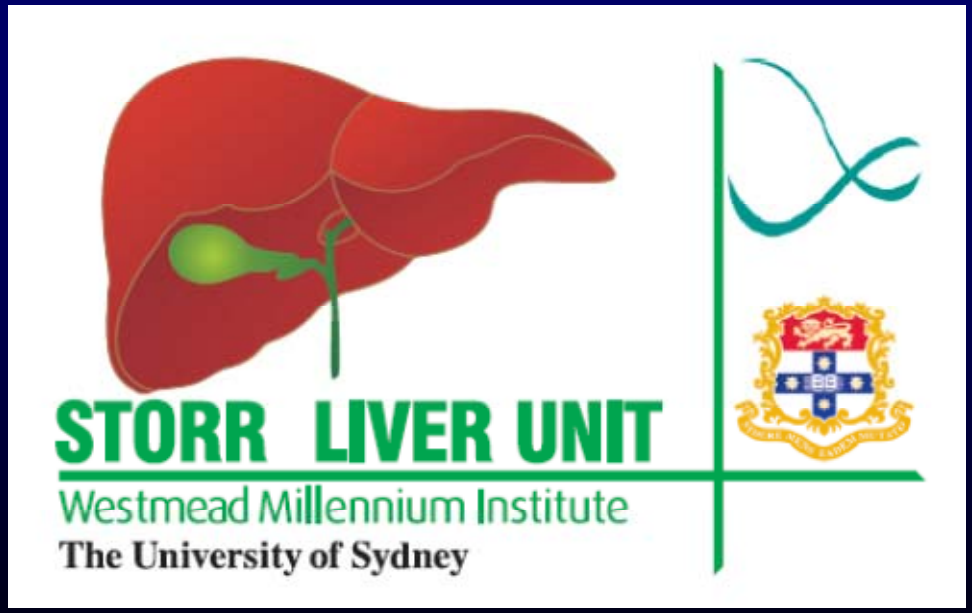
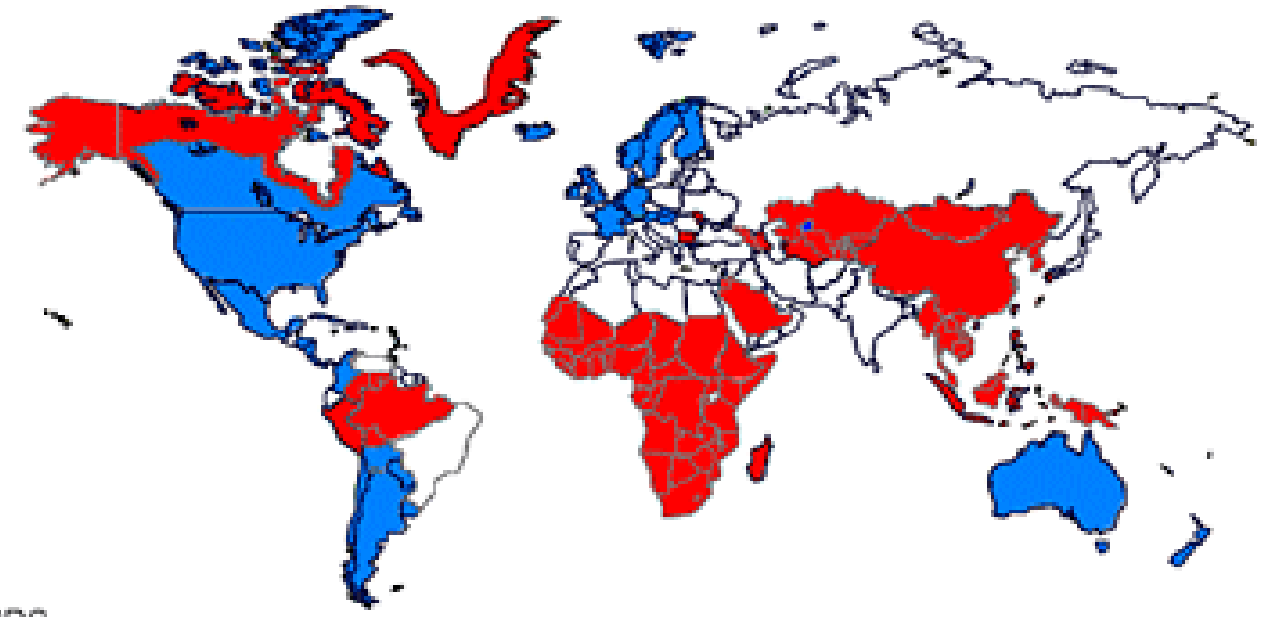
Hepatitis B and Delta Virus: New therapies

Jacob George



HBV: Clinical-Epidemiological Correlations

Endemicity	Location	Age of infection	Mode of transmission	Chronicity	HCC risk
Low	N America W Europe	Early adulthood	Percutaneous Sexual	Rare	Low
High	Subsahara Far East	Birth Toddler	Perinatal Horizontal	Likely	High

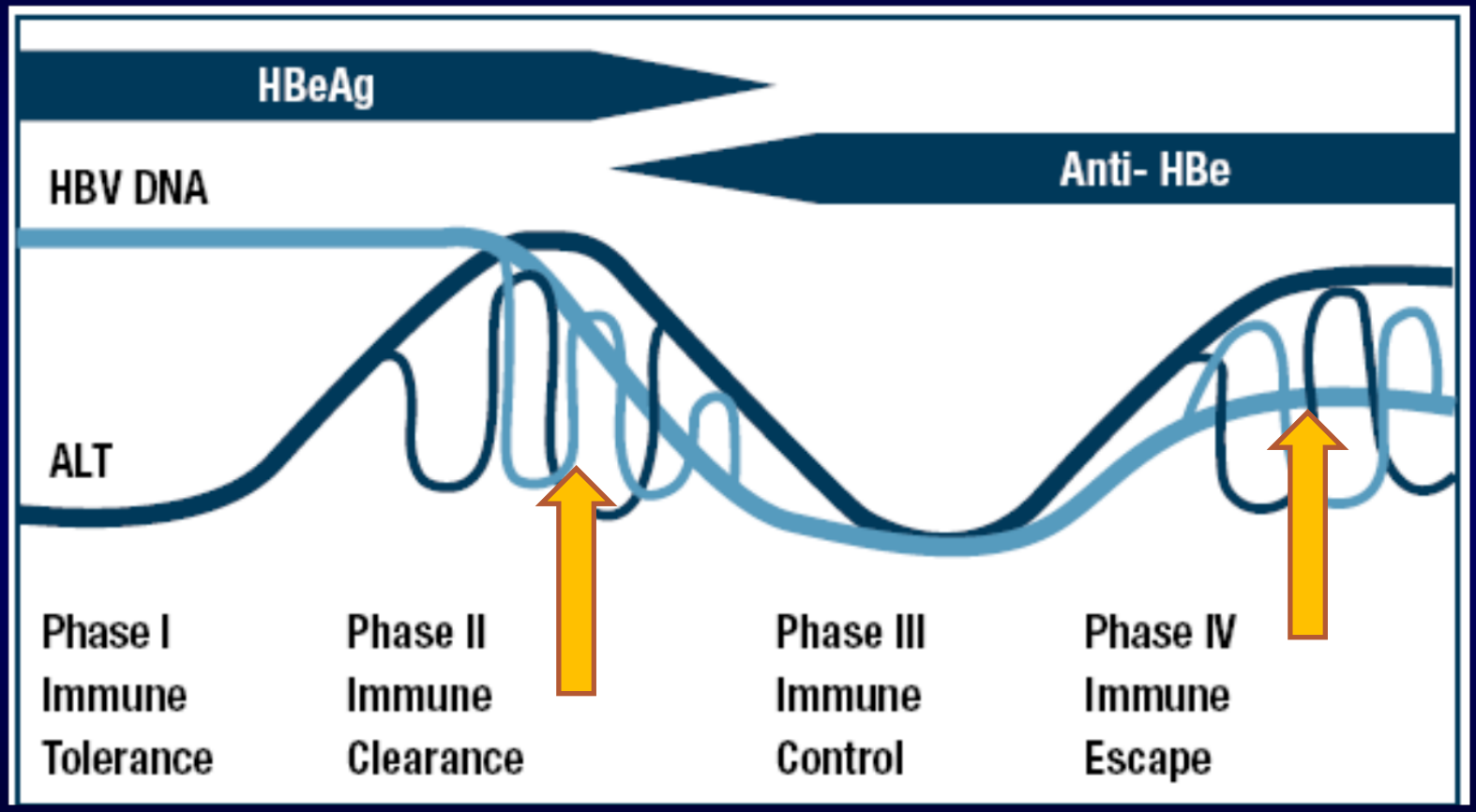


Map adapted from CDC.

Hepatitis B and D

- Causes acute and chronic infection
- Discovered as causes of post – transfusion hepatitis
- Liver disease is caused by host response to infection, not virus itself
- Many asymptomatic in early chronic hepatitis in all countries – but some areas “hyper-endemic”

Natural History of Hepatitis B



Long duration in perinatally acquired infection

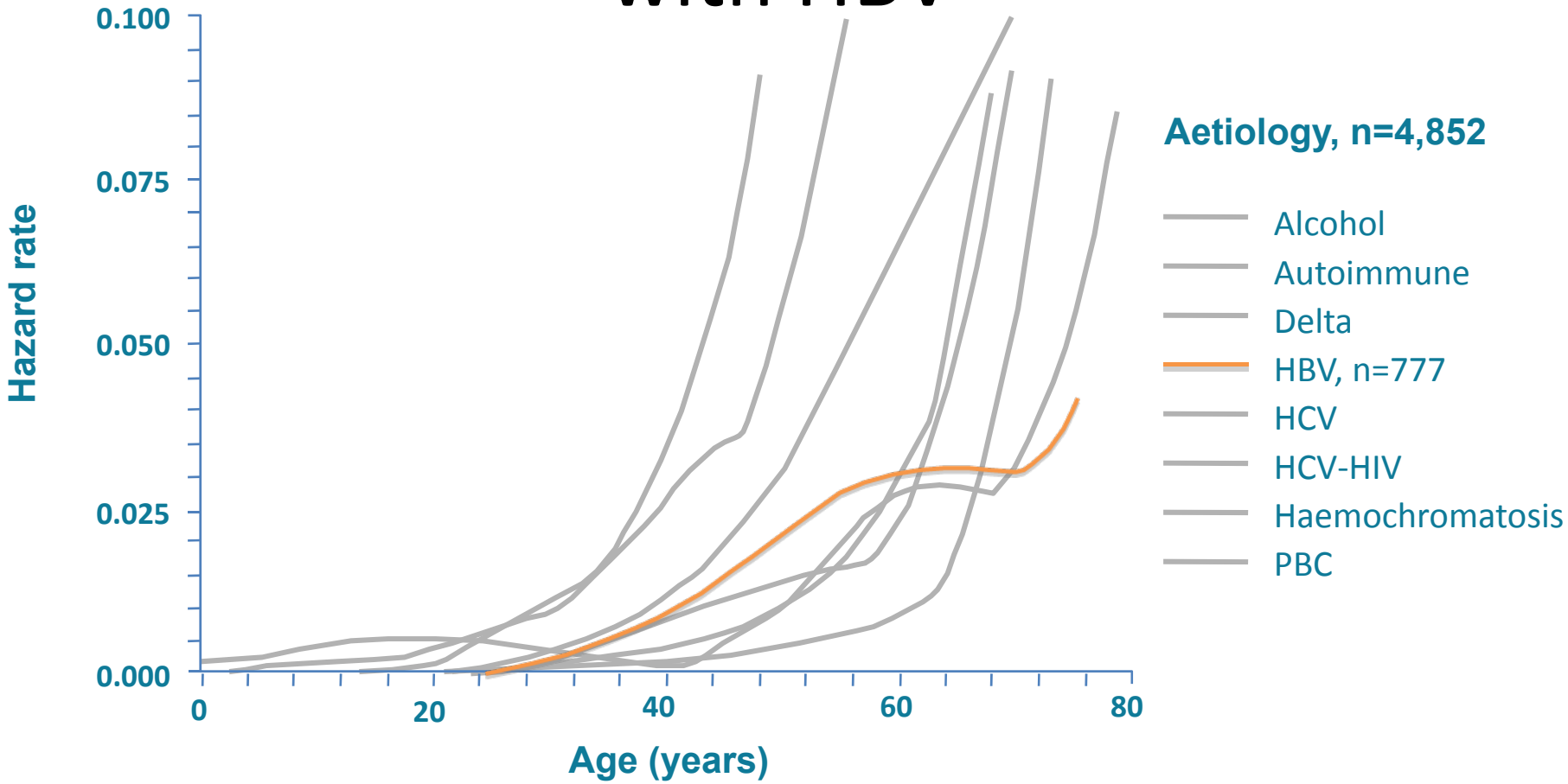
Rapidly progressive liver damage

Varying risk of disease relapse & progression

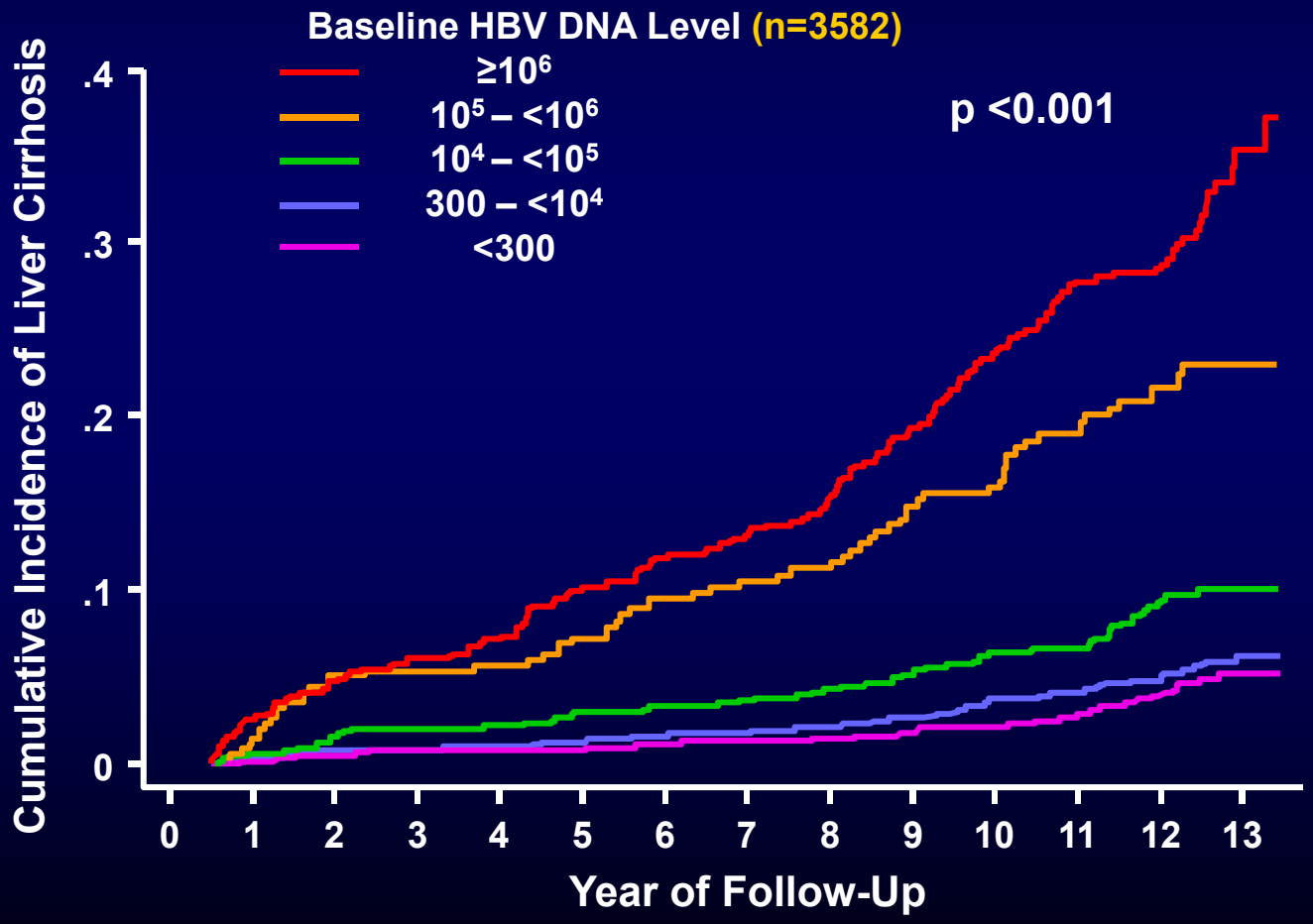
Precore or core promoter mutations

Australia & New Zealand Chronic Hepatitis B Recommendations 1st Edition 2008 Digestive Health Foundation

Age and aetiology of liver disease affect progression to cirrhosis in patients with HBV



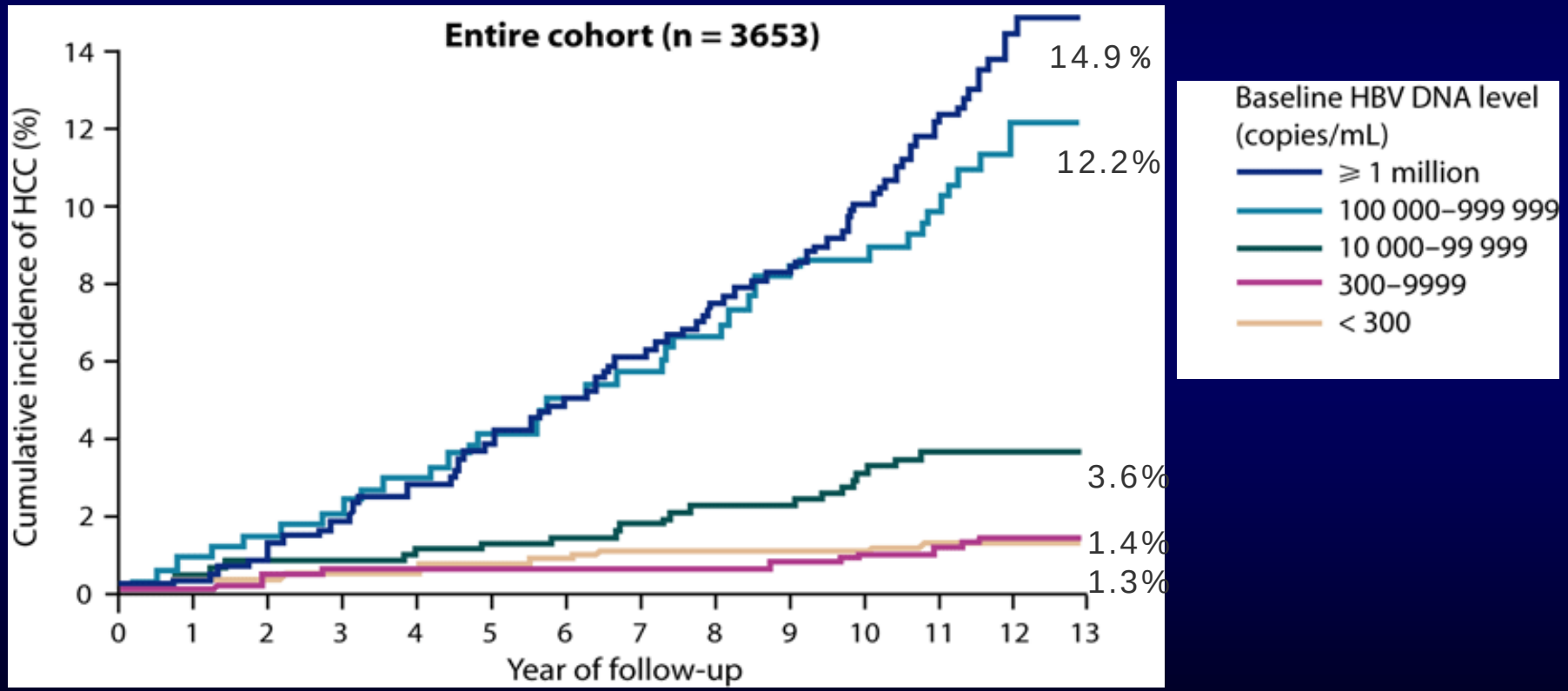
REVEAL: HBV viral load predicts progression to cirrhosis



Iloeje UH et al. 2006 Gastroenterology 130: 678-686

REVEAL: HBV viral load predicts progression to HCC

- Cumulative incidence of HCC by HBV DNA level at study entry



Chen JC, Yang HI, Su J *et al.* Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006; **295**: 65–73.

Decision making in HBV

- Is HBsAg present or not?
  - If present for >6/12, patient has CHB
- Has patient got active liver damage?
  - If ALT is abnormal then patient has active liver disease (Normal ALT vs Reference Range for ALT)
- Is liver damage due to HBV
  - What is the HBV DNA level?
  - (HBV DNA>20,000 IU/ml in HBeAg postitive or HBV DNA>2,000 IU/ml in HBeAg negative)
  - Exclude other causes of liver damage (NASH, Drugs, HCV, HIV etc)
- If answer to Q3 is +, then patient has Active CHB and may need therapy

Treatment options

Immunomodulatory

- **IFN & PEG-IFN**

ADVANTAGES:
Defined Rx duration
No resistance
Durability of HBeAg s/c

DISADVANTAGES:
s/c administration
Side effect profile
Contraindicated in decompensated Δ

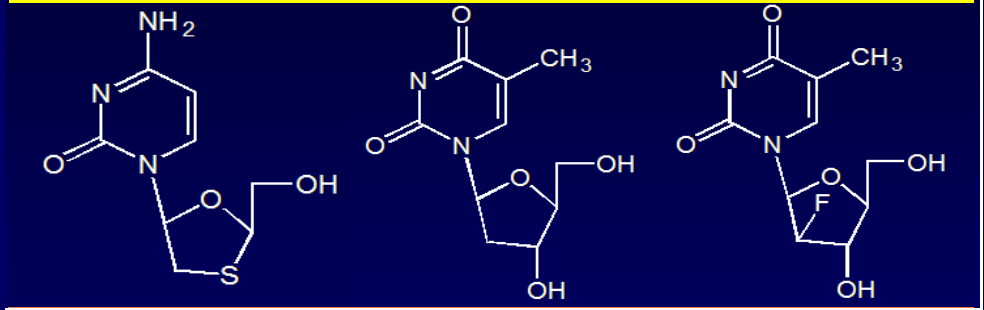
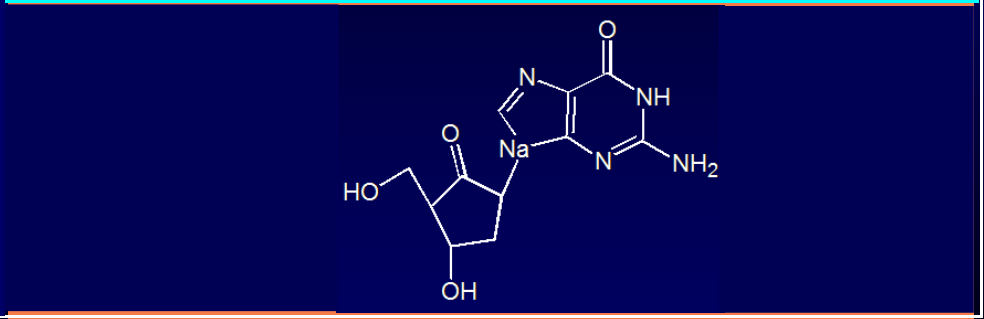
Antiviral

- **Lamivudine**
- **Telbivudine**
- **Entecavir**
- **Adefovir**
- **Tenofovir**

ADVANTAGES:
Safe in patients with cirrhosis
Fewer side effects

DISADVANTAGES:
Prolonged duration of therapy
Emergence of resistance

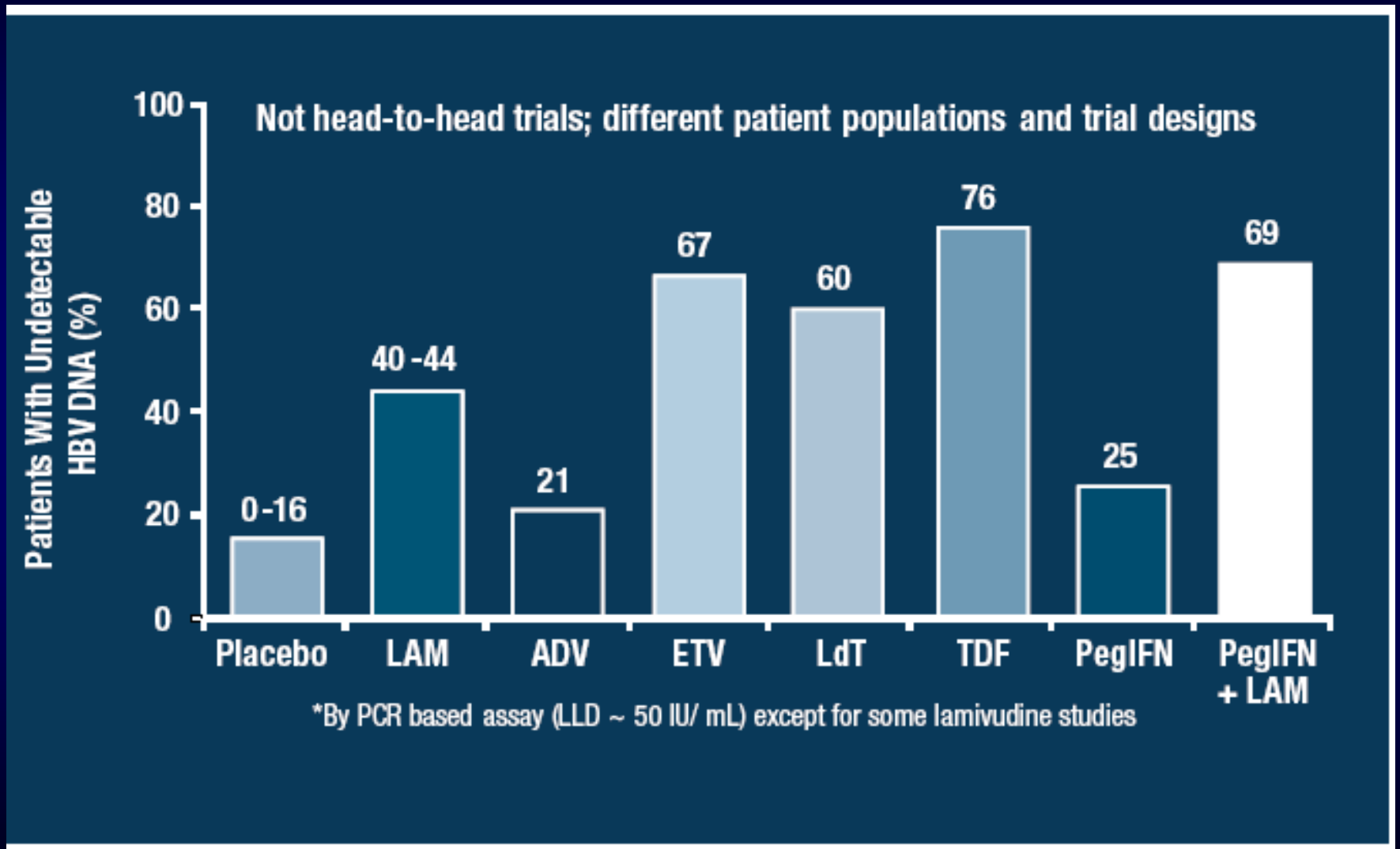
Structures of Common Antivirals

L-nucleoside group	lamivudine (LVD) telbivudine (LdT) clevudine 
acyclic phosphonate group	adefovir (ADV) tenofovir (TDF) 
cyclopentane group	entecavir (ETV) 

Lai CL Hepatitis B Virus 2nd edition; p 15.4

Percentage of patients with undetectable HBV DNA after one year of treatment.

Australia & New Zealand Chronic Hepatitis B Recommendations 1st Edition 2008 Digestive Health Foundation



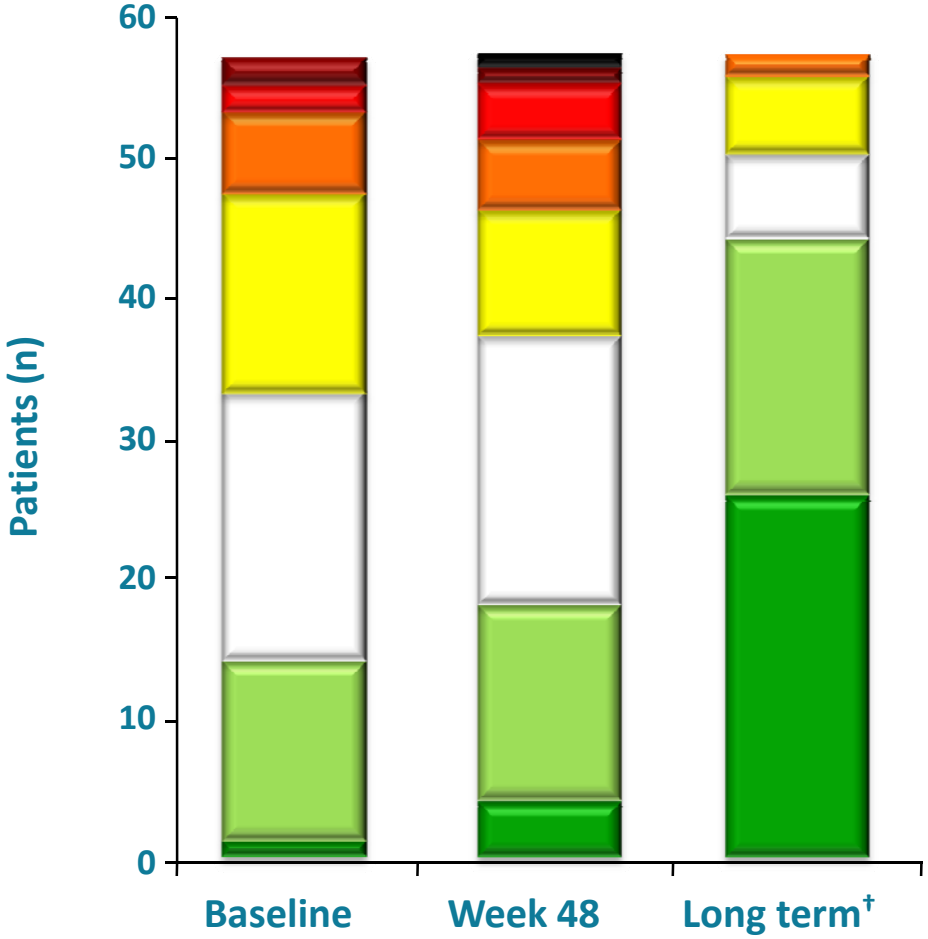
ADV, adefovir; ETV, entecavir; HBeAg, hepatitis B e antigen; LAM, lamivudine; LdT, telbivudine; LLD, lower level of detection; TDF, tenofovir disoproxil fumarate; PegIFN, peginterferon; PCR, polymerase chain reaction.

HBeAg & HBsAg seroconversion rates

Data derived from Dienstag JL NEJM 2008;359:1486-500

Variable	Peg IFN	Lamivudine	Adefovir	Entecavir	Telbivudine	Tenofovir DF
HBeAg positive patients						
HBeAg seroconversion %						
1yr	27	16-21	12	21	22	21
>1yr	NA	50 at 5yr	43 at 3yr	39 at 3yr	30 at 2yr	ND
Durability of response >1yr	82	70-80	91	82	80	ND
HBsAg loss %						
1yr	3	<1	0	2	<1	3
>1yr	NA	3	ND	5	ND	8 at 144 wk
HBeAg negative patients						
HBsAg loss %						
1yr	4	<1	0	<1	<1	0
>1yr	8 at 3yr	ND	5 at 4-5yr	ND	ND	2-5 at 2y?

Improvement in Ishak fibrosis score with long-term ETV

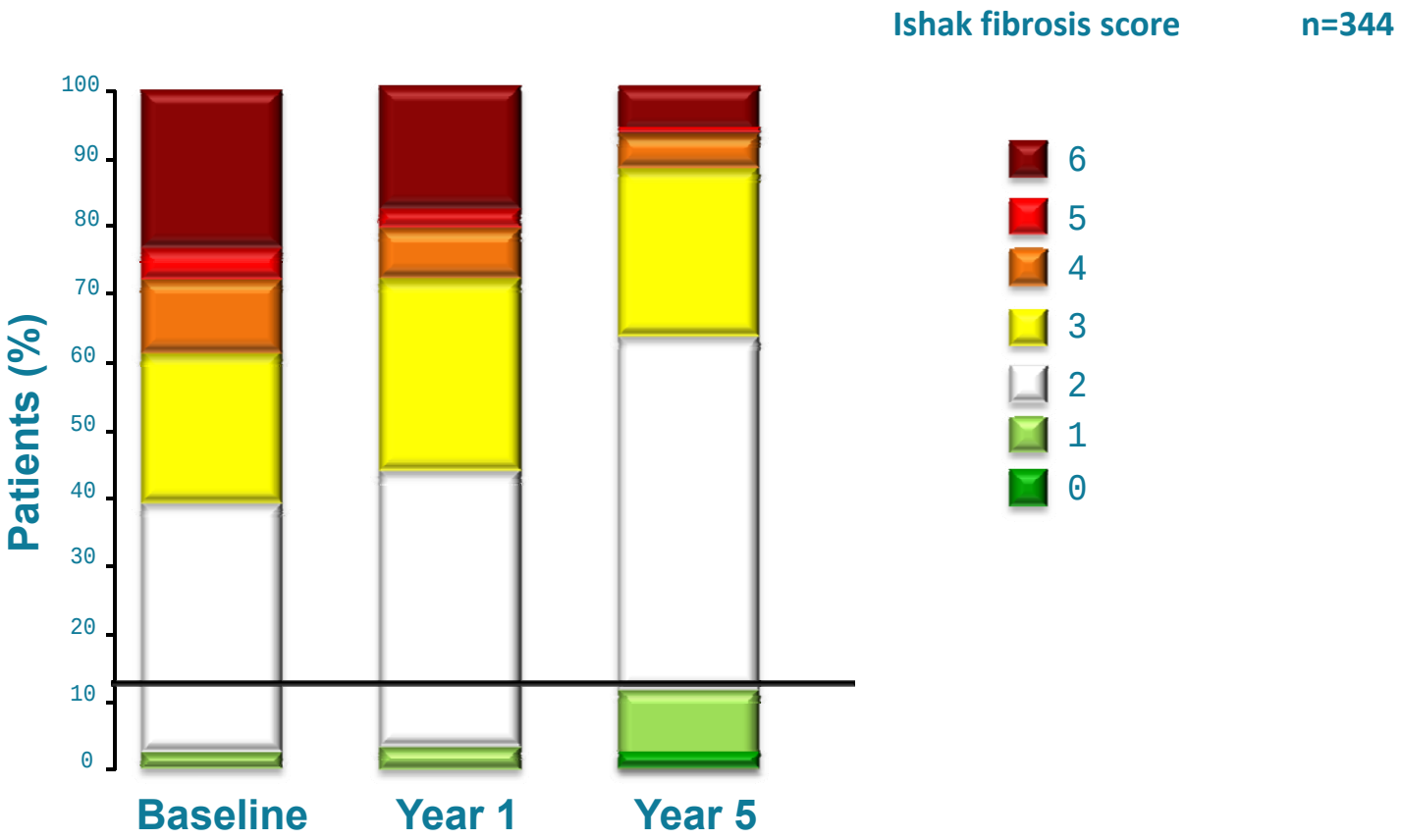


Ishak fibrosis score n=57

- Missing
- 6
- 5
- 4
- 3
- 2
- 1
- 0

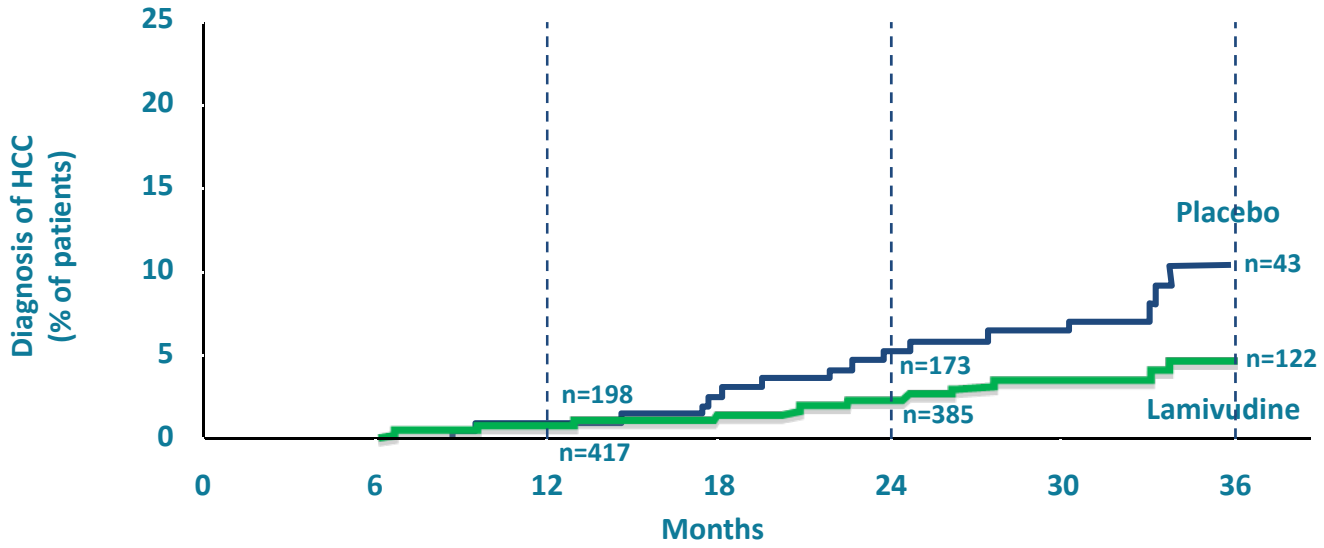
† Up to 7 years (range: 3–7 years) median time: 280 weeks1*

Improvement in Ishak fibrosis score with long-term TDF



Does antiviral therapy decrease the incidence of HCC?

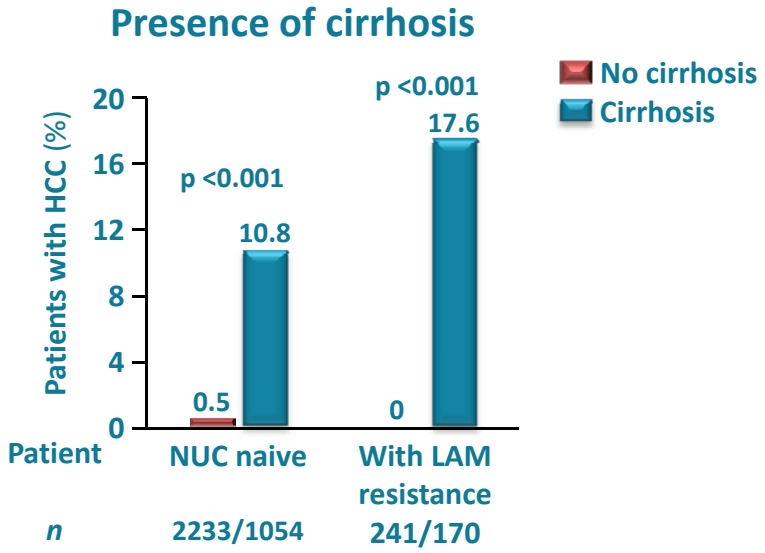
Randomised controlled trial of lamivudine therapy in patients with HBV-related advanced fibrosis/cirrhosis showing that antiviral therapy can decrease the incidence of HCC



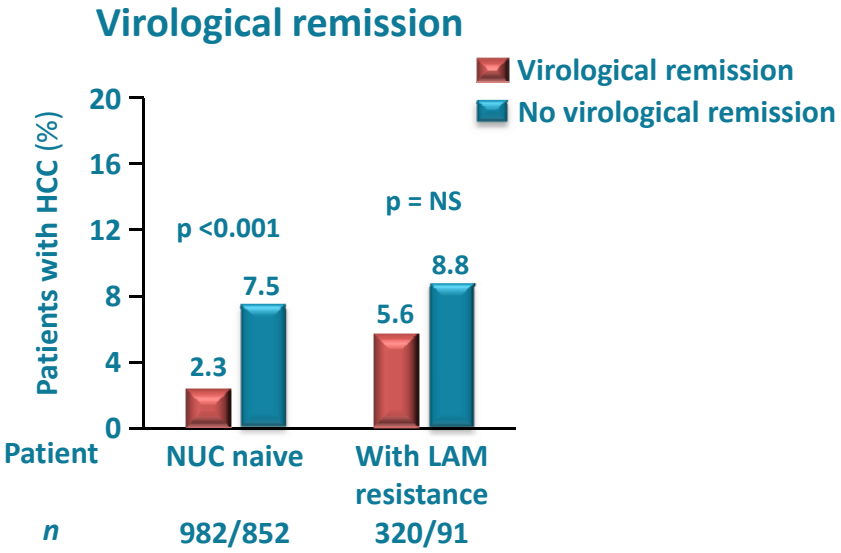
HCC occurred in 3.9 % of lamuvidine-treated group, versus 7.4% of the placebo group (HR=0.47; p=0.047)[1,2]

- Evidence to support that antiviral therapy is associated with decreased risk of HCC

Patients receiving NUC therapy had a significantly lower incidence of HCC compared with untreated patients



Incidence of HCC relative to the presence of cirrhosis and development of lamivudine resistance

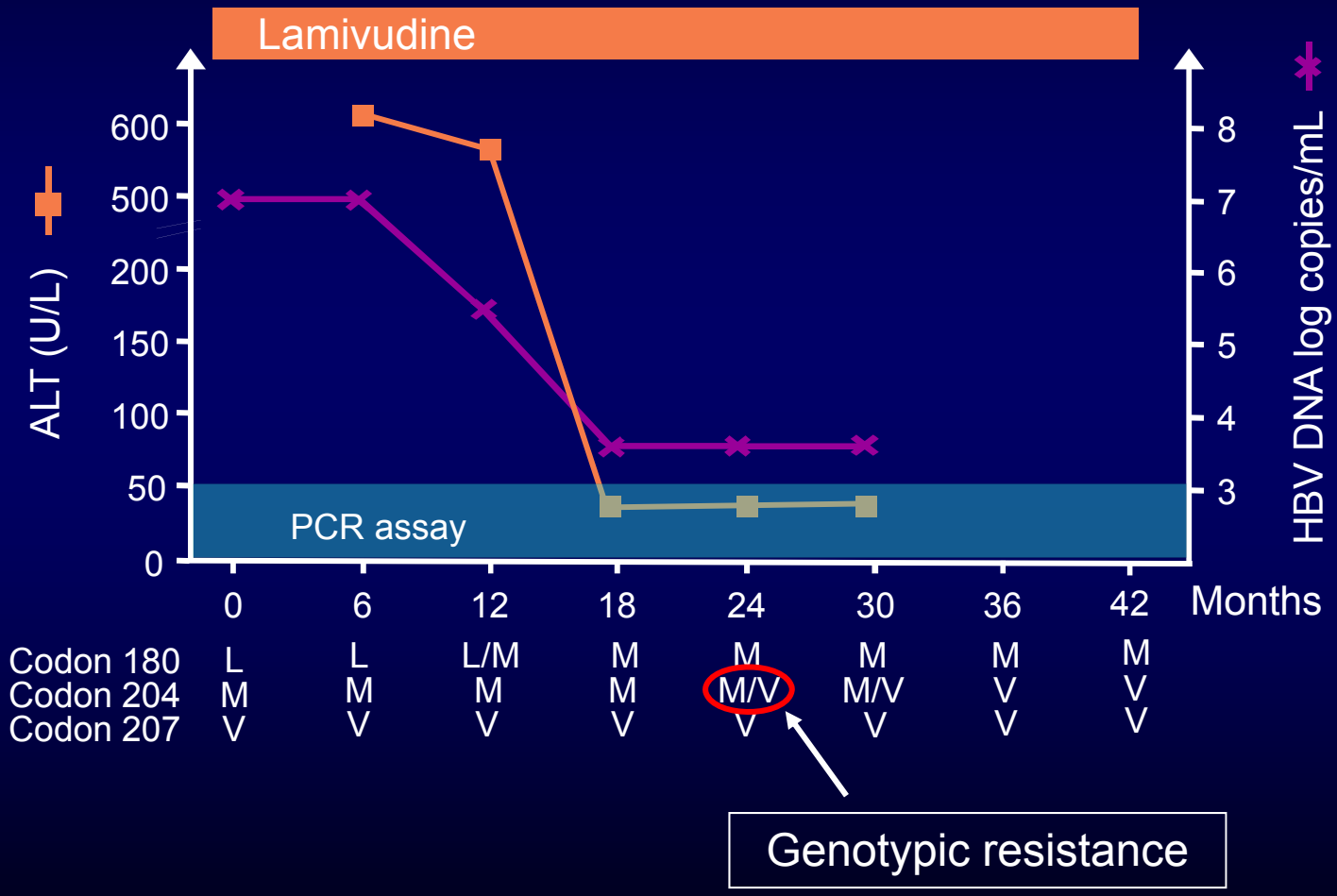


Incidence of HCC relative to the presence of virological remission and development of lamivudine resistance

- Overall, 2.8% of treated vs 6.4% of untreated patients, were diagnosed with HCC during a 46 (32–108) month period (p = 0.003)
- Among the treated patients, cirrhosis, HBeAg negative at baseline, and failure to remain in virological remission were associated with an increased risk of HCC

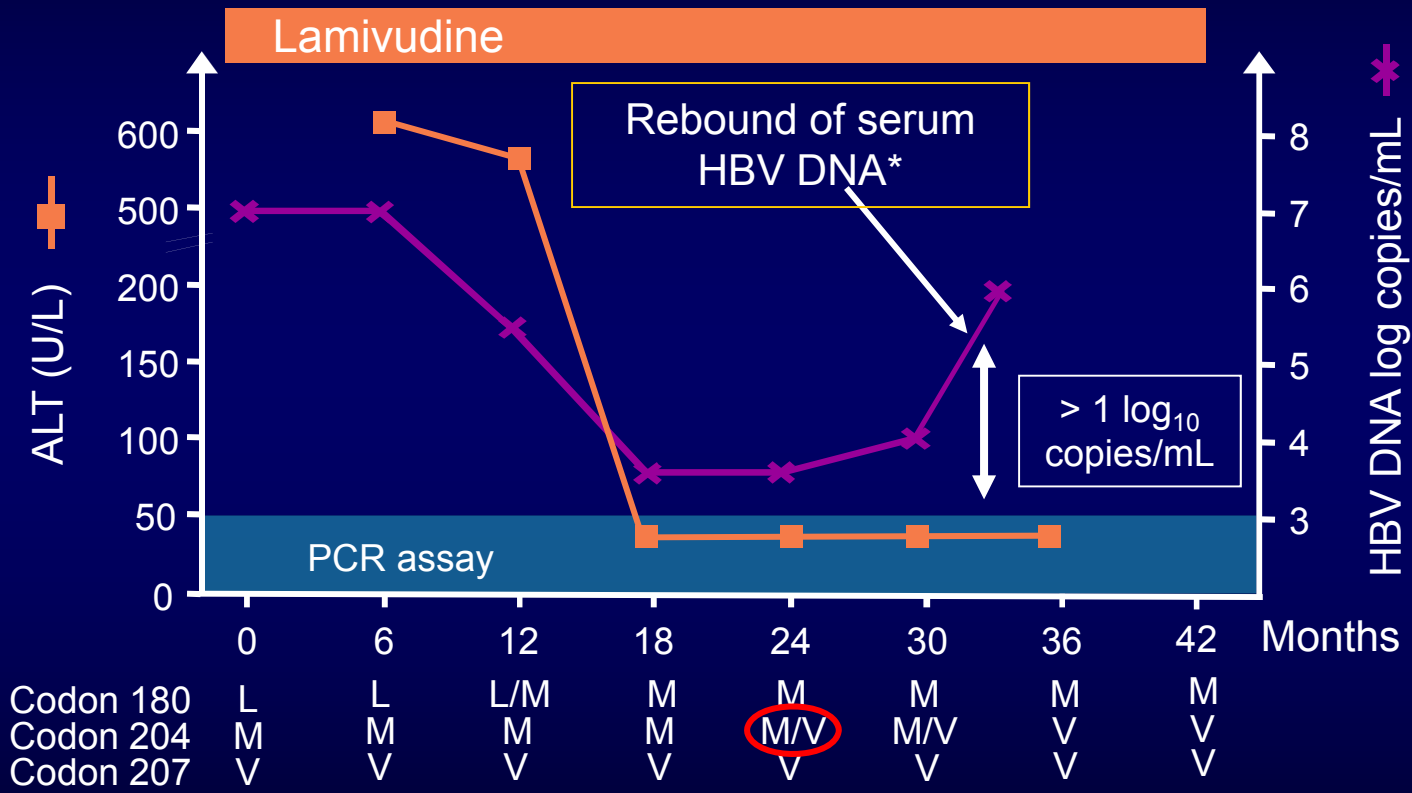

RESISTANCE

Dynamics of resistance emergence
Genotypic resistance



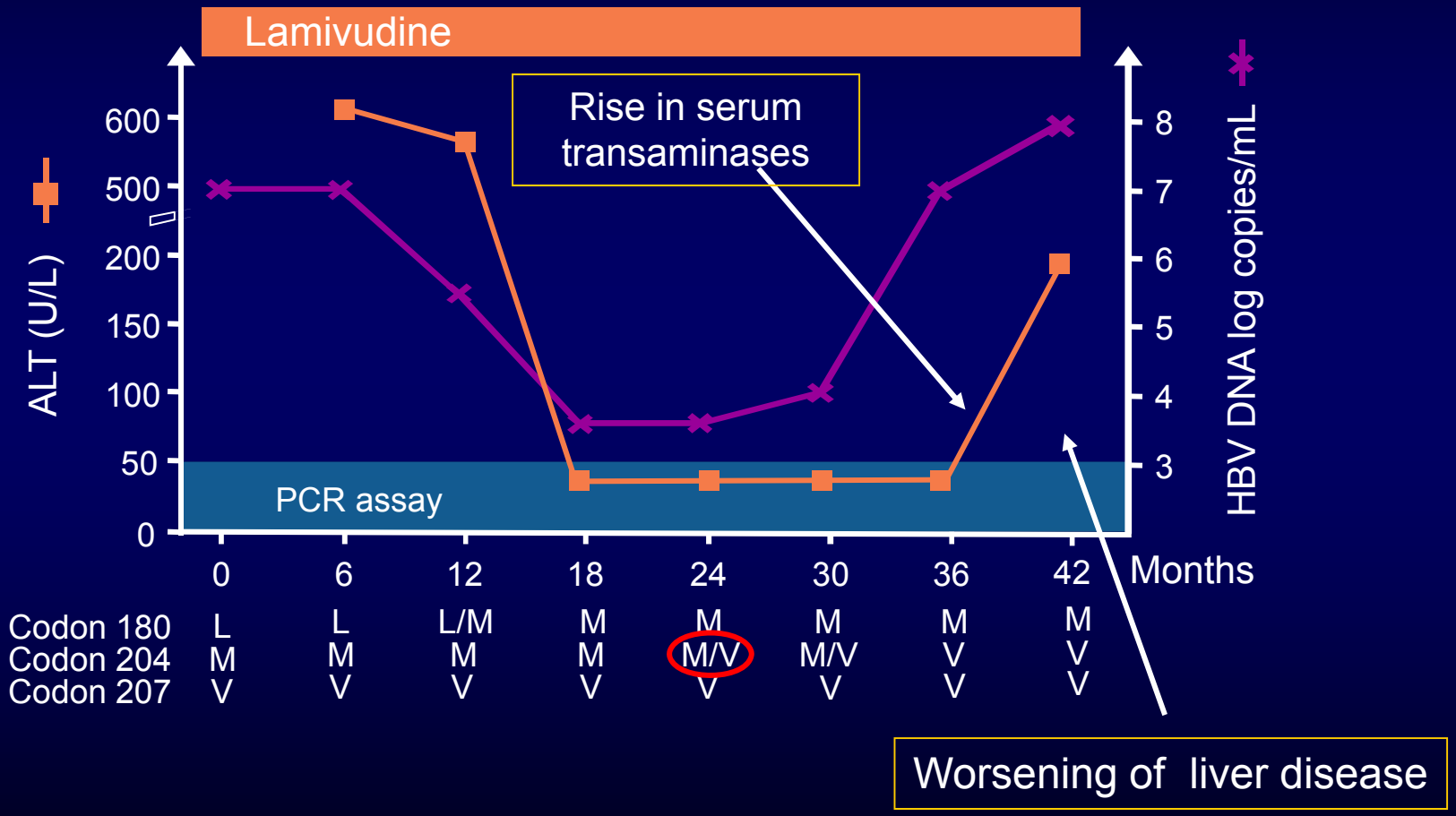
Si Ahmed et al. Hepatology 2000;32:1078–88

Dynamics of resistance emergence
Virologic breakthrough



Si Ahmed et al. Hepatology 2000;32:1078–88

Dynamics of resistance emergence
Clinical breakthrough

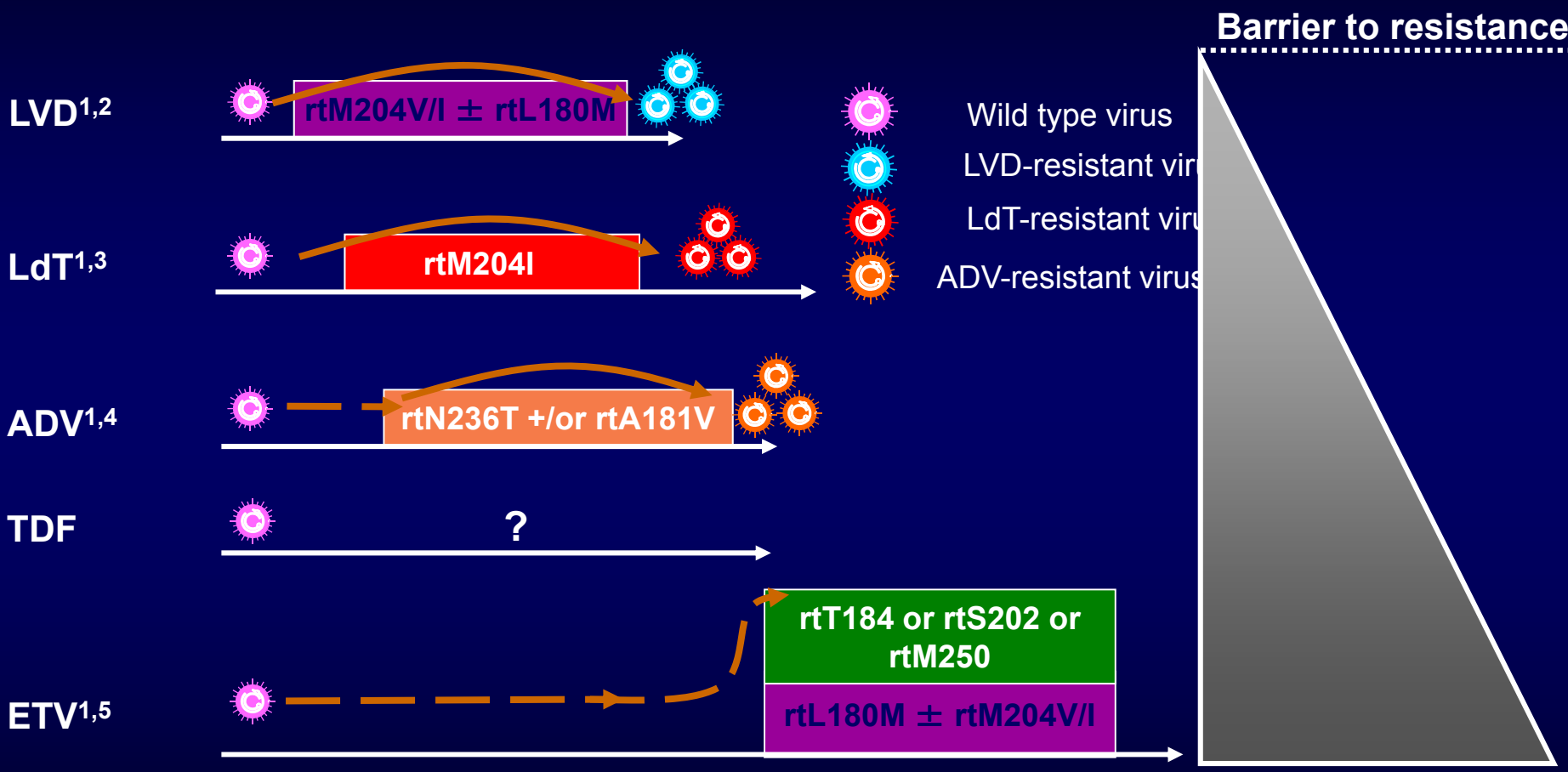


Si Ahmed et al. Hepatology 2000;32:1078–88

Strategies to prevent antiviral resistance

- **Maximise antiviral activity**
  - Agent with high potency, high genetic barrier
  - ? Combination therapy
- **Maximise genetic barriers to resistance**
  - Avoid sequential monotherapy
  - Avoid treatment interruptions
- **Increase pharmacologic barriers**
  - Compliance
  - Early intervention before rebound of viral load

Genetic Barrier of Antiviral Drugs in Nucleoside-Naïve Patients



Genetic barrier increases as the number of specific mutations required for drug resistance increases[6]

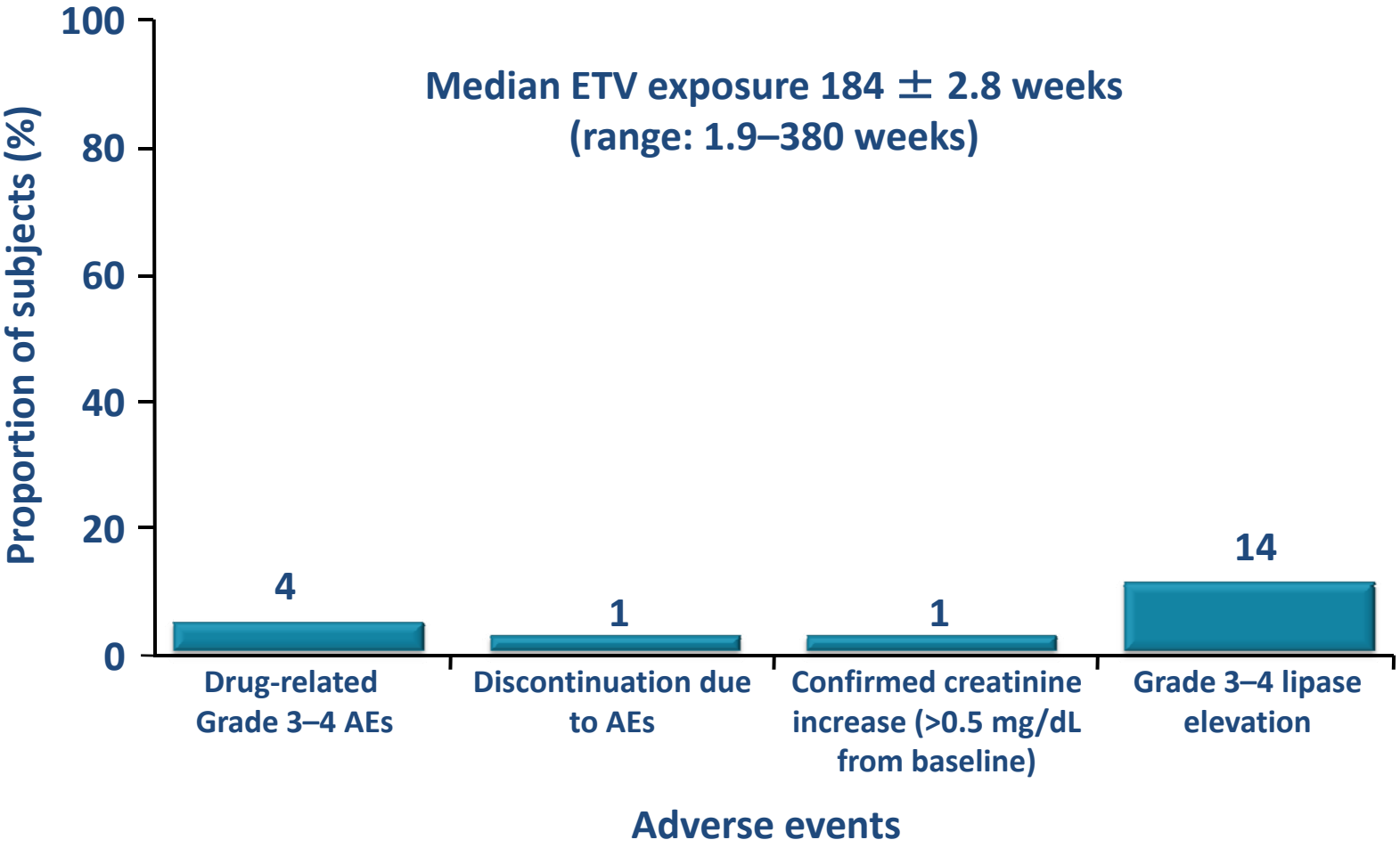
1. Locarnini S, et al. J Hepatol. 2006;44:422-31. 2. Zeffix® (lamivudine) SmPC. February 2008. 3. Sebivo® (telbivudine) SmPC. June 2007. 4. Hepsera® (adefovir) SmPC. October 2007. 5. Baraclude® (entecavir) SmPC. February 2009. 6. Lok AS, et al. Hepatology 2007;46:254-65. 7. Villet S, et al. J Hepatol 2007;46:531-8

Cumulative rates of antiviral resistance reported in clinical trials

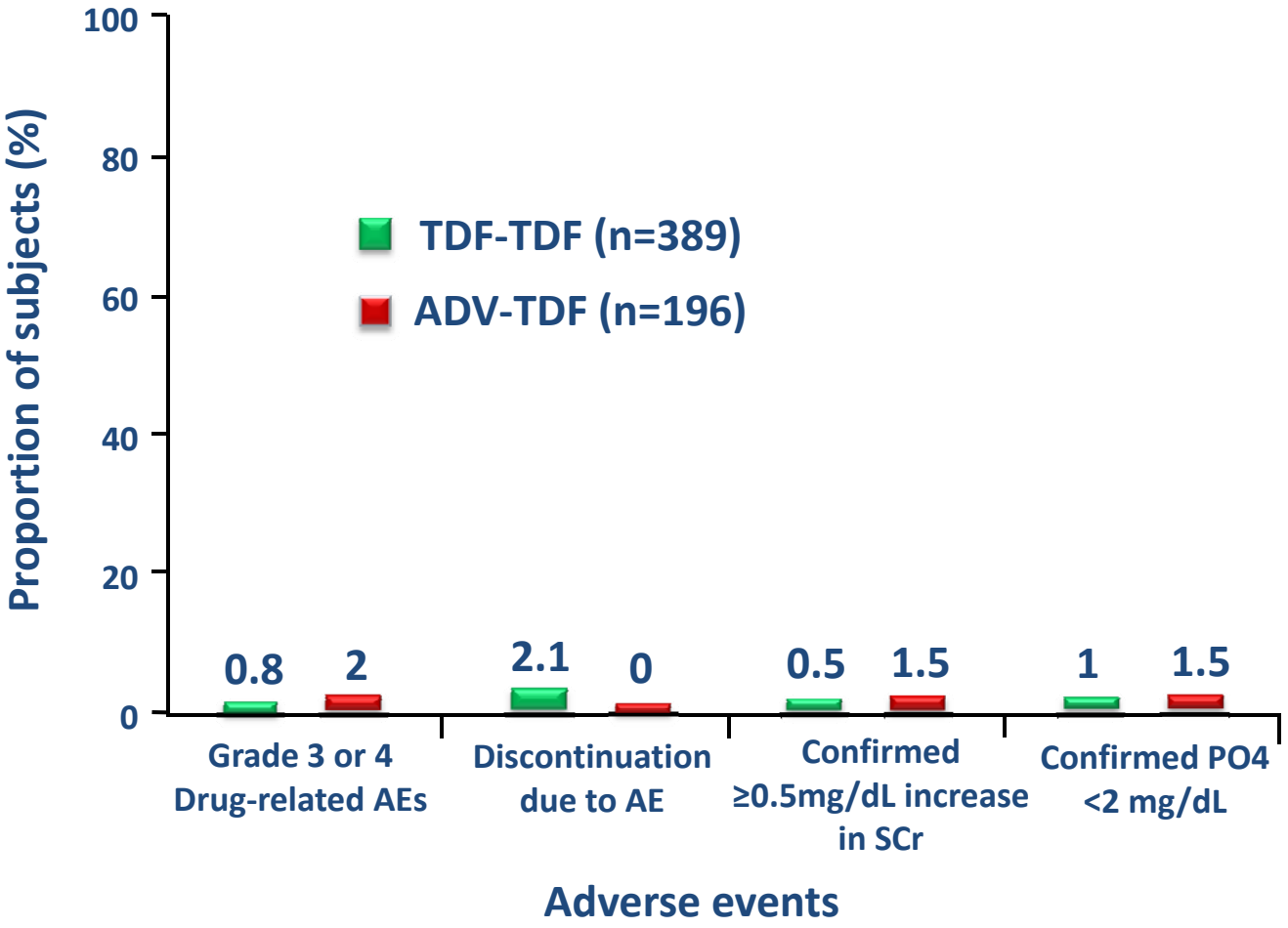
Australia & New Zealand Chronic Hepatitis B recommendations 1st Edition 2008, Digestive Health Foundation 2008

Treatment		Rates of genotypic resistance (%)				
		Yr1	Yr2	Yr3	Yr4	Yr5
Nucleosides	Lamivudine[82, 108, 109]	24	38	49	67	70
	Telbivudine[95, 123]	3-4	8-21			
	Entecavir (treatment naïve patients)[122]	0	0.5	1.2	1.2	1.2
	Entecavir (lamivudine resistant patients)[122]	6	15	36	46	51
Nucleotides	Adefovir (treatment naïve patients)[93]	0	3	11	18	29
	Adefovir (lamivudine resistant patients)[94, 168]	5	20	16		
	Adefovir + lamivudine combination (lamivudine resistant patients)[169]	0	0	0	0	
	Tenofovir (Naïve and lamivudine resistant patients)[99]	0	0	0		

ETV has a generally favourable open-label safety profile up to 380 Weeks* (n=1051)



TDF has a generally favourable clinical trial safety profile up to 5 years*



Immune Compromised Patients

- HBsAg +ve patients
  - Chemotherapy
  - Immune suppression (transplant)
  - Rituximab
  - Bone marrow Tx from non-HBV immune donor
  - Recipient liver graft from anti-HBc +ve donor

Immune Compromise (cont)

- Risk of HBV "flare"
  - Rise in HBV DNA with immune suppression
  - HBeAg sero-reversion
    - » HBeAg -ve → HBeAg +ve
  - Possible reactivation in HBsAg –ve
    - » HBV DNA –ve → HBV DNA +ve
- Immune Reconstitution – clinical flare
  - Rise in ALT, hepatitis flare
  - Fulminant hepatitis, hepatic failure

Chemoprophylaxis – prevent flare

- HBsAg +ve patients
  - Nucleos(t)ide analogue
  - Before chemotherapy, 12 months after
  - Lamivudine approved, newer agents better
- HBsAg –ve, anti-HBc +ve
  - Monitor ALT, HBV DNA
  - If evidence reactivation, commence NA
- Recipient liver from anti-HBc +ve
  - HBIG then chemoprophylaxis

EASL Clinical Practice Guidelines: management of chronic hepatitis B, 2009

Hepatitis B in pregnancy

- Preventing vertical Tx is crucial
  - High rates of chronic infection
- HBsAg +ve mothers
  - HBIG and HBV vaccine for baby
  - Follow up serology after 12 months?
- Mothers with high HBV DNA (> 10^7 IU/mL)
  - Tx up to 10-20% despite HBIG
  - Trials of antivirals in 3rd trimester
  - Lamivudine, tenofovir

Hepatitis D virus

HDV or “Delta”

Hepatitis D virus

- Sole member of *Deltavirus* group
- Unique among animal viruses - like plant viroids
- Defective satellite virus
- Found only in association with its helper virus HBV
- Spherical
- Heterogenous in size
- Envelope derived from HBV

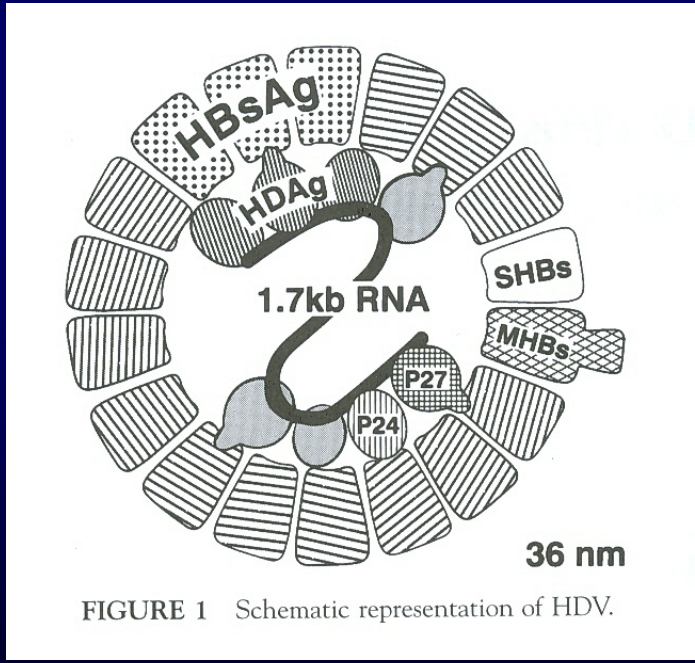
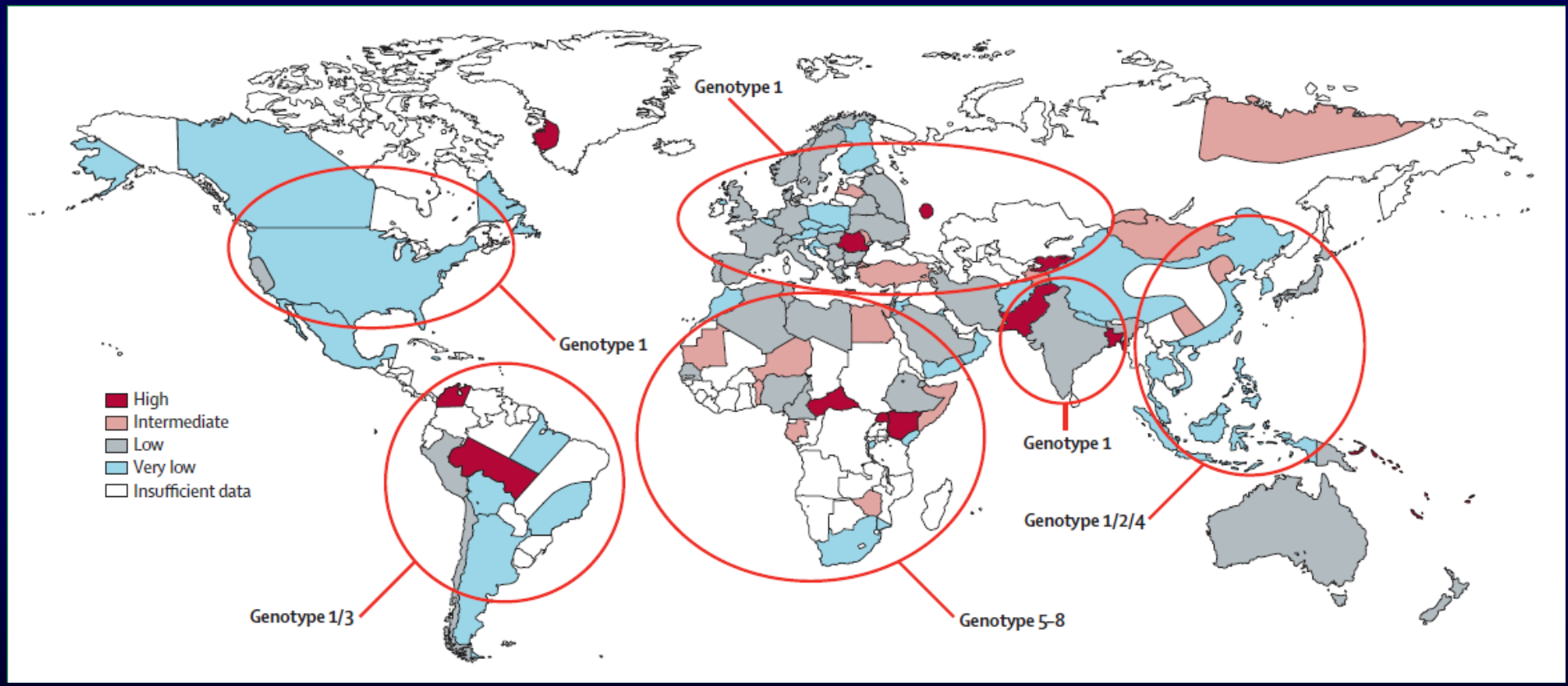


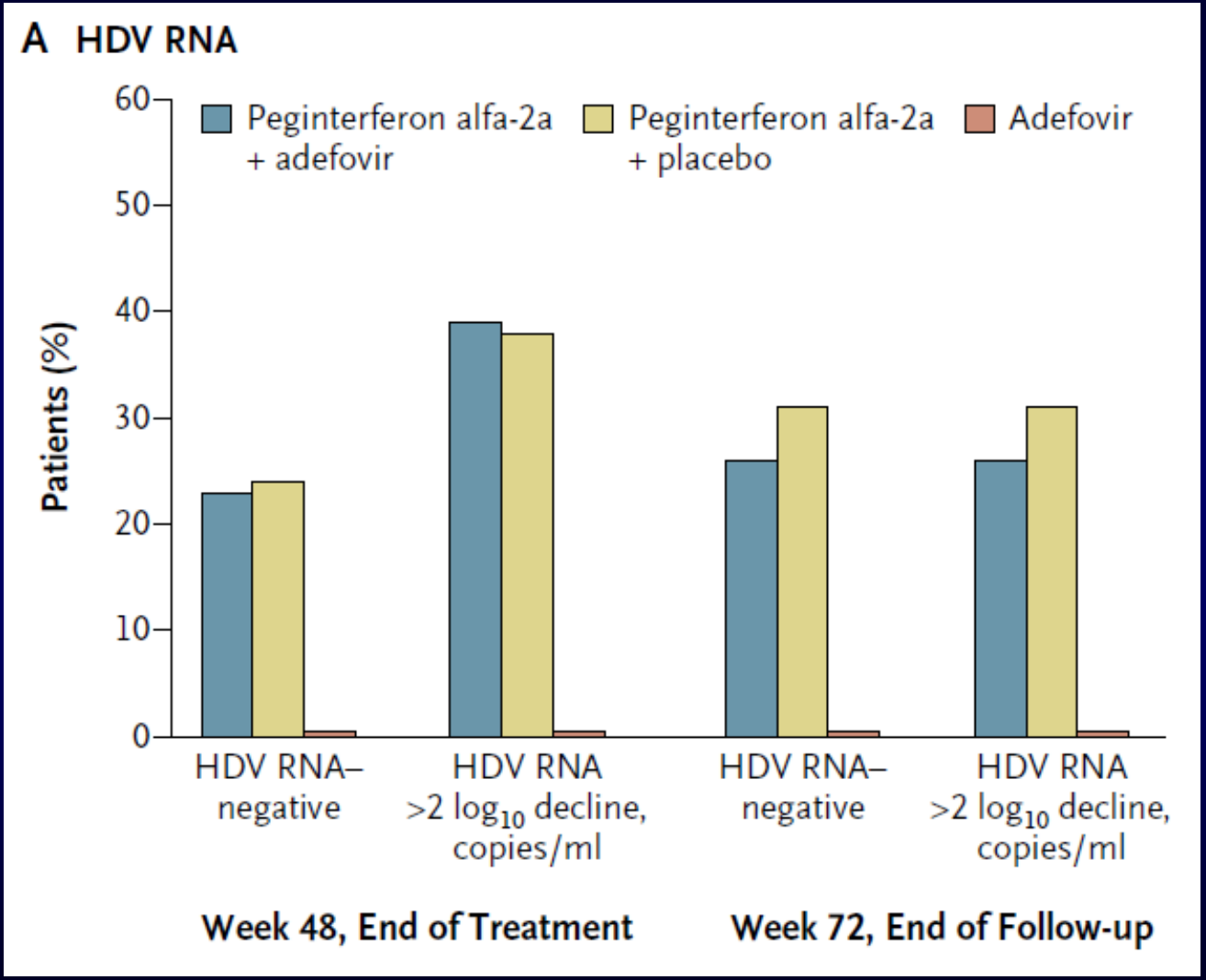
FIGURE 1 Schematic representation of HDV.

Geographic distribution of HDV



Hughes SA, Lancet **2011; 378: 73–85**

Interferon treatment for HDV



Wedemeyer H, N Engl J Med 2011;364:322-31

Meta-analysis VR at EOT

IFN treatment 12X more likely to be associated with VR

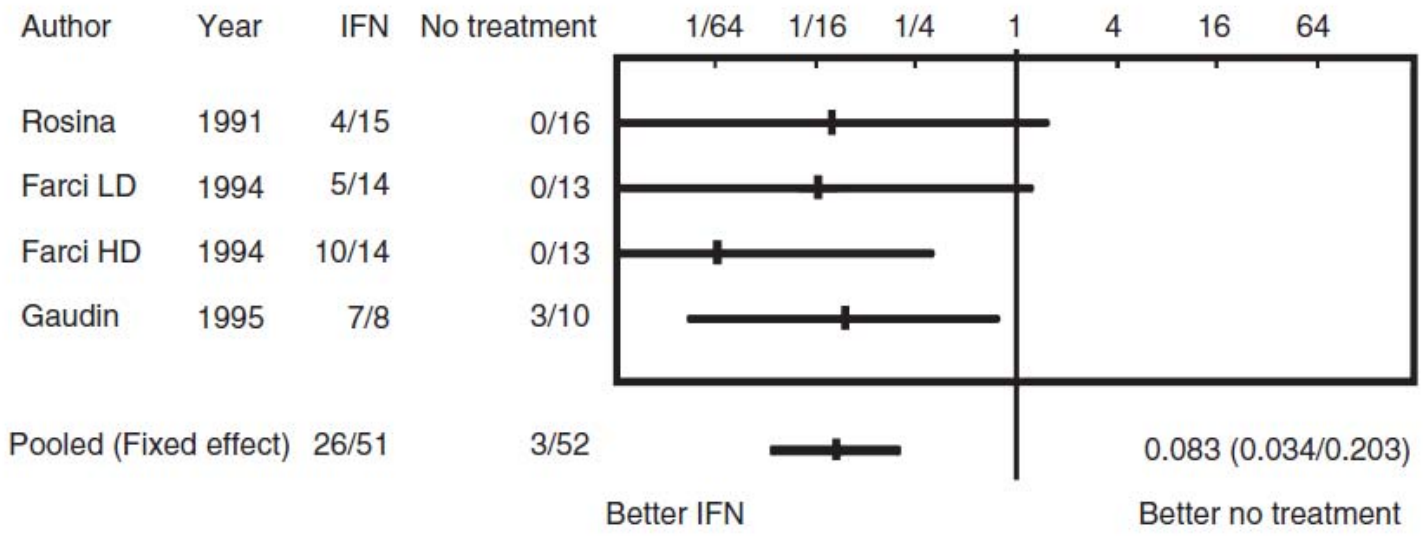
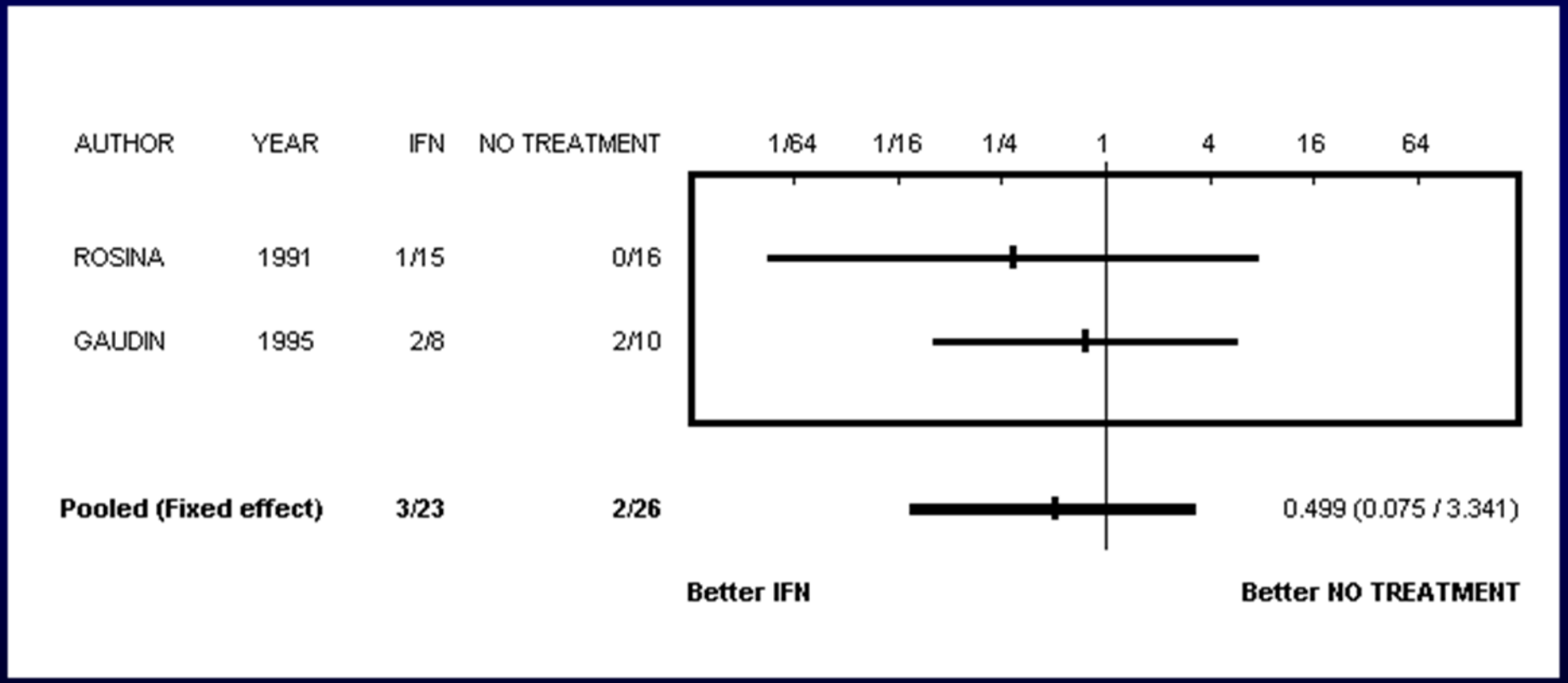


Figure 2 | Virological response at the end of treatment: forest plot of trials of IFNa monotherapy vs. no intervention. Data were expressed as OR (95% CI) in a log scale. HD, high dose; LD, low dose.

Triantos C, Aliment Pharmacol Ther 2012; 35: 663–673

Meta-analysis at EOFUP

IFN treatment 2X more likely to be associated with response (N Sig)



Triantos C, Aliment Pharmacol Ther 2012; 35: 663–673

Thank you !