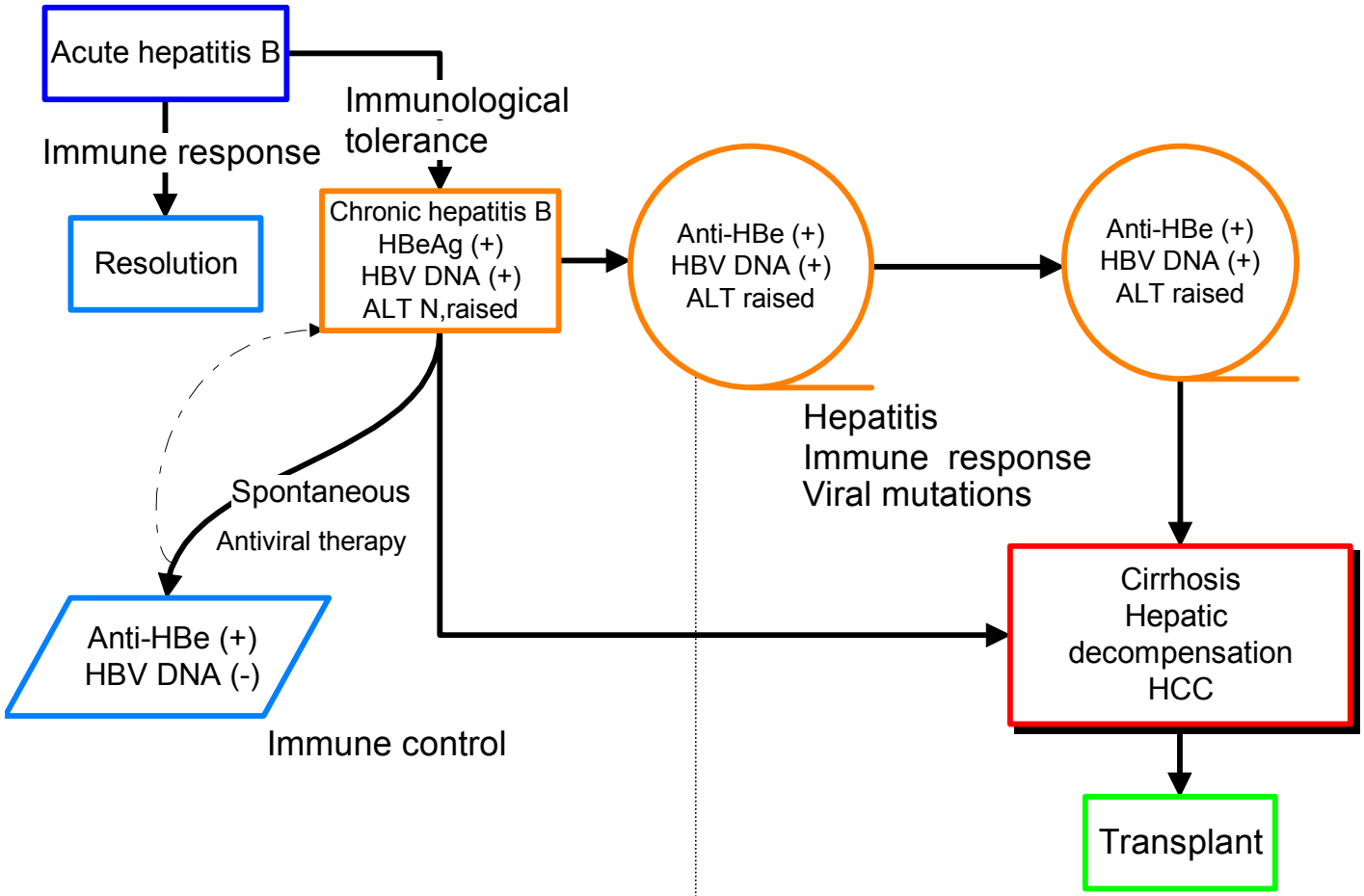
Viral hepatitis Prevention Board

Clinical aspects of hepatitis B

Natural History and serological markers acute and chronic hepatitis B



HBeAg positive and negative disease

- HBeAg positive disease (wild type)
- Young individuals with hepatitis B
  - High levels of HBV DNA (usually > 10^7 copies/ml)
  - May have normal ALT
  - "Immunotolerant phase" of the disease
- Or with raised ALT in active disease (immuno-active phase)
- Seroconversion rates higher in patients with raised ALT and genotype B (vs C) and genotype D (vs A)

- Anti-HBe-positive disease
- HBsAg positive and anti-HBe positive
- Older
- HBV DNA typically > 10^5 copies/ml
- Genotypic explanations for absent HBeAg
- Serum ALT elevated
- Variable course, fluctuating ALT, mixture of wild type and HBeAg negative virus
- Biopsy shows necro-inflammation and varying fibrosis

Chronic hepatitis B: serological markers
Anti-HBe-positive disease

- HBsAg positive and anti-HBe positive
- Older
- HBV DNA typically > 10^5 copies/ml
- Genotypic explanations for absent HBeAg
- Serum ALT elevated
- Variable course, fluctuating ALT, mixture of wild type and HBeAg negative virus
- Biopsy shows necro-inflammation and varying fibrosis

Inactive carrier state

- Spontaneous remission in disease activity
  - HBeAg negative, anti-HBe positive
  - Lower HBV DNA levels ($<10^5$ copies/ml)
- Little or no necroinflammation or fibrosis (depending on timing of seroconversion)
- May be a retrospective diagnosis as some propensity to reactivation

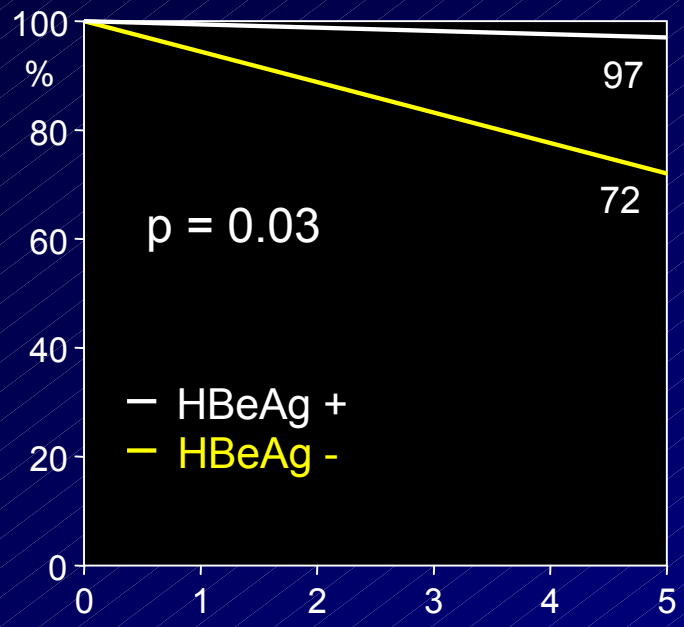
Prognostic factors for progression to cirrhosis

factors	*p* value
• older age	0.0001
• HBV-DNA persistence	0.0001
• virus genotype C	0.001
• recurrent acute flares	0.001
• histologic staging	0.0002
• alcohol consumption	0.001
• HCV, HDV coinfection	0.001
• HIV coinfection	0.02

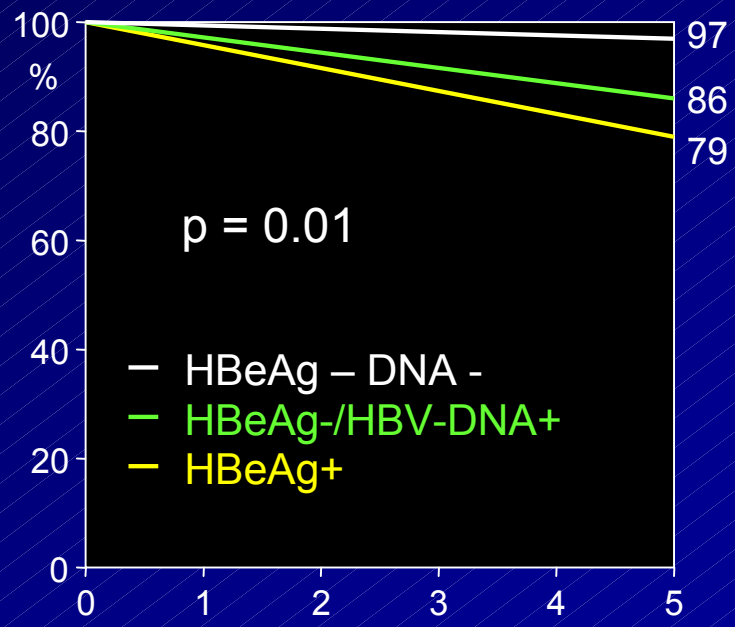
Fattovich, J Infect Dis 1987; Liaw, Hepatology 1988; Fattovich, Gut 1991; Roudot-Thoraval, Hepatology 1997; Ikeda, J Hepatol 1998; Colin, Hepatology 1999; Kao, Gastroenterology 2000; Brunetto, J Hepatol 2002

Prognostic factors of survival in cirrhosis B

De Jongh, Gastroenterology 1992; 103: 1630-5

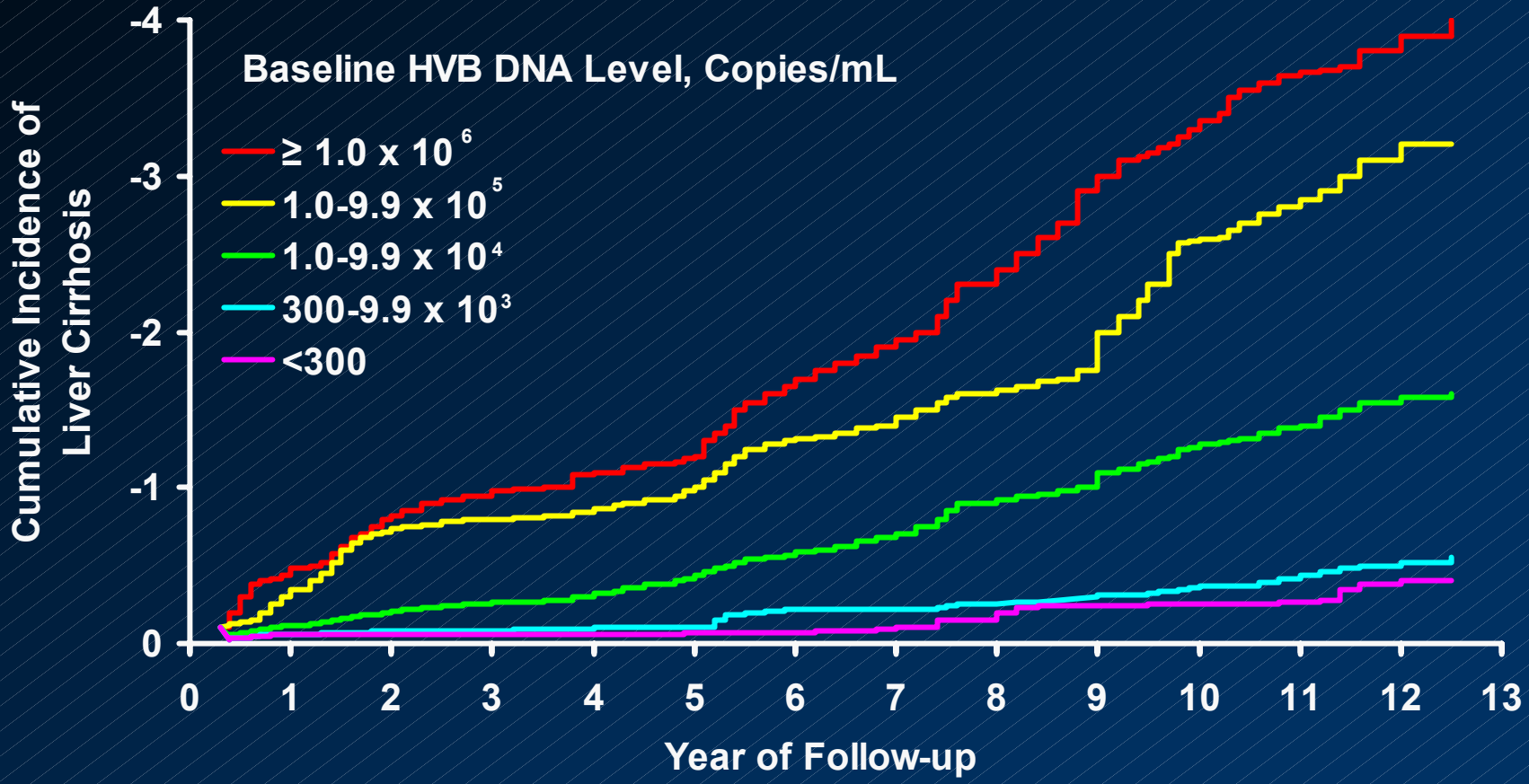


Eurohep, Am J Gastroenterol 2002

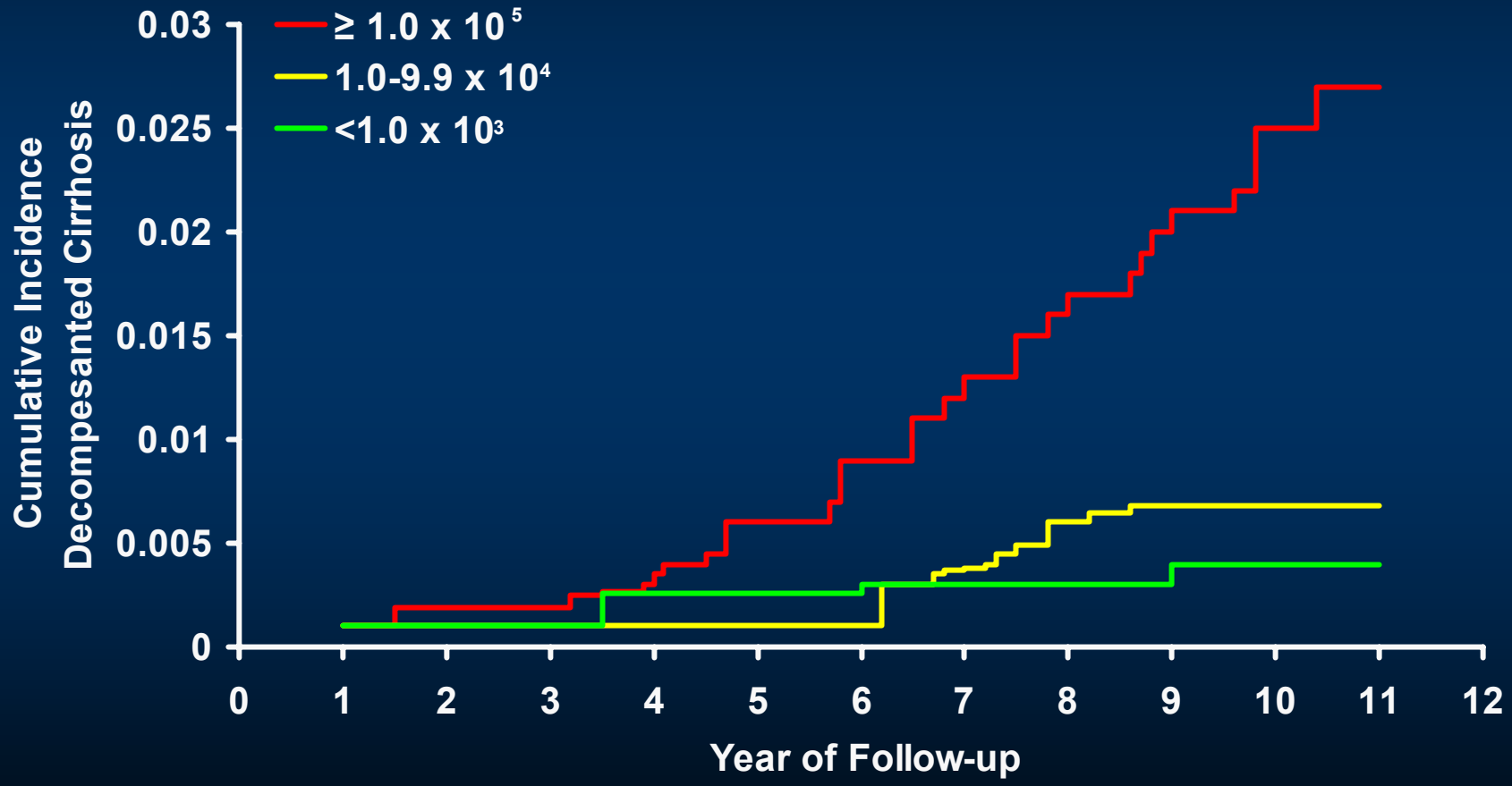


HBV-DNA + vs HBV-DNA -	RR	95% CI
HCC	0.89	0.3 - 2.6
Decompensation	4.0	1.0 - 15
Liver-related death	5.9	1.6 - 21

Cumulative Incidence of Liver Cirrhosis according to baseline HBV-DNA – *Illoeje et al.*

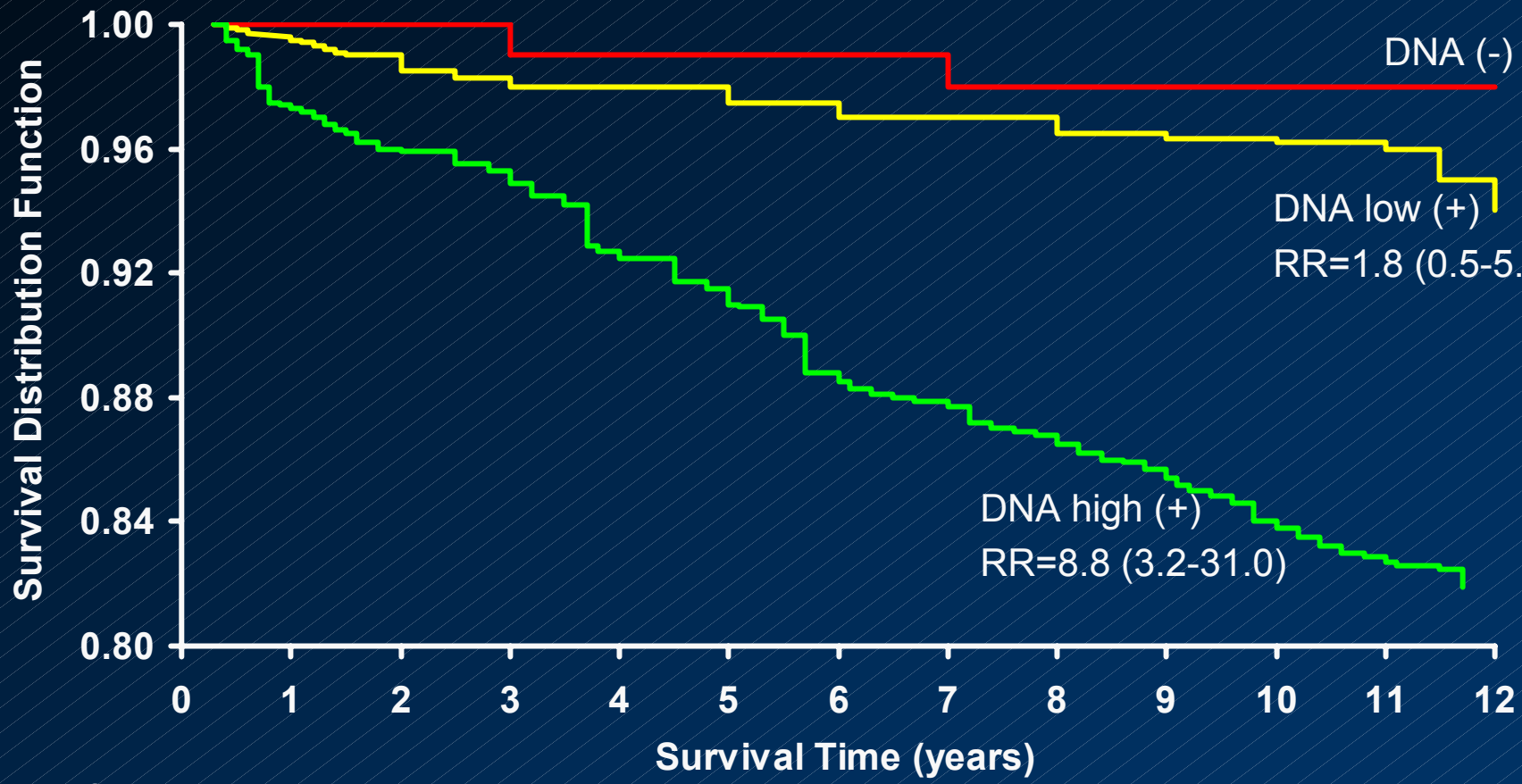


Cumulative Incidence of Decompensated Cirrhosis by Entry HBV DNA



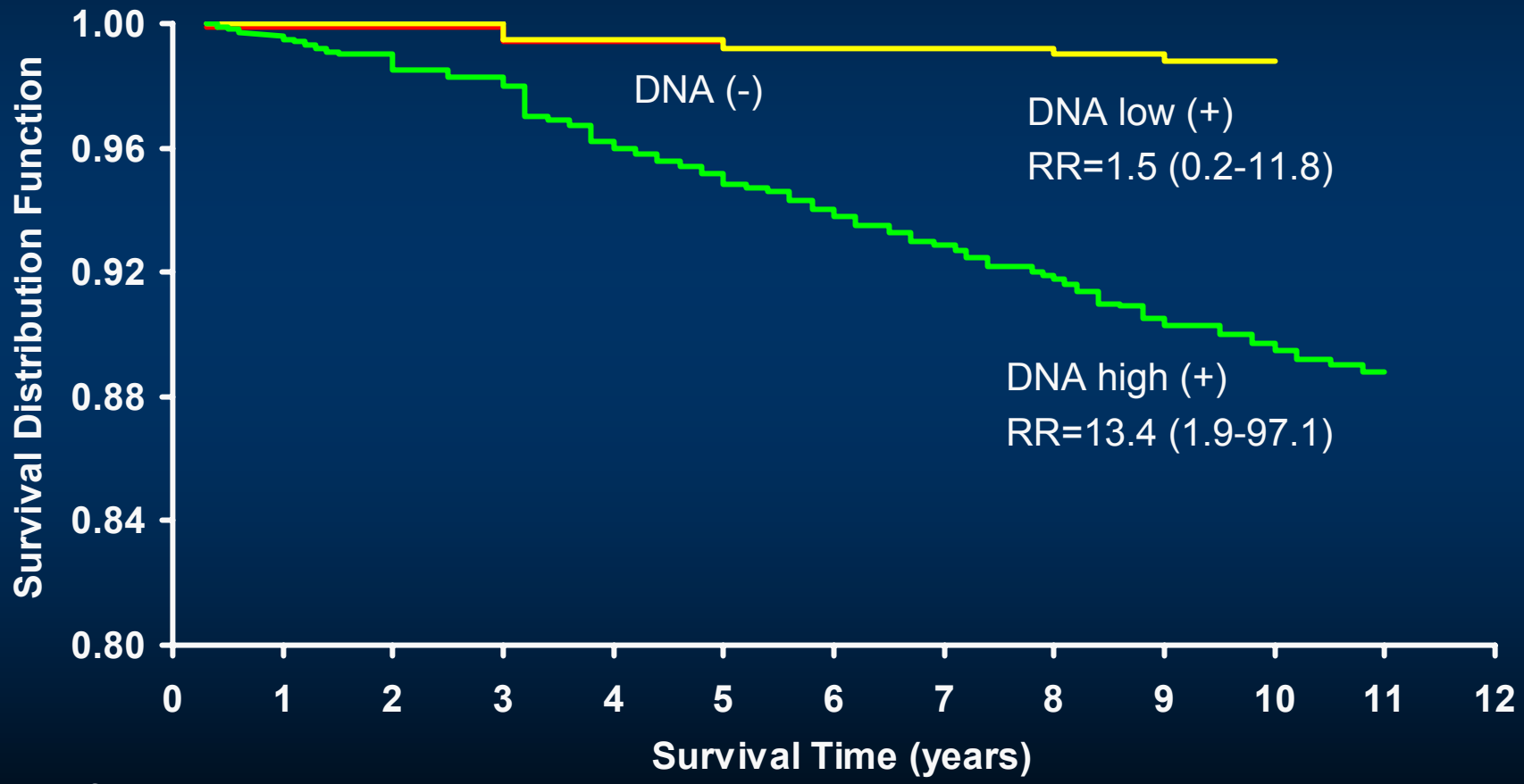
EASL 2005

HCC Mortality according to baseline HBV-DNA – *Chen et al.*



P for trend <0.01

Liver Disease Mortality according to baseline HBV-DNA – *Chen et al.*



P for trend <0.01

EASL 2005

Incidence and multivariate analysis risk of cirrhosis

HBV DNA	Number	Person yr FU	Number cases cirrhosis	Incidence	RR
<300	944	10,877	42	386	1
300-9.9x10^3	1210	13,926	64	495	1.3
1.0-9.9x10^4	649	7,314	58	792	2.2
1.0-9.9x10^5	344	3590	66	1838	5
>1x10^6	627	6406	165	2757	8.7

N= 3774

Iloeeje et al, EASL 2005 # 496

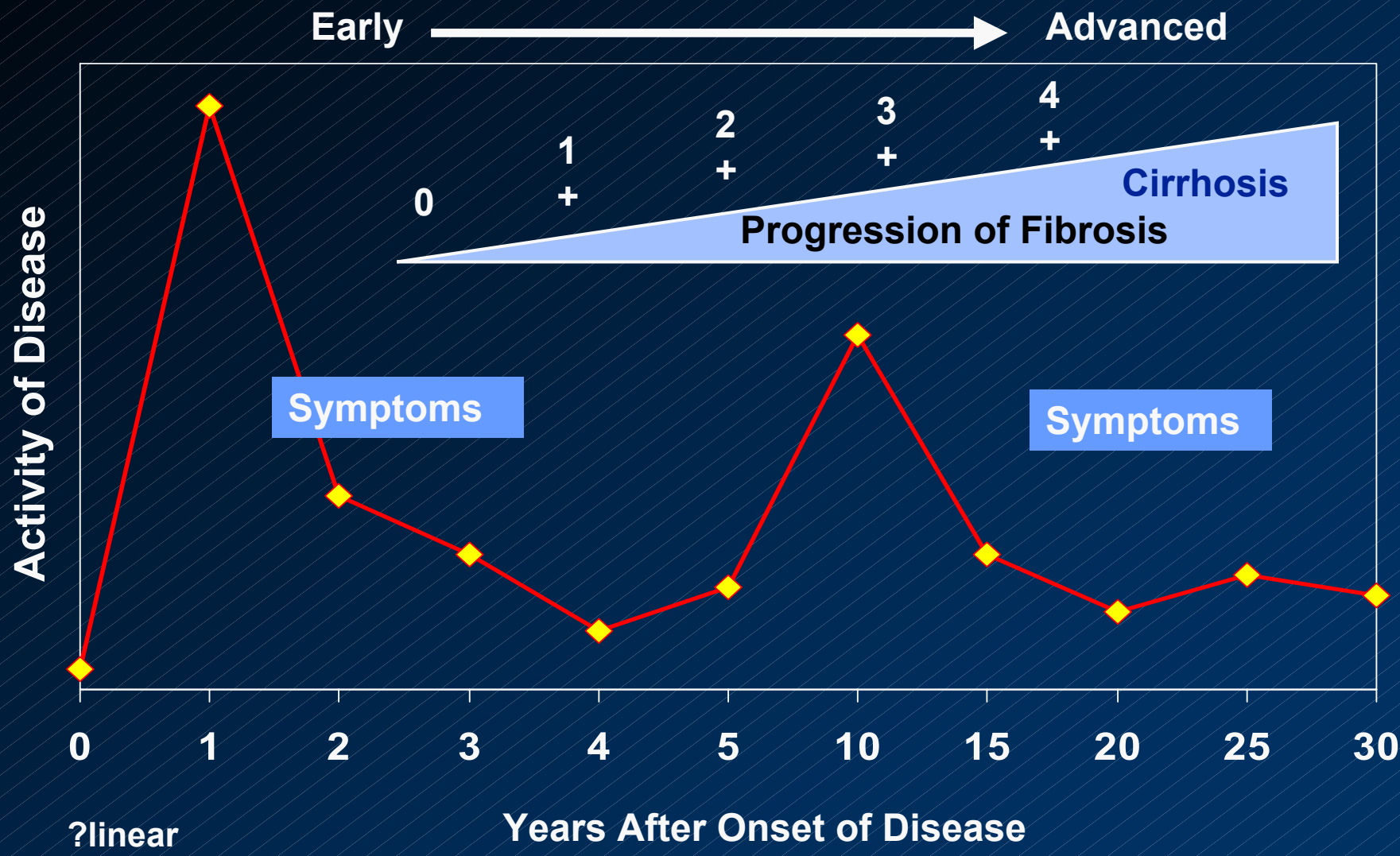
Incidence and multivariate analysis risk of HCC Serum HBV DNA in subjects with normal ALT

HBV DNA	Number	Person yr FU	Number cases HCC	Incidence	RR
<300	908	10,547	13	123	1
300-9.9x10^3	1178	714	16	116	1.1
1.0-9.9x10^4	647	7452	21	281	2.4
1.0-9.9x10^5	338	3749	33	880	8
>1x10^6	530	5859	60	1024	12.3

N= 3774

Iloeje et al, EASL 2005 # 495

Activity versus Stage



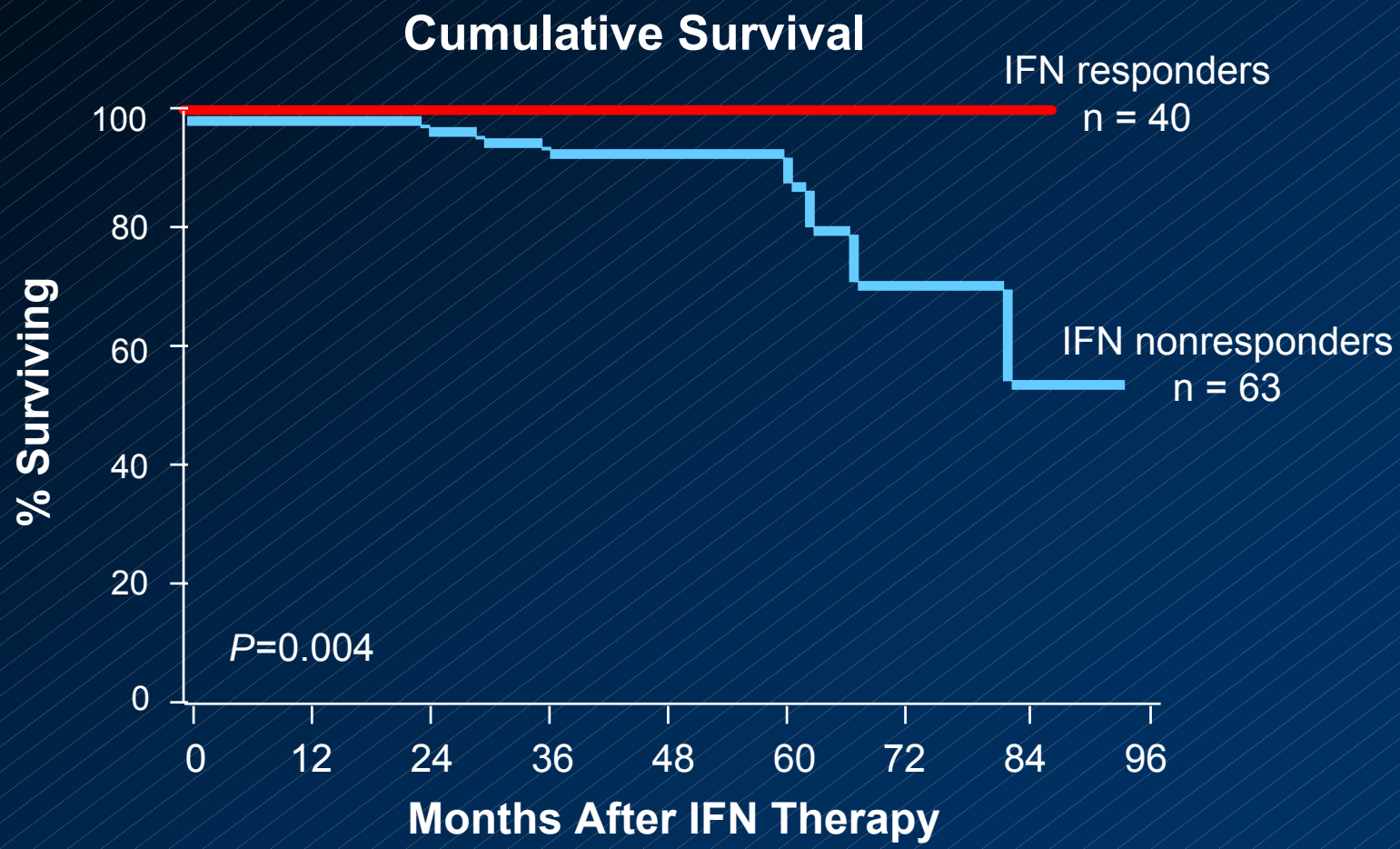
?linear

?invariable

From Hoofnagle et al

Reducing mortality via treatment: Interferon alpha Proof of Principle

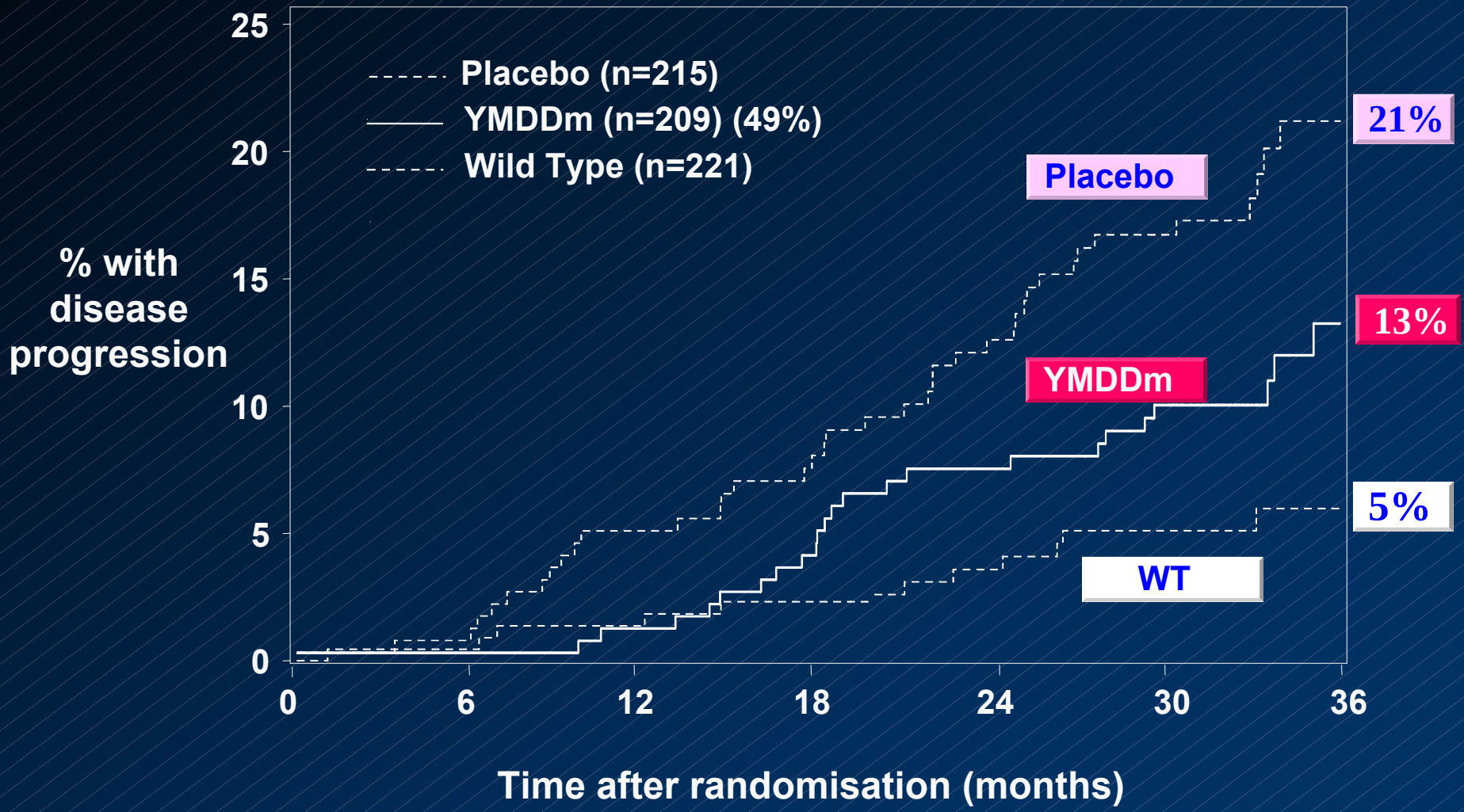
Long-term Follow-up of Patients With Chronic Hepatitis B Treated With IFN-α



Niederau C, et al. *New Engl J Med.* 1996;334:1422-1427.

Reducing mortality via treatment: lamivudine
Proof of Principle

Time to Disease Progression



Liaw et al, NEJM 2004

Chronic Hepatitis B

Assessment

- Clinical features: hepatitis symptoms, symptoms & signs of decompensation
- Biochemical: ALT & other liver tests
- Virological: HBsAg, HBeAg, anti-HBe, HBV DNA levels, genotype, mutants
- Histological: liver biopsy findings of inflammation, necrosis and fibrosis.

HBV genotypes: Signficance

- Far East
  - Genotype B less active disease than genotype C
  - Genotype B lower prevalence of HBeAg
  - Genotype B higher rates of spontaneous seroconversion
  - Genotype B higher rates of response to interferon
- Europe
  - Genotype A higher rates of response than genotype D to interferon
- Probably little, no difference in response to nucleoside analogues
- Genotypes: May affect rate development of lamivudine resistant mutants
- Difference in core promoter vs pre-core mutations

Place of liver biopsy

- Provides unique source of information
- Value being questioned (particularly in HCV)
  - Problems biopsy
    - Low finite risk, but cost and delay and barrier to treatment
- Remains standard for interpretation of disease stage and grade
  - Technological advances may change need for biopsy
- Role in practice will be refined

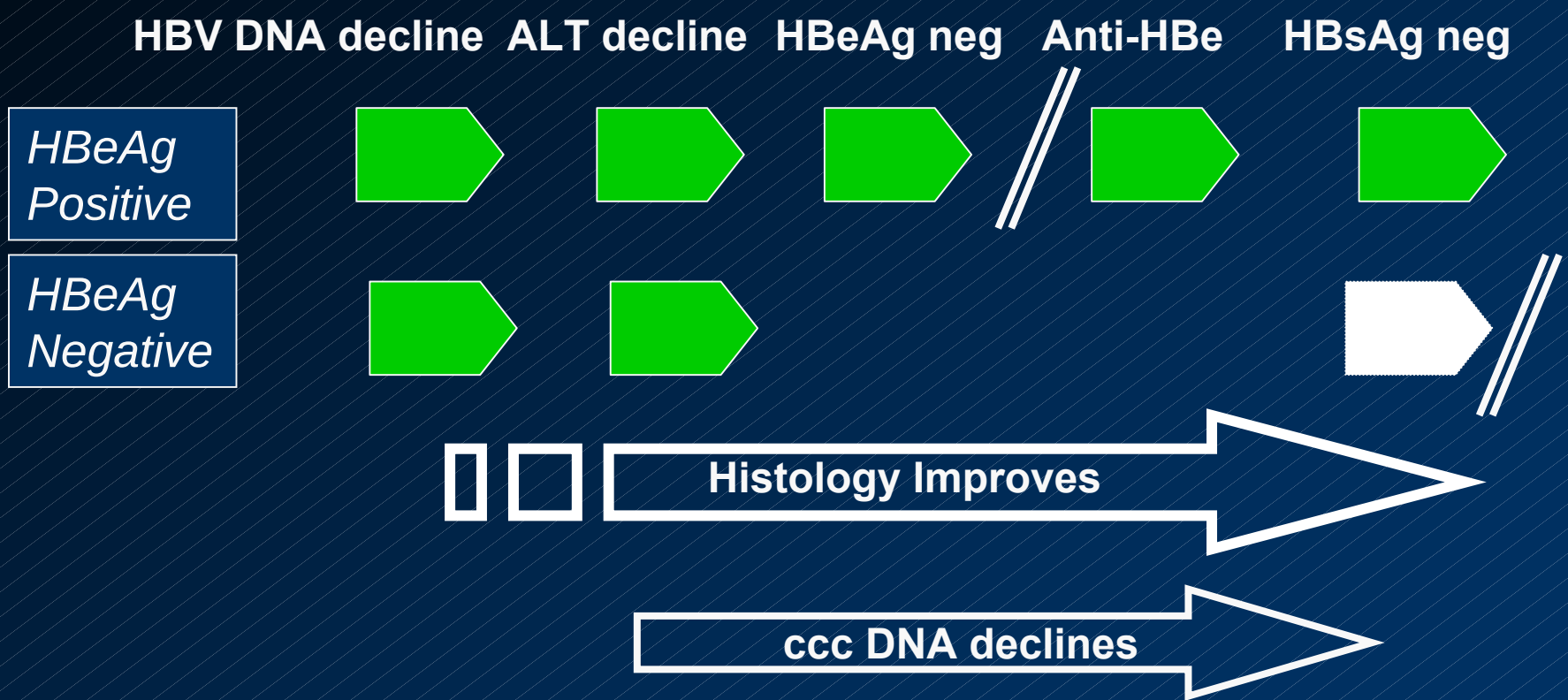
Indications for treatment
Baseline HBV DNA

- Predicts Disease?
  - As part of spectrum of markers
  - Requires repeated assessments; overlap
- Predicts Prognosis?
  - In part
  - Requires additional assessments of activity
- Predicts Infectivity?
  - Yes
- Provides indication for treatment?
  - Yes, with appropriate clinical and laboratory assessments

HBV DNA
Disease monitoring

- Predicts response to treatment?
  - HBeAg positive:
    - Decline suggests favourable paradigm
    - ? Absolute or relative measures required
  - Anti-HBe positive?
    - Decline suggests favourable paradigm
    - ? Absolute or relative measures required
- Predicts Emergence of Resistance?
    - High viral load associated with resistance
    - Slow decline associated with viral resistance
    - Other complex factors determine resistance

HBV treatment: End points of Antiviral Response:



Current Treatments for hepatitis B

- Alpha interferon (Pegylated interferons)
- Lamivudine
- Adefovir Dipivoxil
  - (Tenofovir)
- (Entecavir)

Approaches to therapy of hepatitis B HBeAg positive and negative

- Finite course of therapy
- Continuous, long-term therapy (indefinite)
- Undefined, depending upon response

Lamivudine

- Lamivudine [(–)-b-L-20,30-dideoxy-30-thiacytidine]
- Nucleoside analogue with antiviral activity.
- Ushered in new era of oral administered antiviral agents
  - New questions raised regarding
    - Indications for treatment
    - End points of treatment
    - Disease monitoring
    - Drug resistance
      - PCR based HBV DNA testing

HBV Lamivudine: 10 year experience

- Pharmacology
- Response
  - Predictors of response
  - Histological response
  - Nature of response
  - Role of genotype
  - Paediatric response
- Immune regulation and lamivudine
- Withdrawal of lamivudine
- Combination therapy
- Resistance
- Clinical course with breakthrough
- Use in transplantation
- Use with chemotherapy
- Use in fulminant hepatitis
- Use in extrahepatic disease
- Use in pregnancy
- Toxicity
- Pharmacoeconomics

The HBV Nucleos(t)ide Pipeline

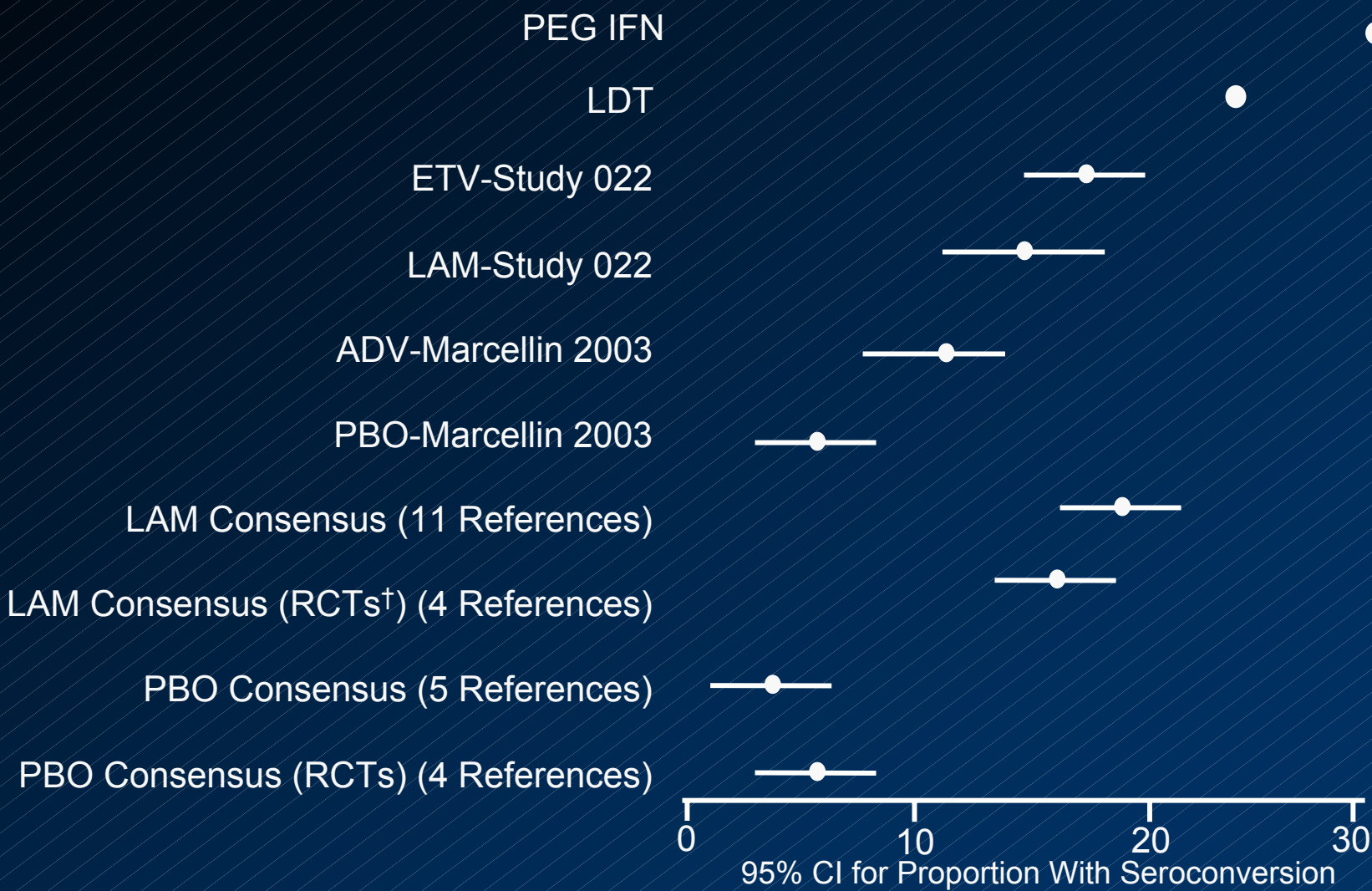
Nucleoside Analogs	Nucleotide Analogs (phosphonates)
Lamivudine (L)	Hepsera (D)
Entecavir (D)	Tenofovir (D)
Emtricitabine (L)	Alamifovir (D)
Telbivudine (L)	Hepavir B (D)
Clevudine (L)	
Elvucitabine (L)	
Valtorcitabine (L)	
Amdoxovir (D)	
Racivir (L)	
MIV 210 (D)	
β-L-FddC (L)	

Activity is dependent on first phosphorylation by a host cell nucleoside kinase

Activity is not dependent on the first phosphorylation step

Yellow = Prodrug

HBeAg Seroconversion rates



*Seroconversion is defined as the proportion off patients with loss of HBeAg and acquisition of HBeAg

†RCTs=Randomized controlled trials

From Dienstag et al EASL 2005 #481

Disadvantage of using monotherapy and engendering resistance

- Treatment failure likely
- Failure associated with exacerbation of disease
- Increase population with resistant strains
- May increase precedent for resistance or deleterious mutations with other agents
- Opportunity cost; drug unusable.

Lamivudine as comparitor arm: HBeAg positive

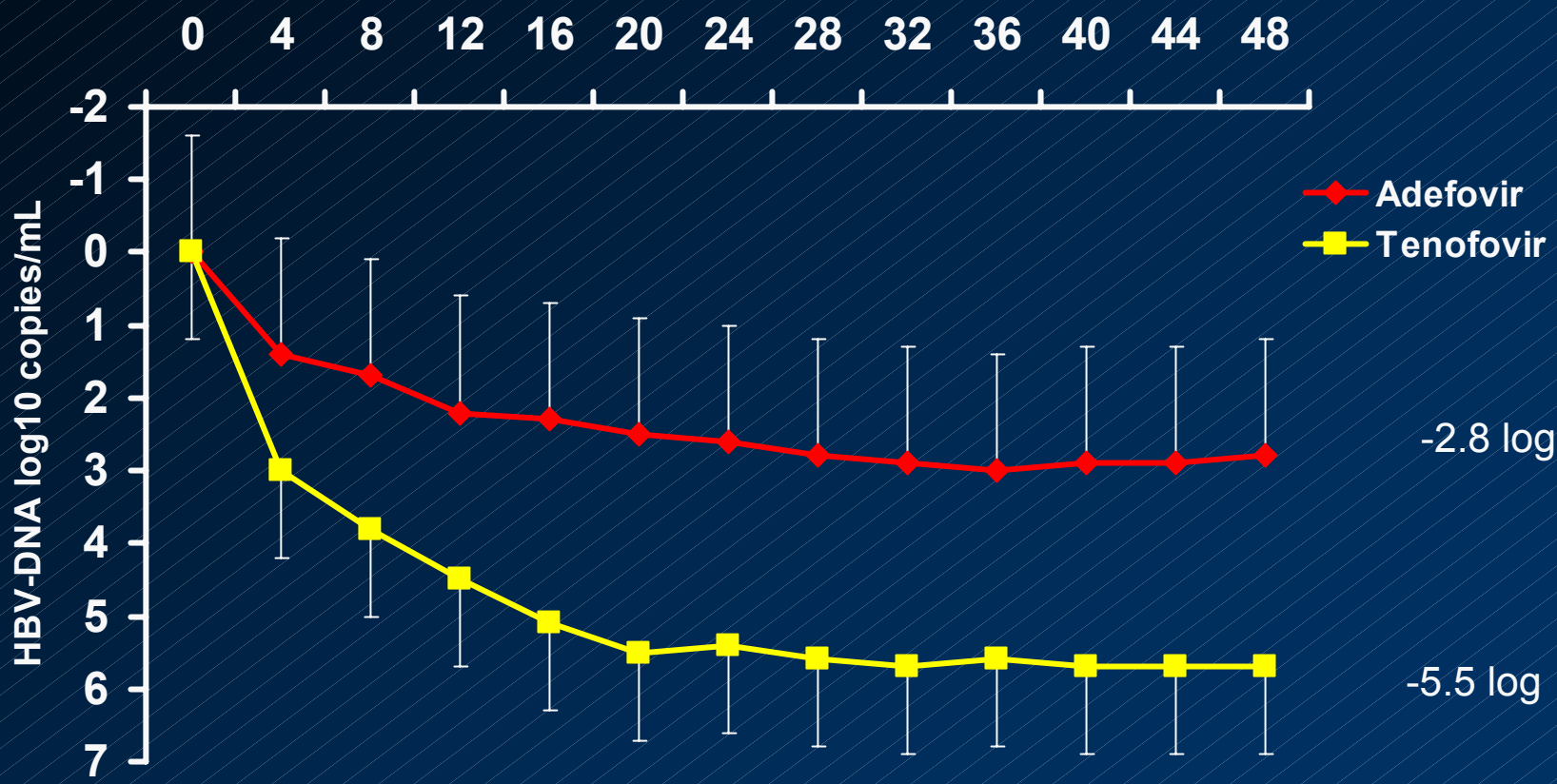
	Lam	PEG IFN (2a)	Lam 100	Entecavir 0.5 mg	Lam	LdT 600, pooled
n	272	214	355	354	463	458
Histol Resp*	38%	34%	62 %	72 %	56	64
Log_{10} decline	-5.8	-4.5	-5.4	-6.9	-5.5	-6.5
DNA < 400*	40 (5) %	25 (14) %	38 %	69 %	40 %	60 %
HBeAg seroconversion	20 (19) %	27 (32) %	18 %	21 %	22 %	21 %
Resistance*	27%	ND	18%	2%	10 %	3 %

*< 200 c/ml LdT, Resistance various defn, Histol response various

Lamivudine resistance HBV

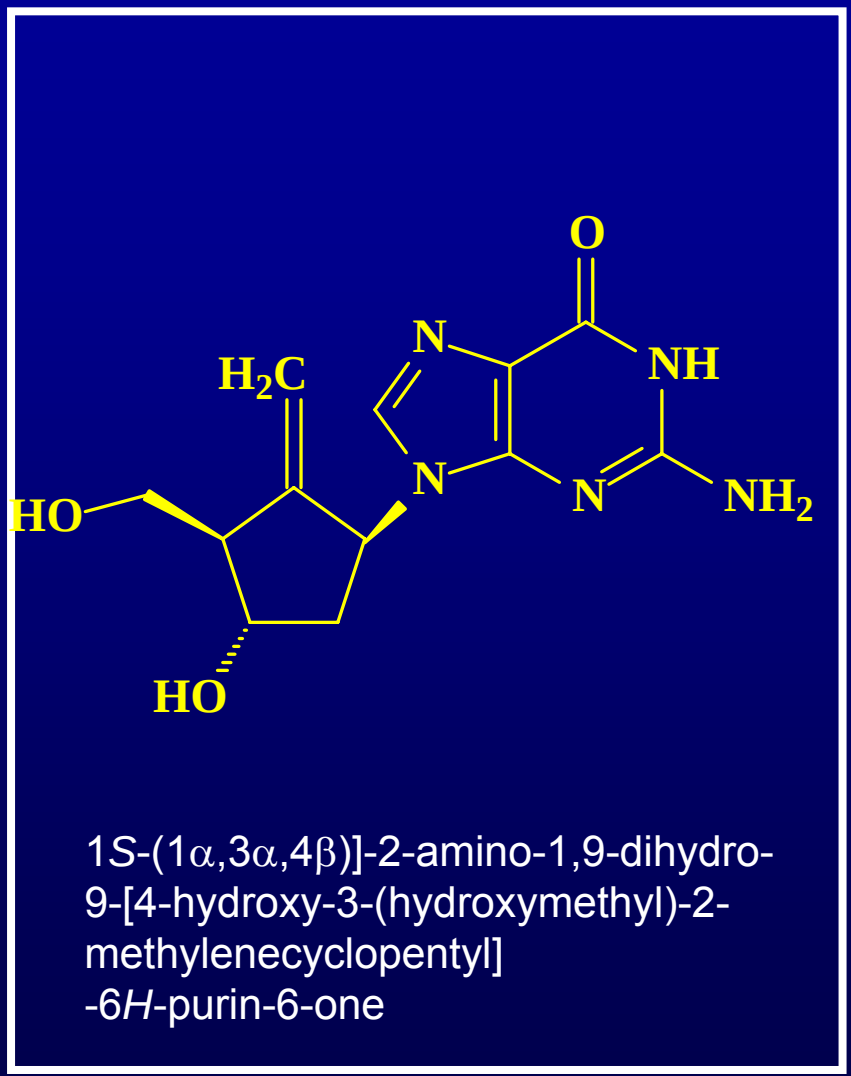
- Incomplete suppression of viral replication
  - Degree of benefit?
  - Is continued therapy beneficial?
- Will selection of increasingly fit, equally pathogenic virus occur by viral adaptation
- Background factors
  - genetic diversity in patients' viral population
  - HBV genotype
  - HLA type

Adefovir vs Tenofovir: HBV DNA loss



Van Bommel et al Hepatology 2004

Entecavir (ETV)

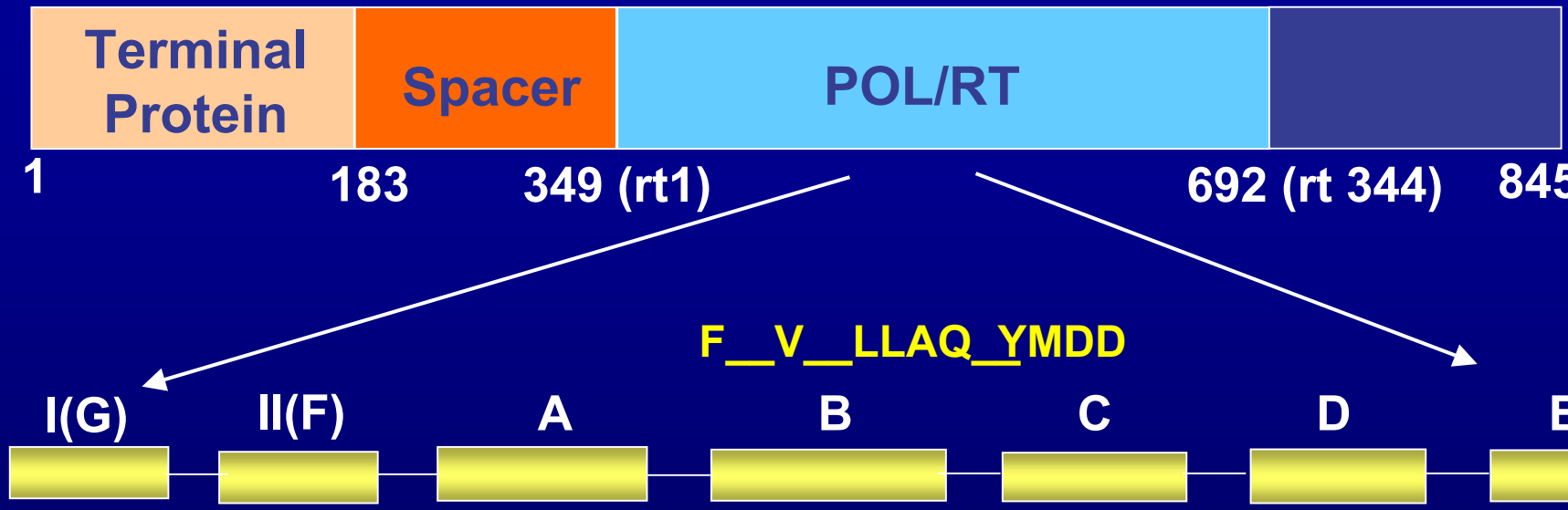


1*S*-(1α,3α,4β)]-2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6*H*-purin-6-one

- Inhibits priming, reverse transcription of (-) strand and synthesis of (+) strand
- Active against LAM-R in vivo but less pronounced against L180M +M204V/I
- 2 dosages developed:
  - 0.5mg in naïve patients
  - 1.0mg in LAM–R patients

Chang et al, AASLD 2004. Shouval et al, AASLD 2004 .Scherman et al, AASLD 2004

HBV Pol Resistance Mutations



LMV Resistance	rtL80V/I	rtV173L/rtL180M	rtM204V/I/S			
ADV Resistance	rtV84M	rtA181T/V		rtQ215S	rtN236T	
ETV Resistance		rtS184G	rtS202I			rtM250V
L-dT Resistance			rtM204I			
ADV + LMV Resistance		rtL180M + rtA181V				
TDF Resistance			rtA194T			
ABC Resistance					rtH234Y	

Disadvantage of using monotherapy drug with high frequency resistance

- Treatment failure likely
- Failure associated with exacerbation of disease
- Increase population with resistant strains
- May increase precedent for resistance or deleterious mutations with other agents
- Opportunity cost; drug unusable.

HBeAg positive patients
Group 1 (High ALT)

- High seroconversion rates > 50%
  - (T cell response)
  - Monotherapy suffices
    - Minority of patients
- But: Patients may not be adversely effected by combination therapy
- Advantage two drugs may give a more predictable response
- *Drawbacks: cost and side effects*

HBeAg positive patients
Group 2 (Not so high ALT)

- Prolonged monotherapy
  - Eventually leads to seroconversion and withdrawal of therapy; resistance?
    - *Gradual attrition of cccDNA, invoke T cell response?*
- Or prolonged combination therapy
    - Proof of principle of efficacy lacking,
    - proof of reduced resistance shown
    - Difficulty and cost of designing long term trials
  - Eventually leads to seroconversion and withdrawal of therapy
- Or sequential
    - Mistake?
- Piggyback therapy to enhance response
    - criteria for adding therapy?

HBeAg negative disease

- Monotherapy with drugs with low rate of resistance may suffice
- Resistance may still occur but at acceptable rates?
- PEG IFN – Long term suppression rates after finite course?

Current Decision Making Hepatitis B UK

- Treatment form part of the control of the disease
- Disparities in judgements
- Clinical and theoretical paradigms not always reconciled with economic decisions (NICE guidelines
- Hepatitis B complex disease
  - Clinical care of hepatitis B still evolving
  - Influenced by introduction of new nucleoside and nucleotides
  - Rapid evolution of data
  - Short term studies show effectiveness
  - Longer term studies reduce disease morbidity