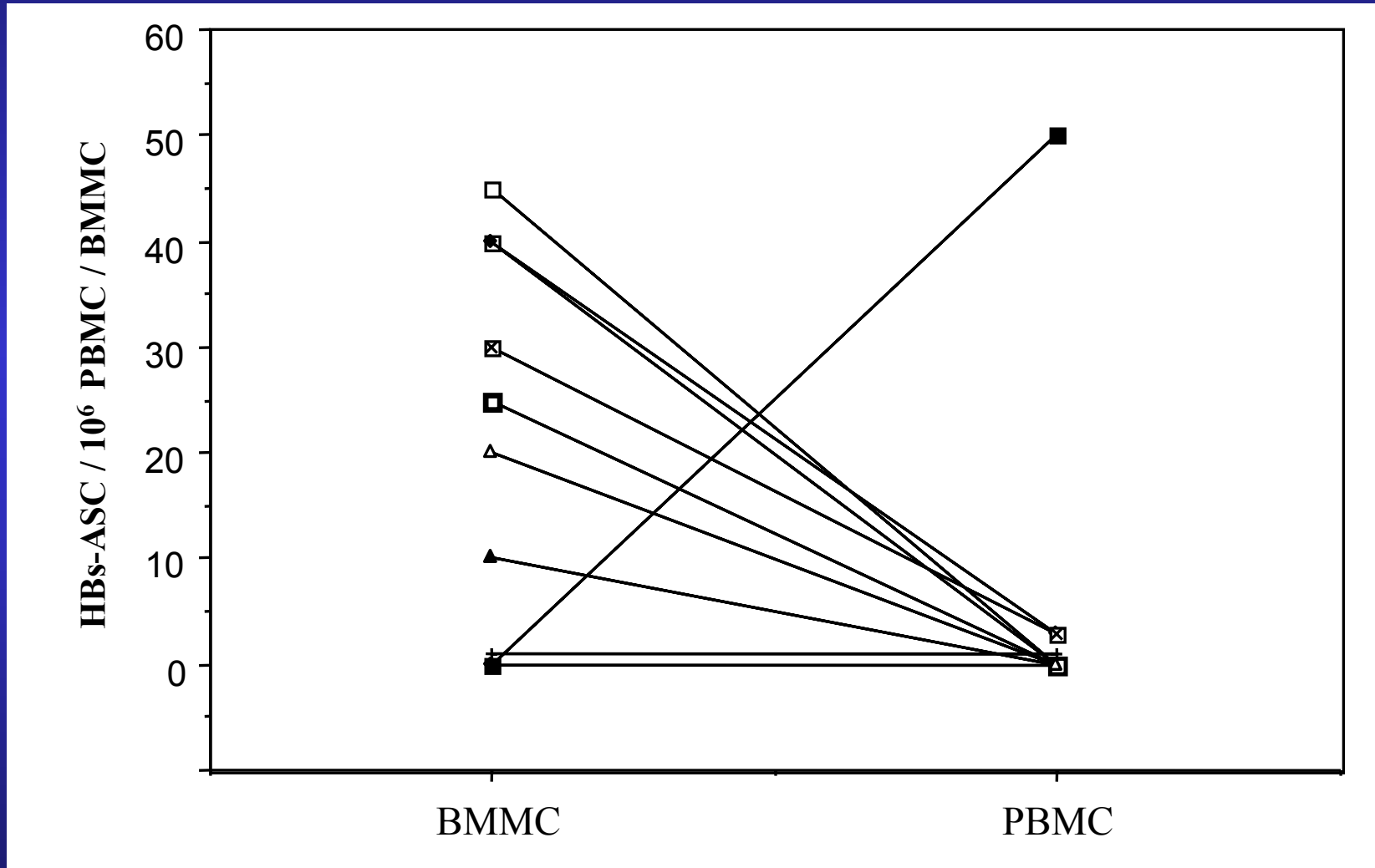


HBsAg	+	+	+	+	+	-
HBV-DNA		+		+		- (PCR -)
anti-HBs	-	-	-	-	-	70 U/l

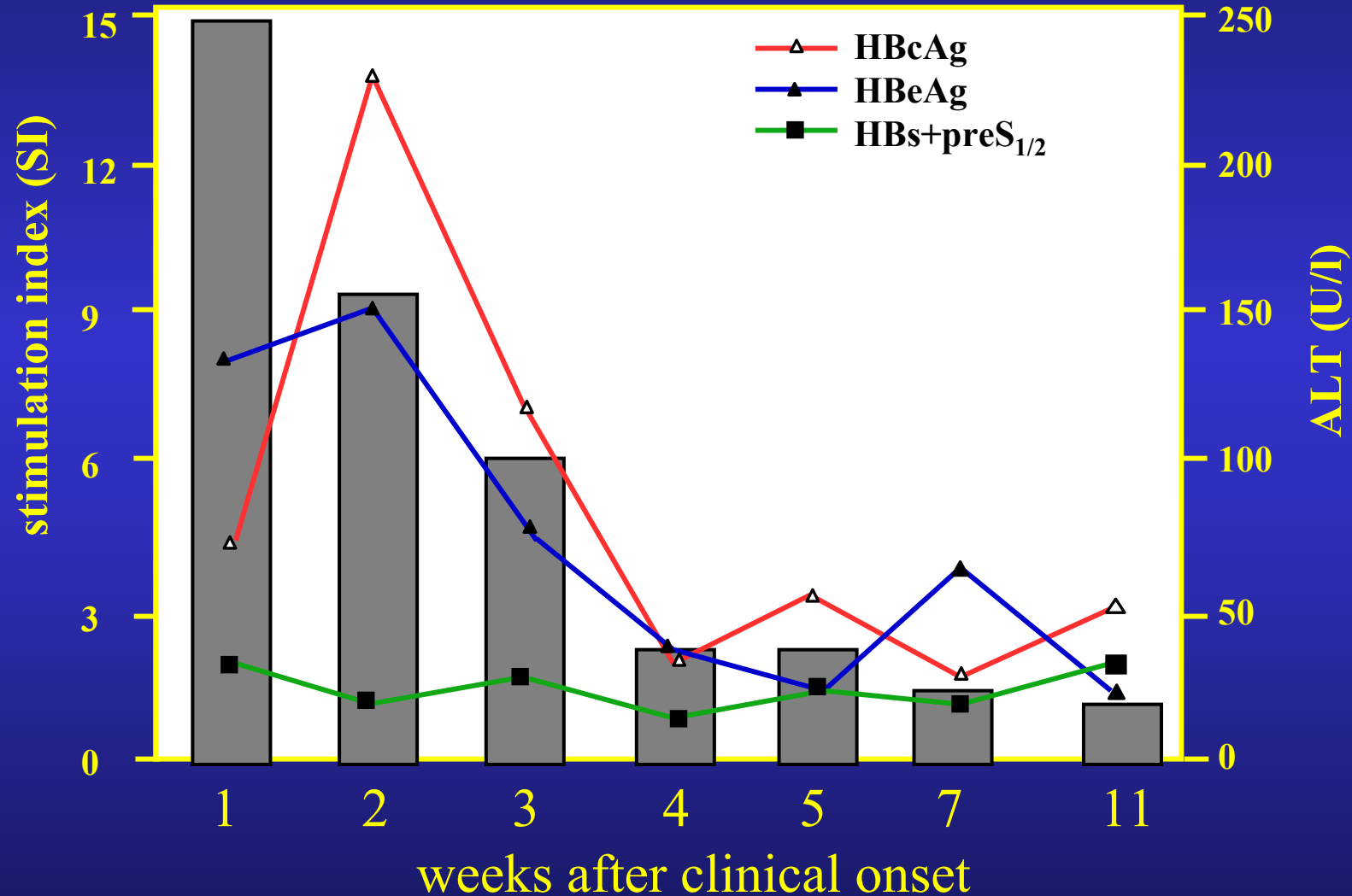
HBs specific B cells in acute and chronic HBV infection



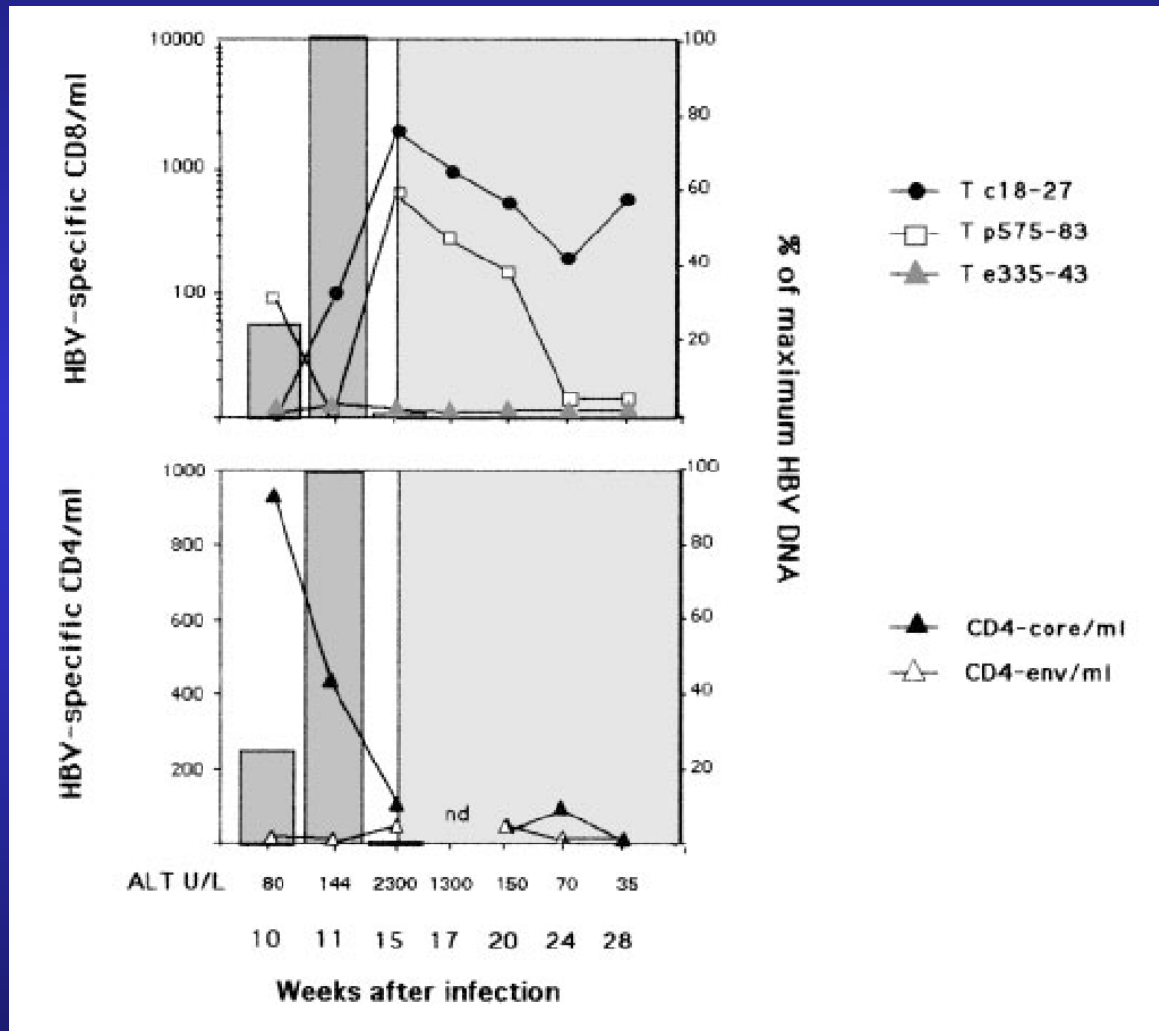
Enrichment of HBs specific B cells in bone marrow



HBV specific Th cells in acute hepatitis B

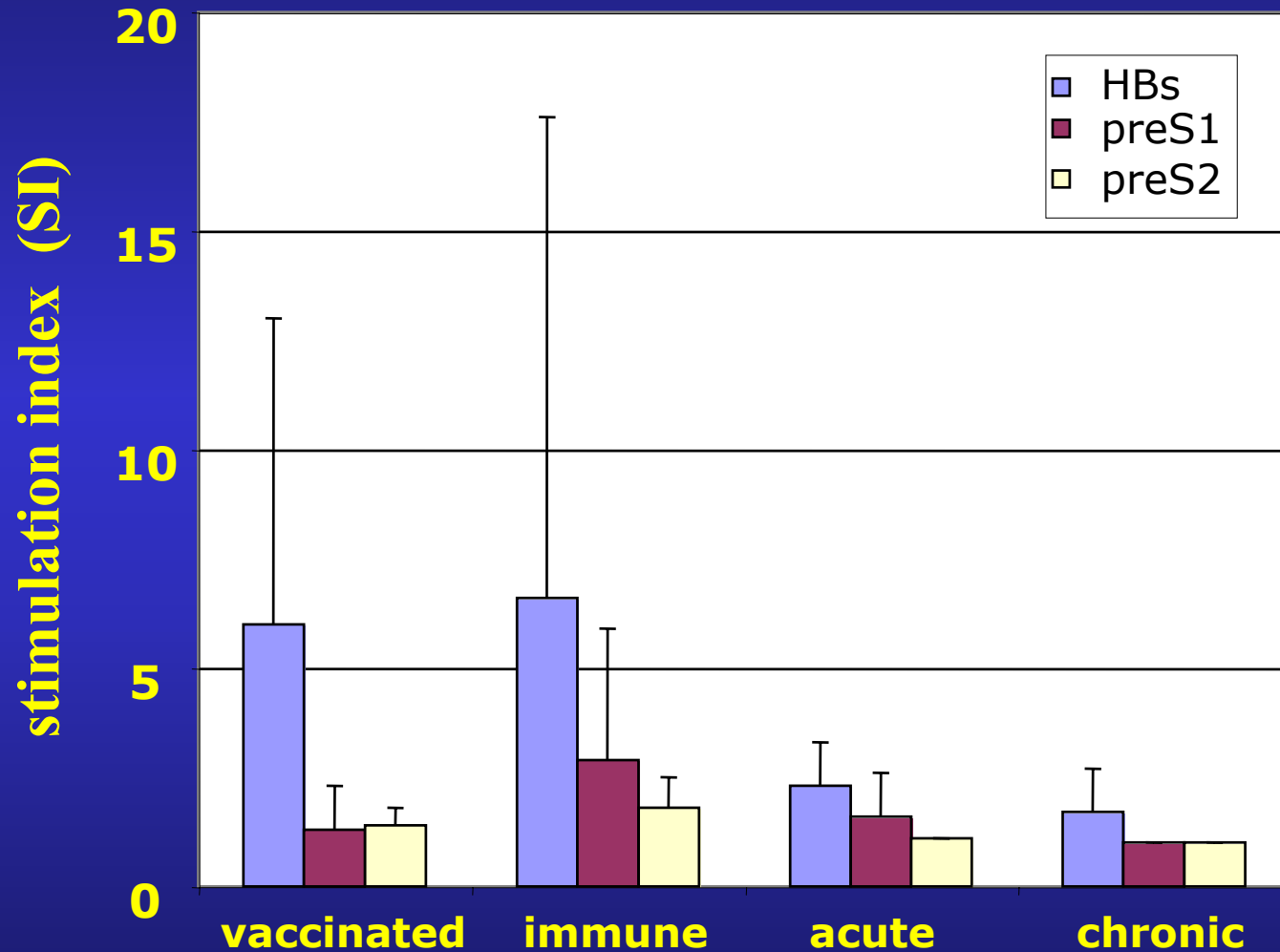


Correlation of HBc specific CTL and Th cells with HBV clearance in acute infection

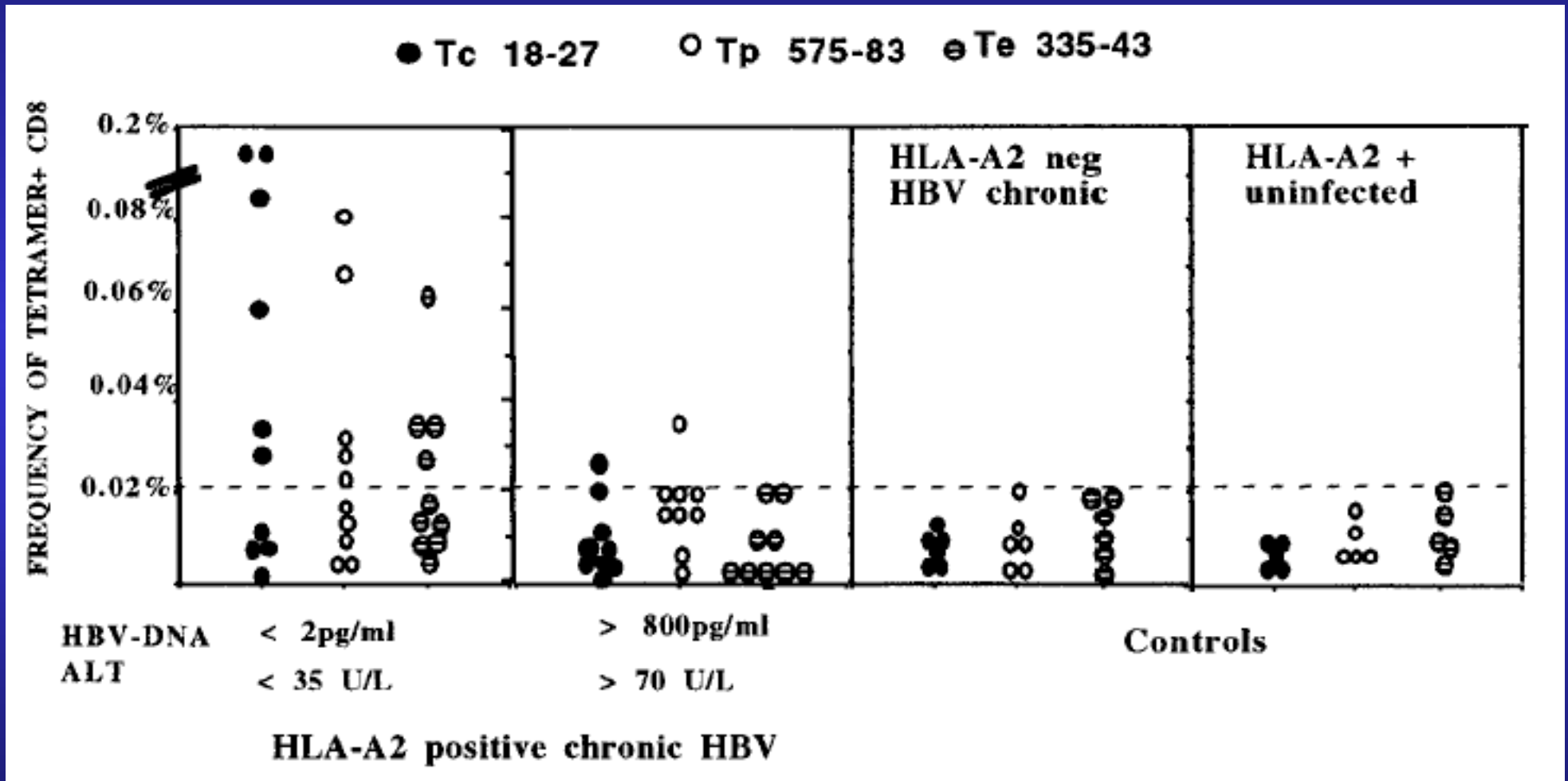


Webster G. et al., Hepatology 2000; (also Maini M. et al., Gastroenterology 1999)

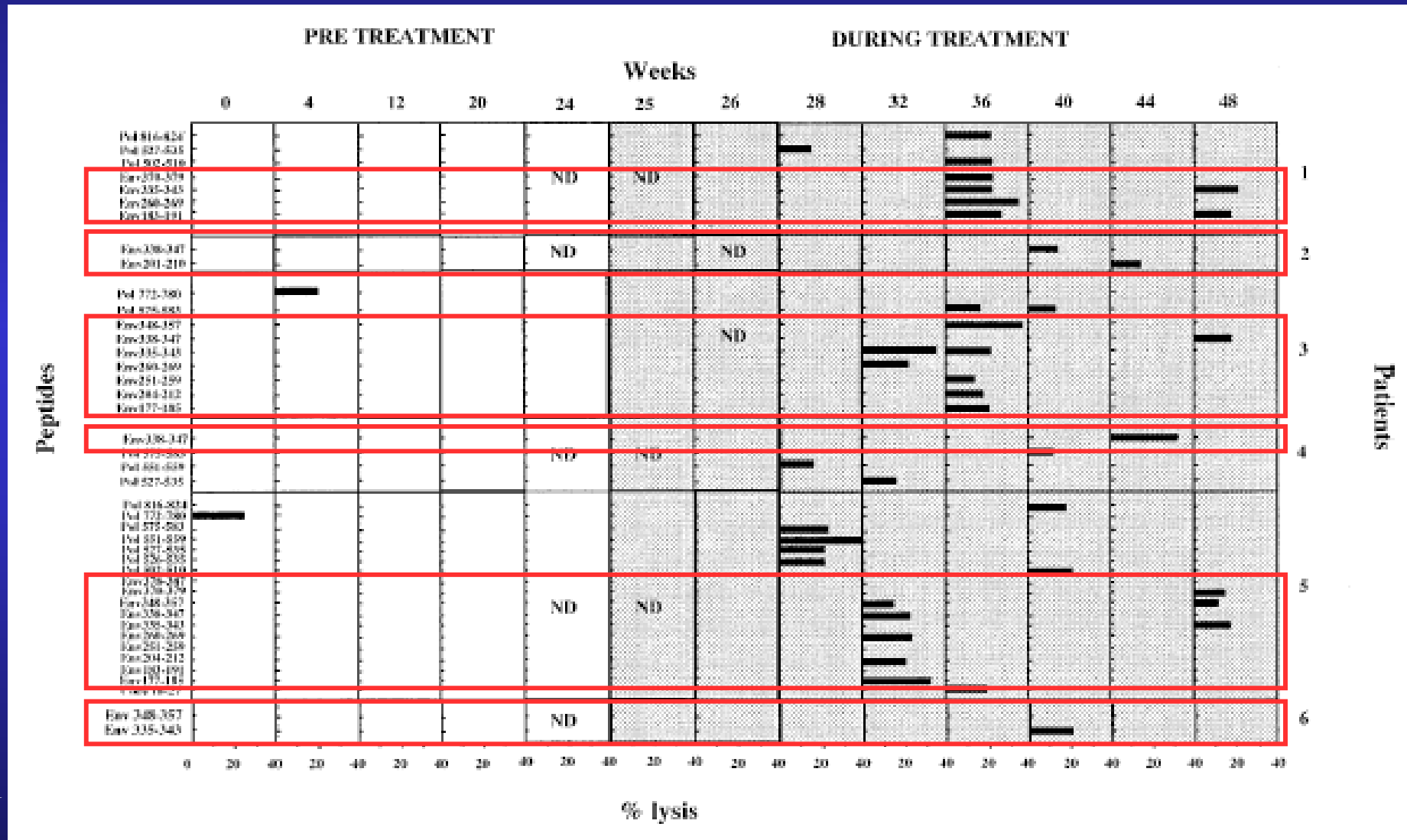
Envelope specific Th cells in chronic hepatitis B



HBV specific CTL in *chronic* hepatitis B



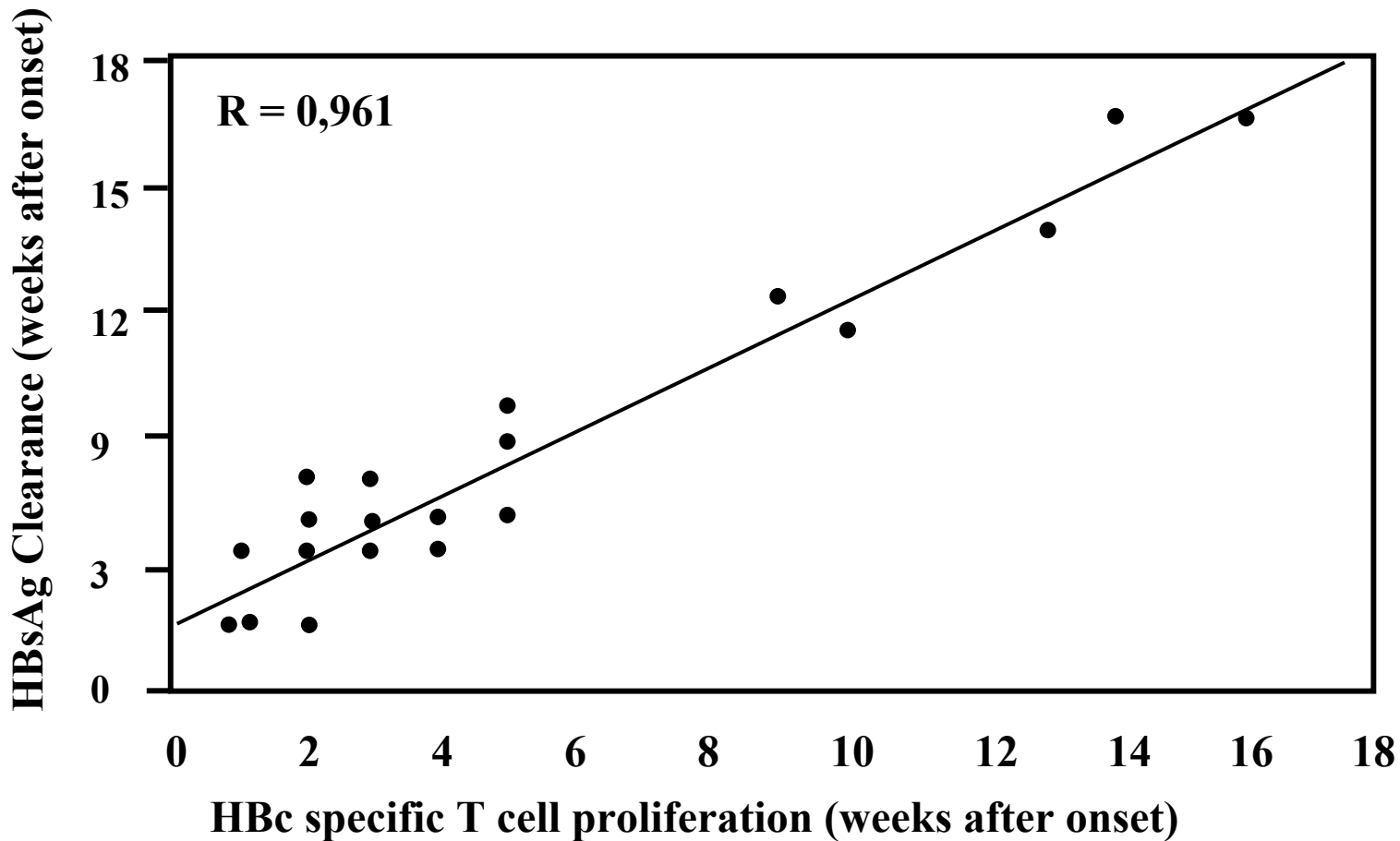
HBV specific CTL during treatment with lamivudine



Summary:

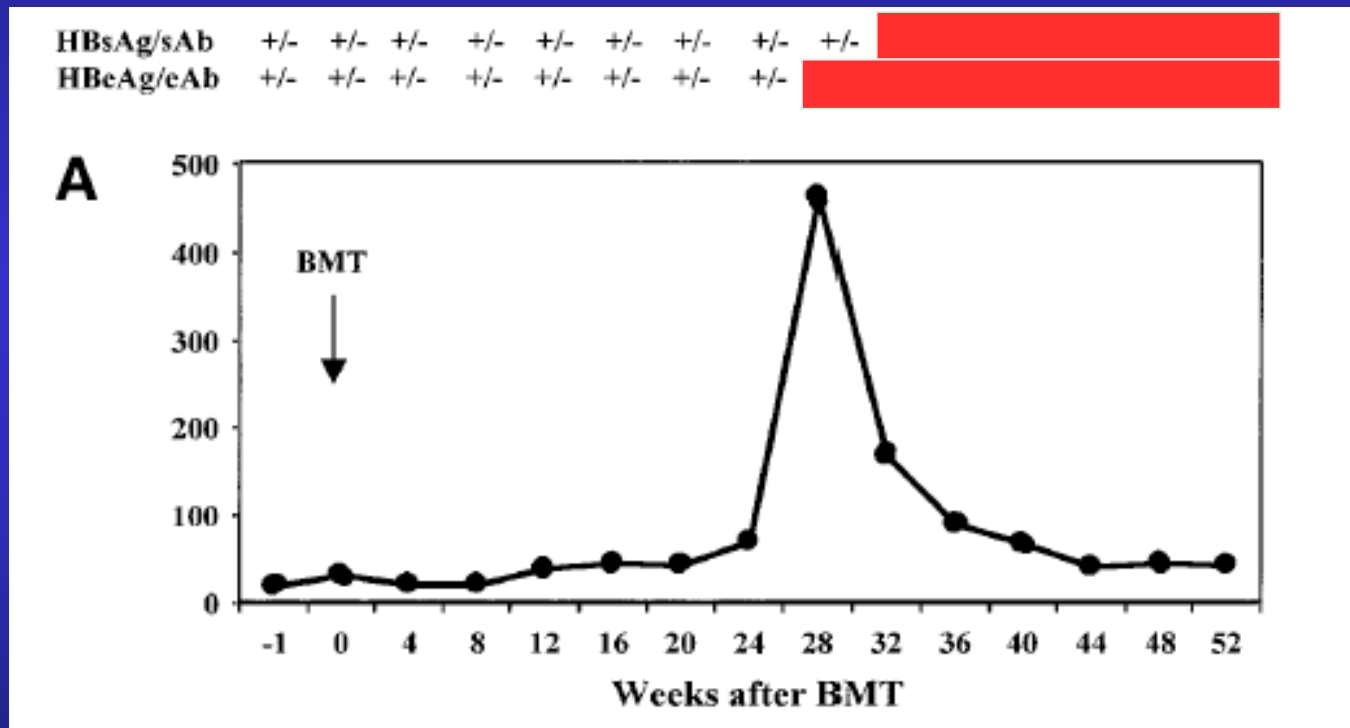
- in *acute* hepatitis B:
 - high frequencies of circulating anti-HBs secreting B cells before HBs seroconversion, migrating to lymphoid organs later on
 - weak envelope specific CTL and Th cell responses during seroconversion
- in *chronic* hepatitis B:
 - correlation of complexed anti-HBs and anti-preS 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