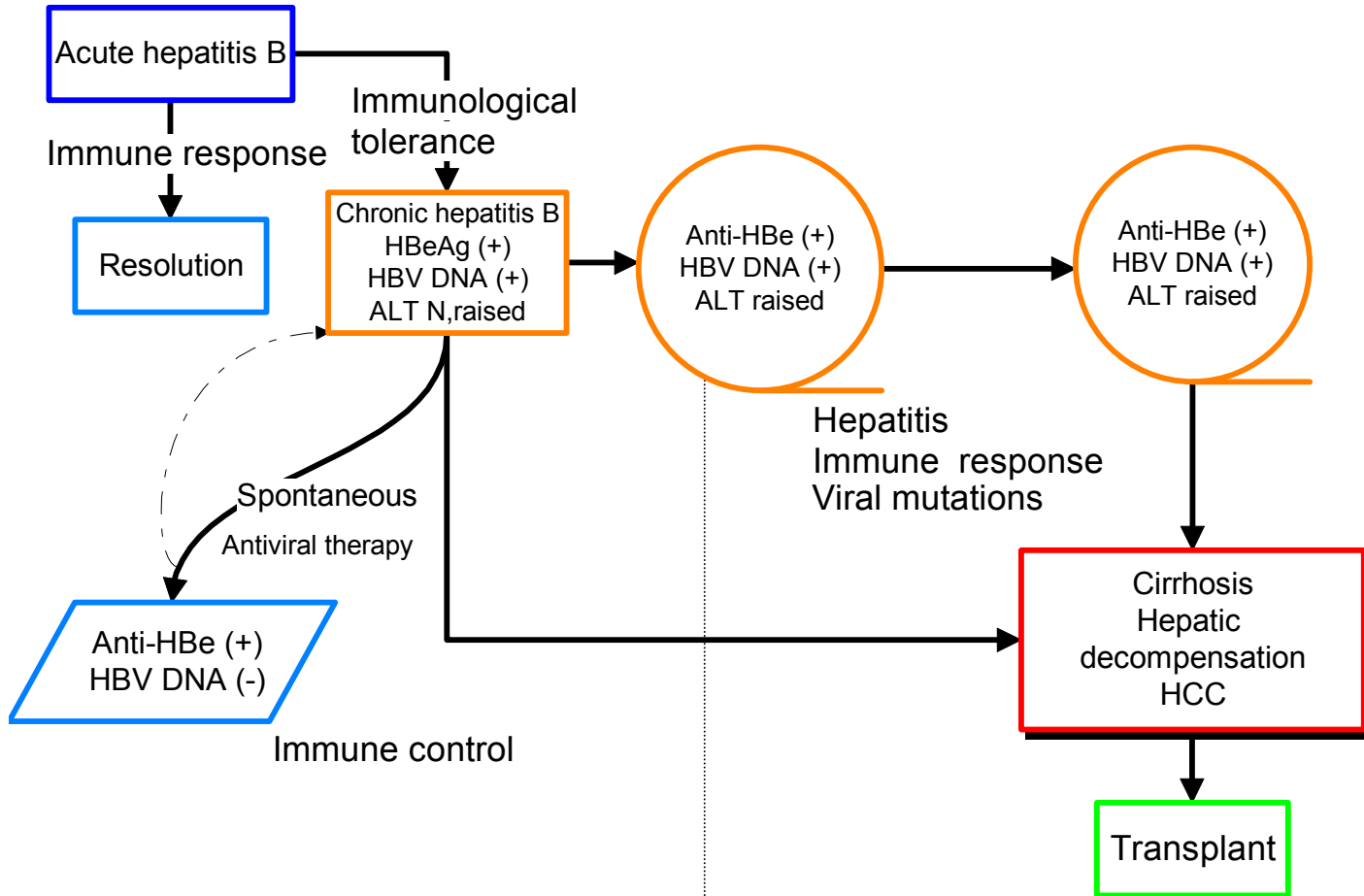


# Viral hepatitis Prevention Board

**Clinical aspects of hepatitis B**

# Natural History and serological markers acute and chronic hepatitis B



# HBeAg positive and negative disease

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- 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

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- 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

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- 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
-

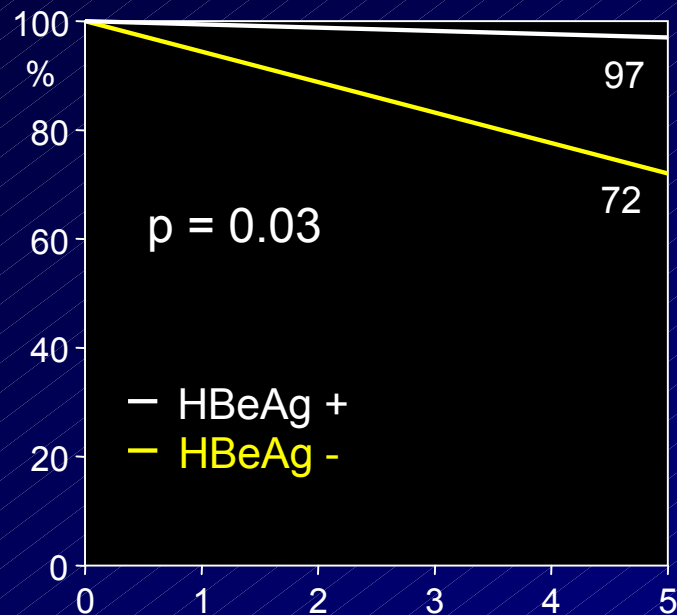
# Prognostic factors for progression to cirrhosis

factors	<i>p</i> 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

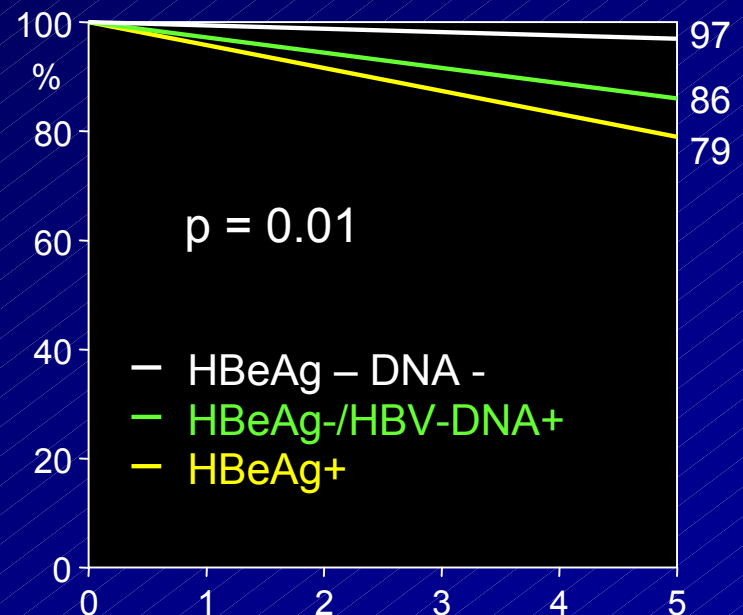
Fattovich, J Infect Dis 1987; Liaw, Hepatology 1988; Fattovich, Gut 1991;  
Roudot-Thoraval, Hepatology 1997; Ikeda, J Hepatol 1998;  
Colin, Hepatology 1999; Kao, Gastroenterology 2000; Brunetto, J Hepatol 2002

# Prognostic factors of survival in cirrhosis B

De Jongh, Gastroenterology 1992; 103: 1630-5

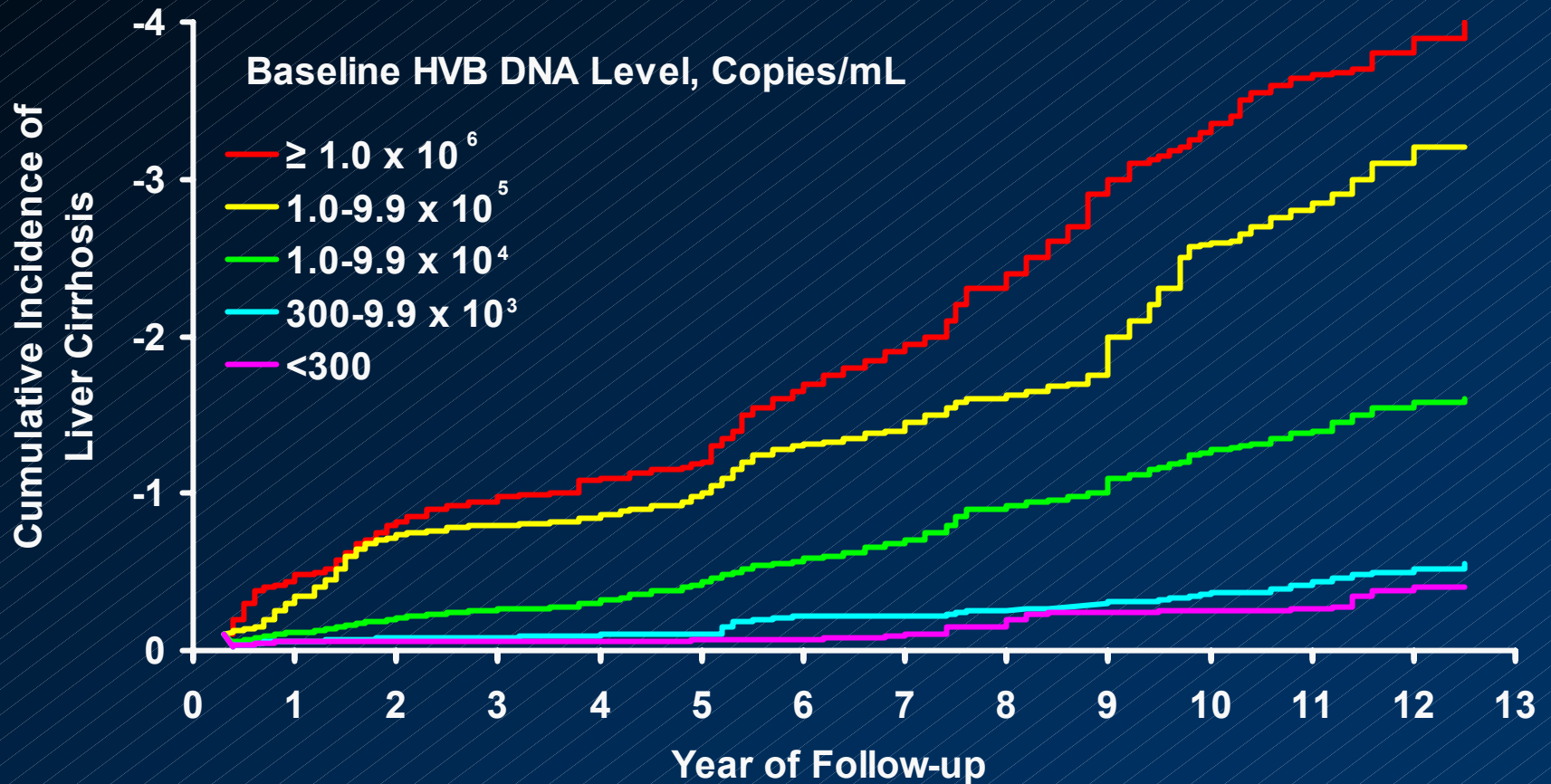


Eurohep, Am J Gastroenterol 2002

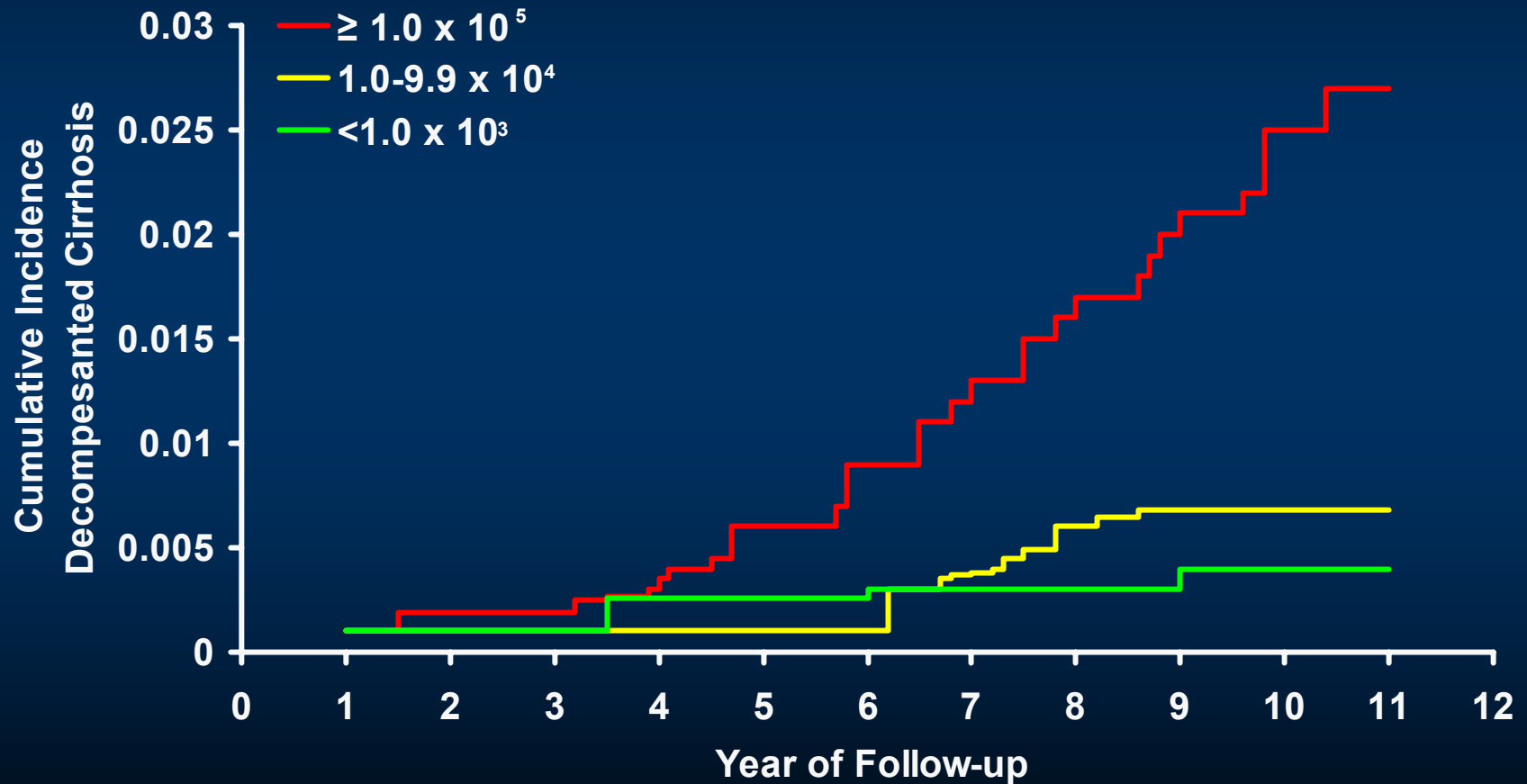


HBV-DNA + vs HBV-DNA -	RR	95% CI
HCC	0.89	0.3 - 2.6
Decompensation	4.0	1.0 - 15
Liver-related death	5.9	1.6 - 21

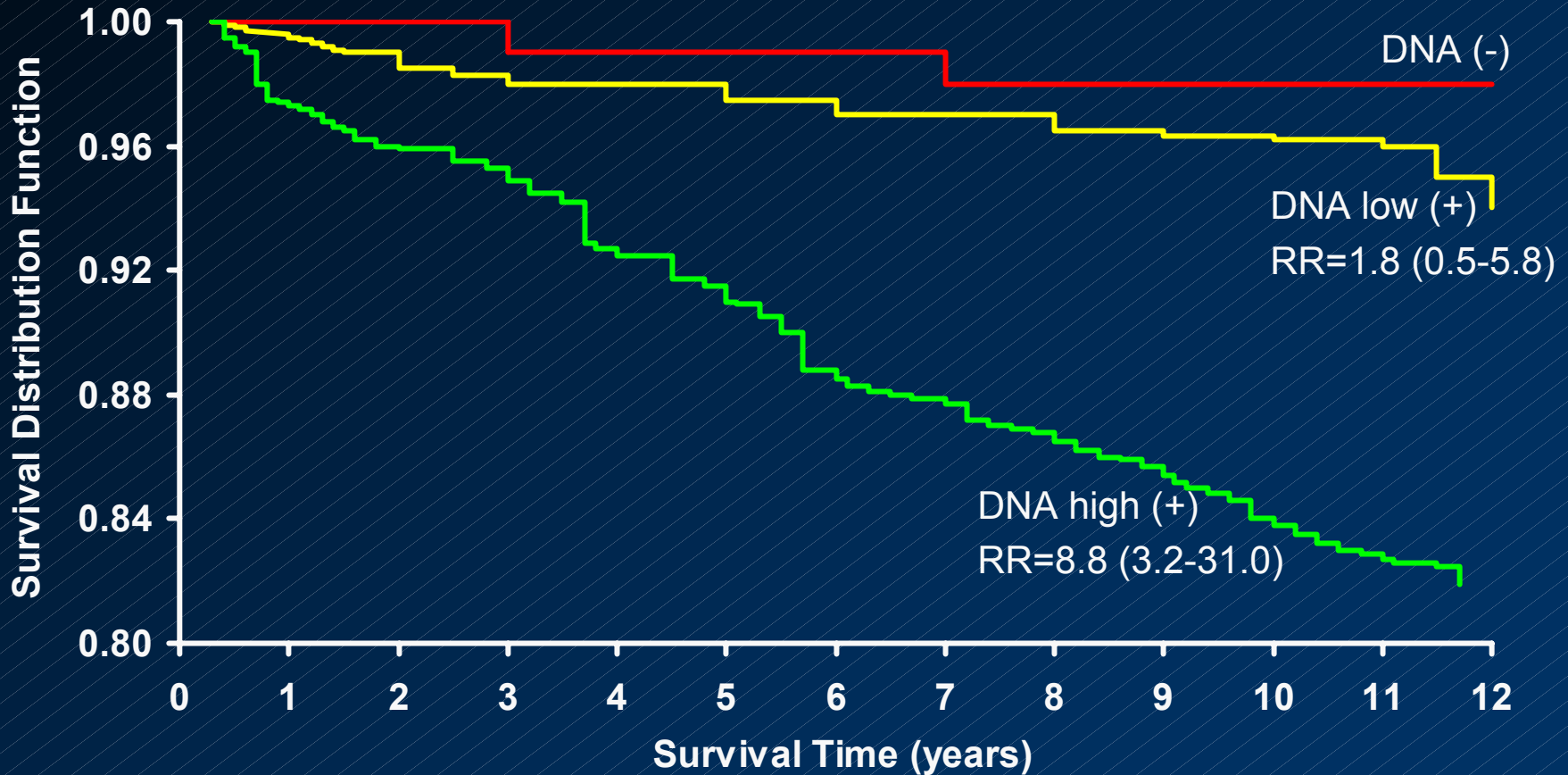
# Cumulative Incidence of Liver Cirrhosis according to baseline HBV-DNA – *Illloeje et al.*



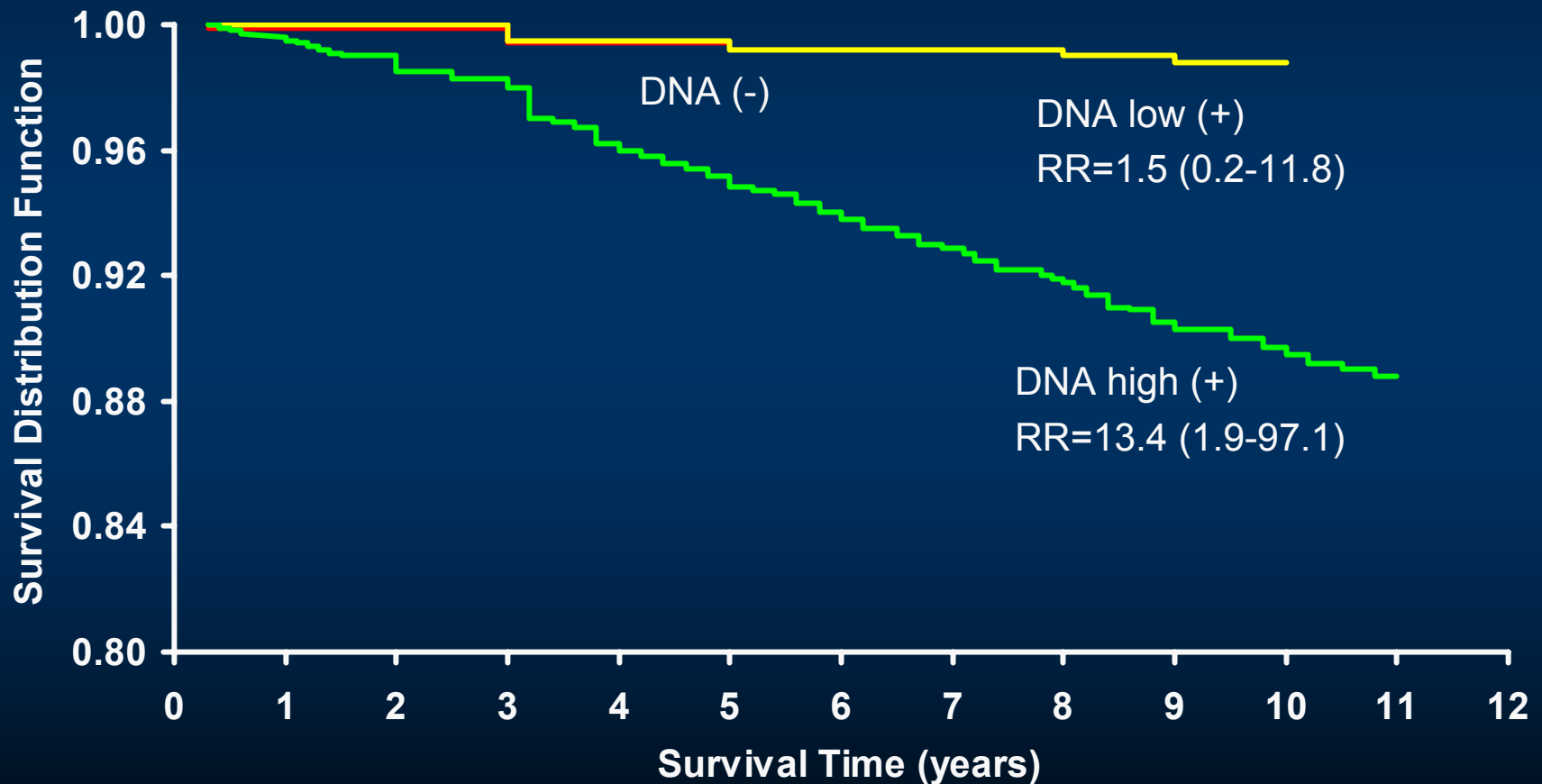
# Cumulative Incidence of Decompensated Cirrhosis by Entry HBV DNA



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



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



P for trend <0.01

# 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 <sup>3</sup>	1210	13,926	64	495	1.3
1.0-9.9x10 <sup>4</sup>	649	7,314	58	792	2.2
1.0-9.9x10 <sup>5</sup>	344	3590	66	1838	5
>1x10 <sup>6</sup>	627	6406	165	2757	8.7

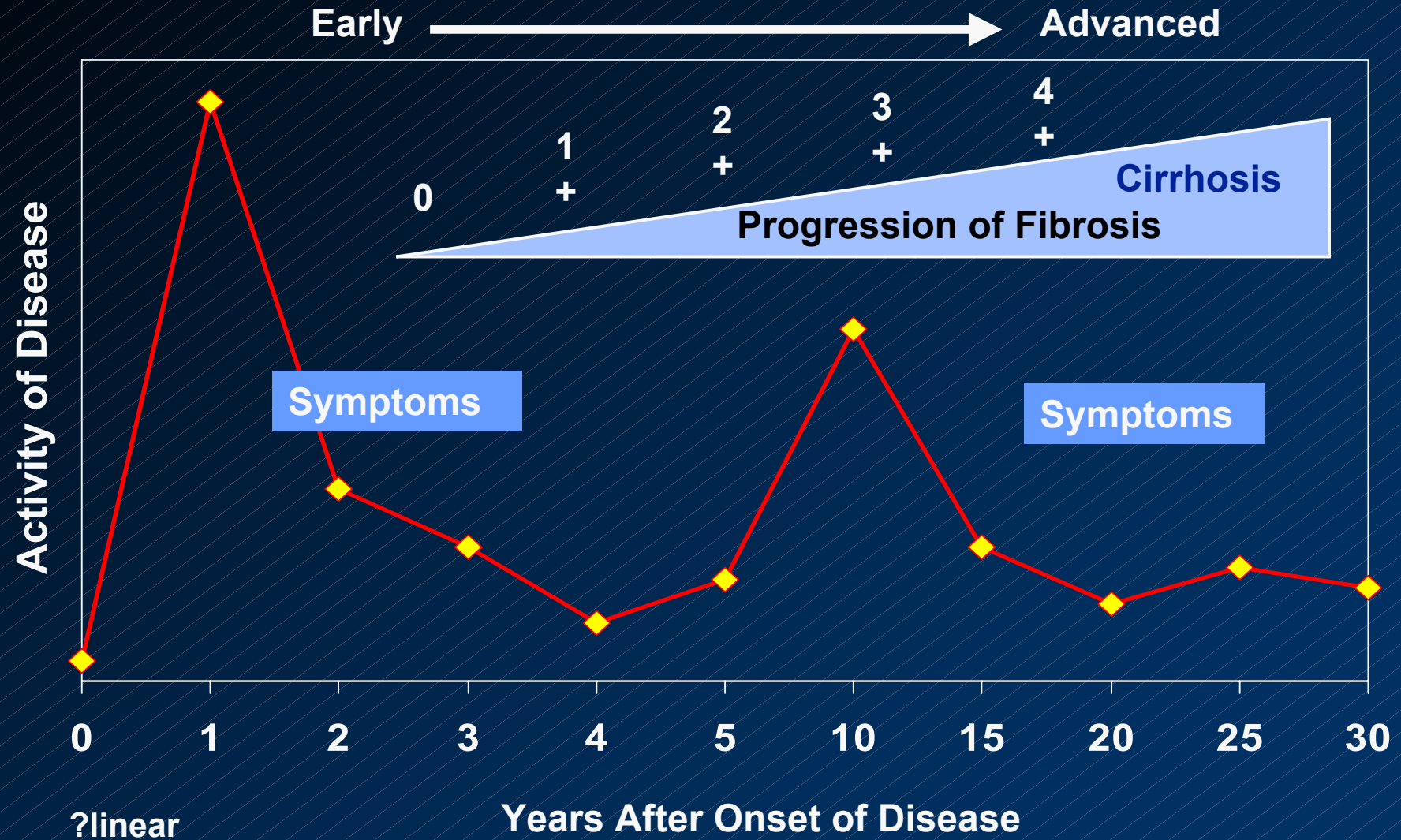
# Incidence and multivariate analysis risk of HCC

## 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 <sup>3</sup>	1178	714	16	116	1.1
1.0-9.9x10 <sup>4</sup>	647	7452	21	281	2.4
1.0-9.9x10 <sup>5</sup>	338	3749	33	880	8
>1x10 <sup>6</sup>	530	5859	60	1024	12.3

N= 3774

# Activity versus Stage



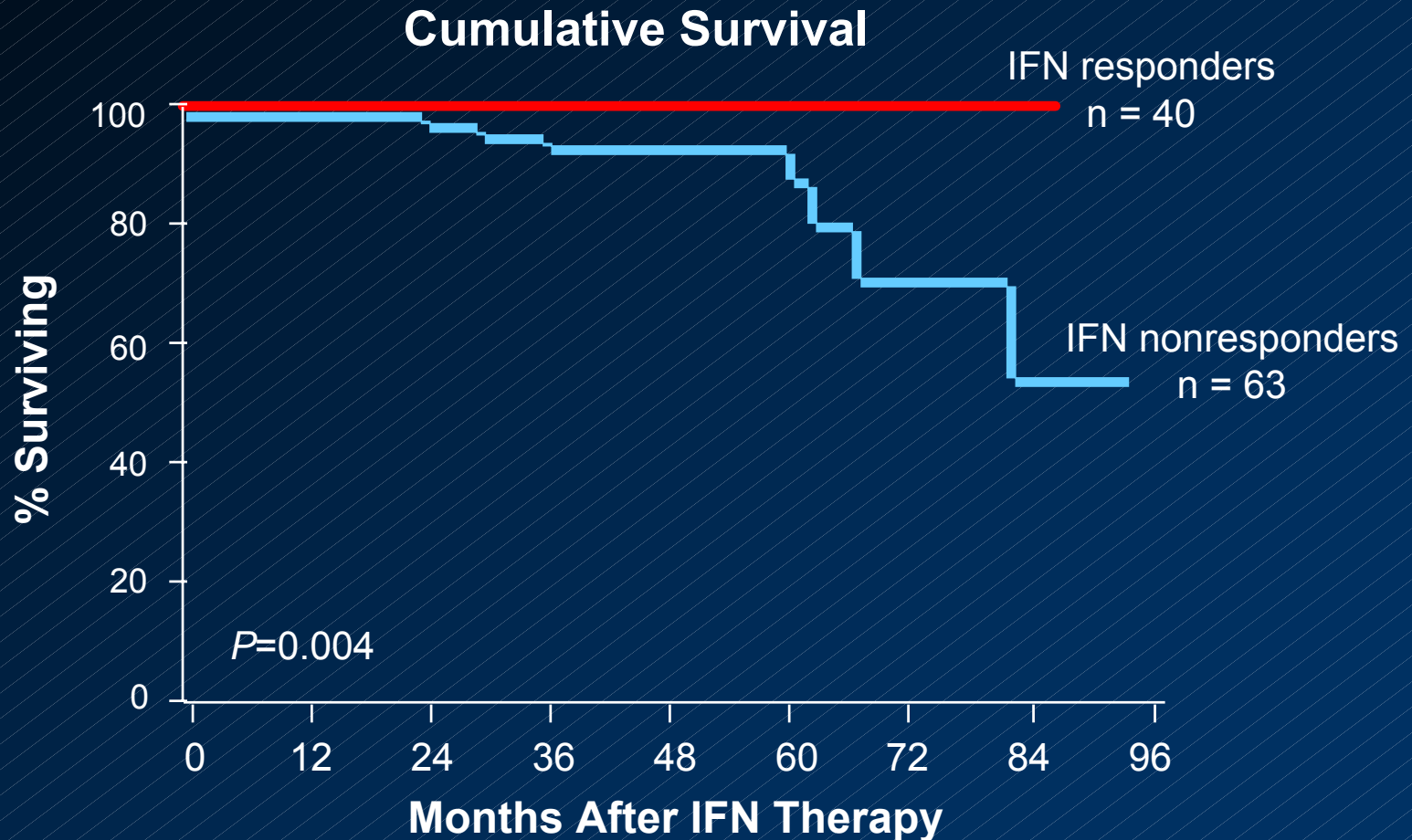
?linear

?invariable

From Hoofnagle et al

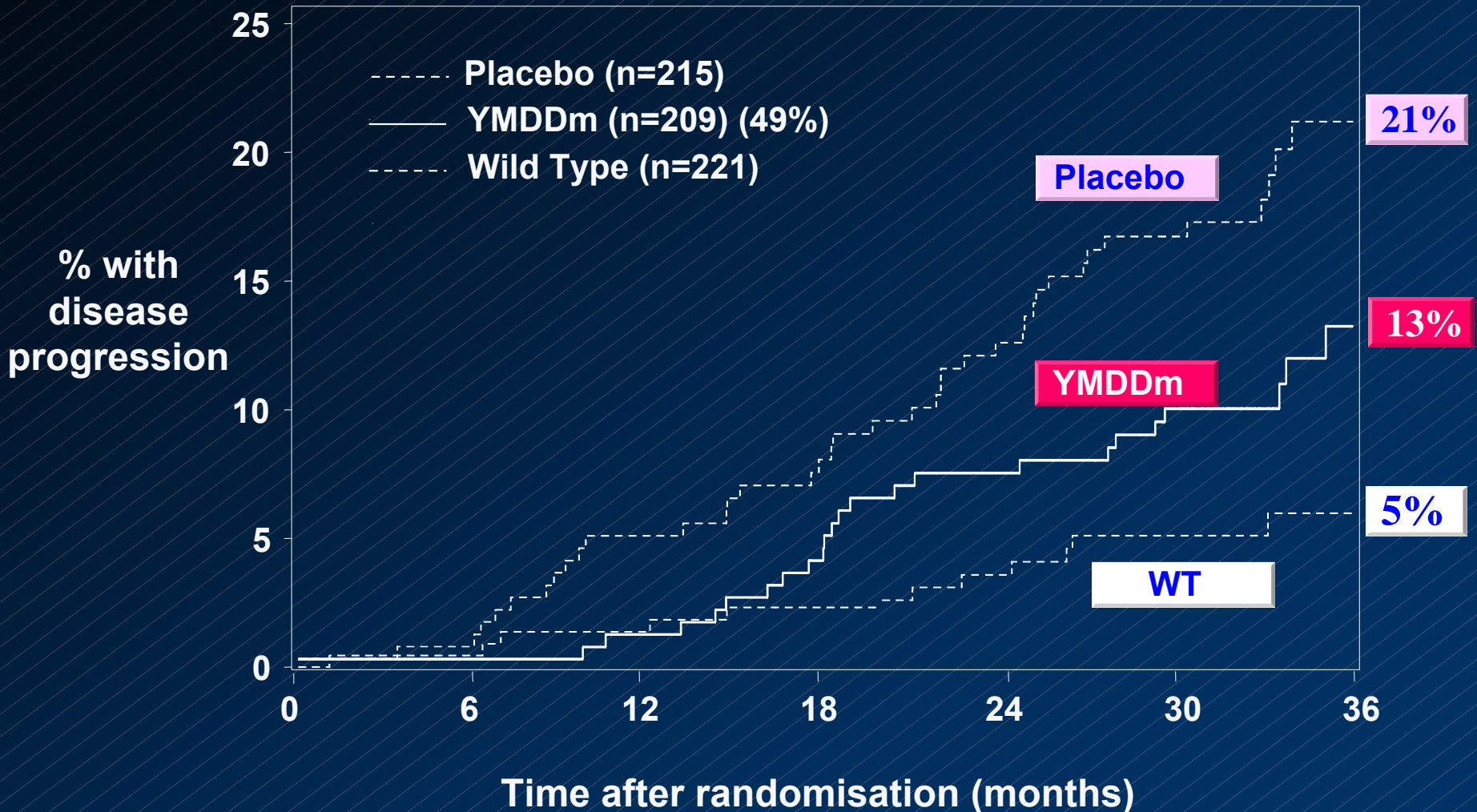
# Reducing mortality via treatment: Interferon alpha Proof of Principle

Long-term Follow-up of Patients With Chronic Hepatitis B  
Treated With IFN- $\alpha$



# Reducing mortality via treatment: lamivudine Proof of Principle

## *Time to Disease Progression*



# *Chronic Hepatitis B*

## **Assessment**

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- **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: Significance

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- 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
-

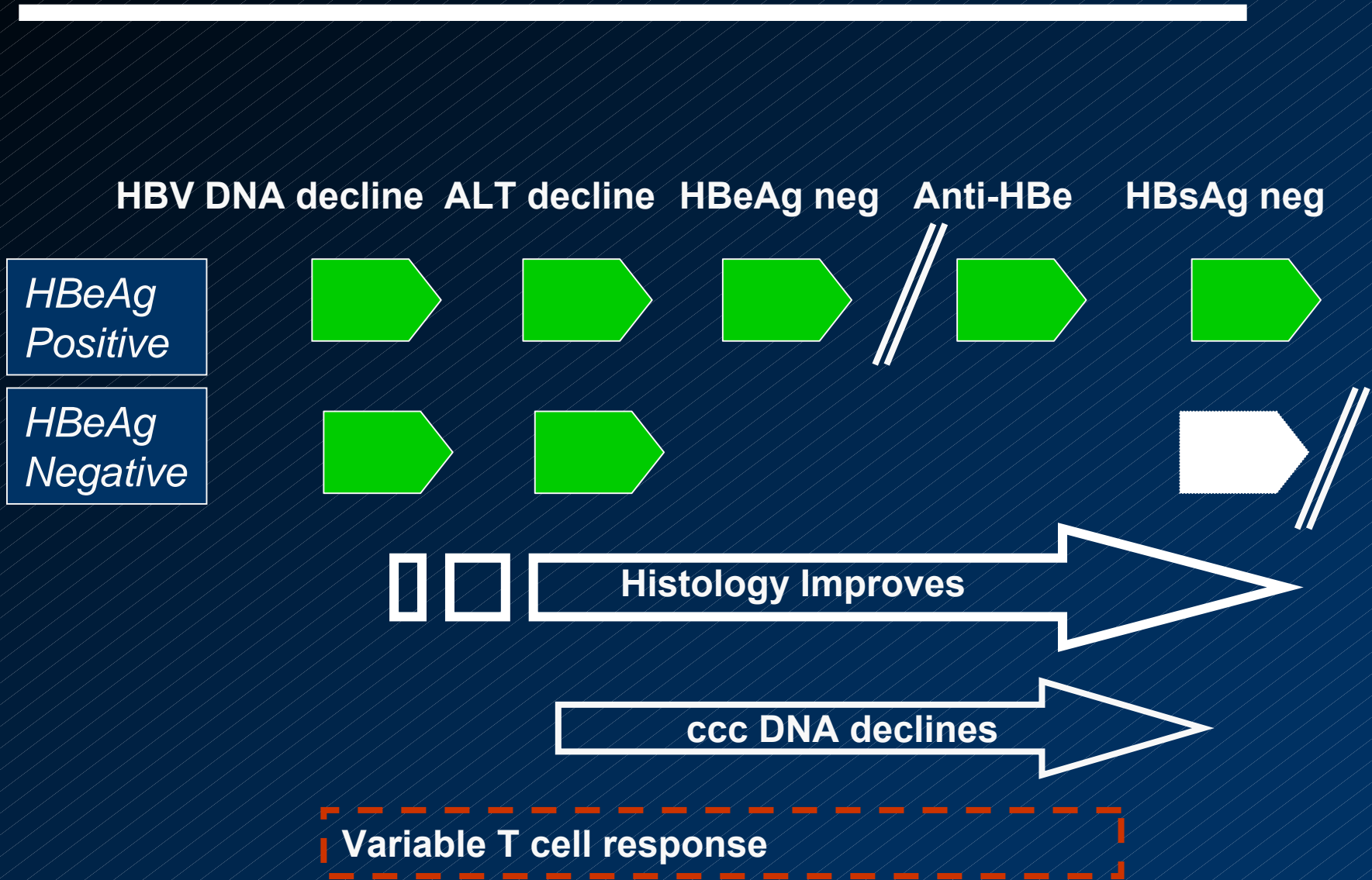
# HBV DNA

## 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

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- Lamivudine [(–)-β-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

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## Nucleoside Analogs

## Nucleotide Analogs (phosphonates)

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

Lamivudine (L)  
Entecavir (D)  
Emtricitabine (L)  
Telbivudine (L)  
Clevudine (L)  
Elvucitabine (L)  
**Valtorcitabine (L)**  
Amdoxovir (D)  
Racivir (L)  
**MIV 210 (D)**  
 $\beta$ -L-FddC (L)

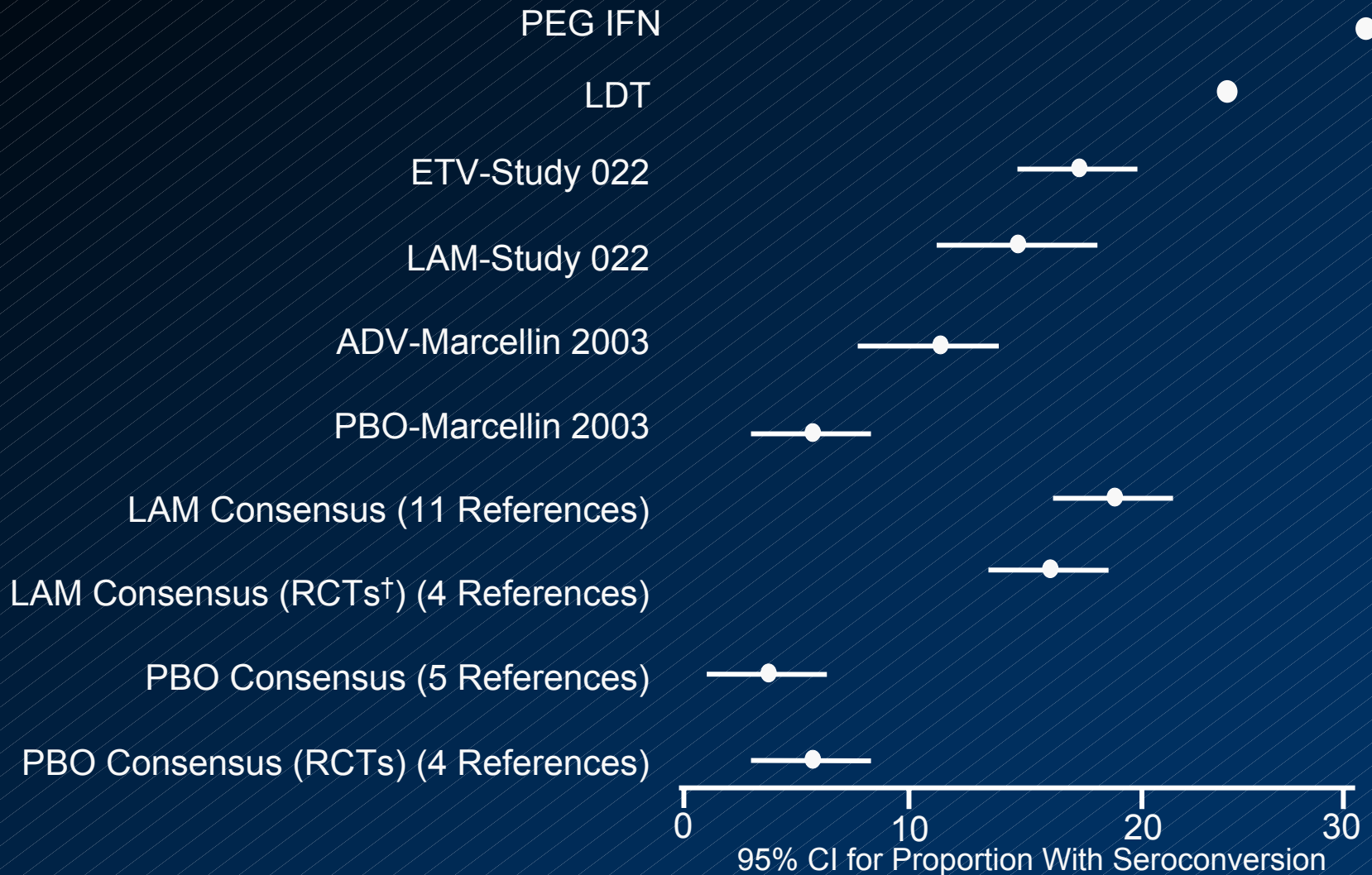
**Hepsera (D)**  
**Tenofovir (D)**  
**Alamifovir (D)**  
**Hepavir B (D)**

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

# 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 <sub>10</sub> 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 %

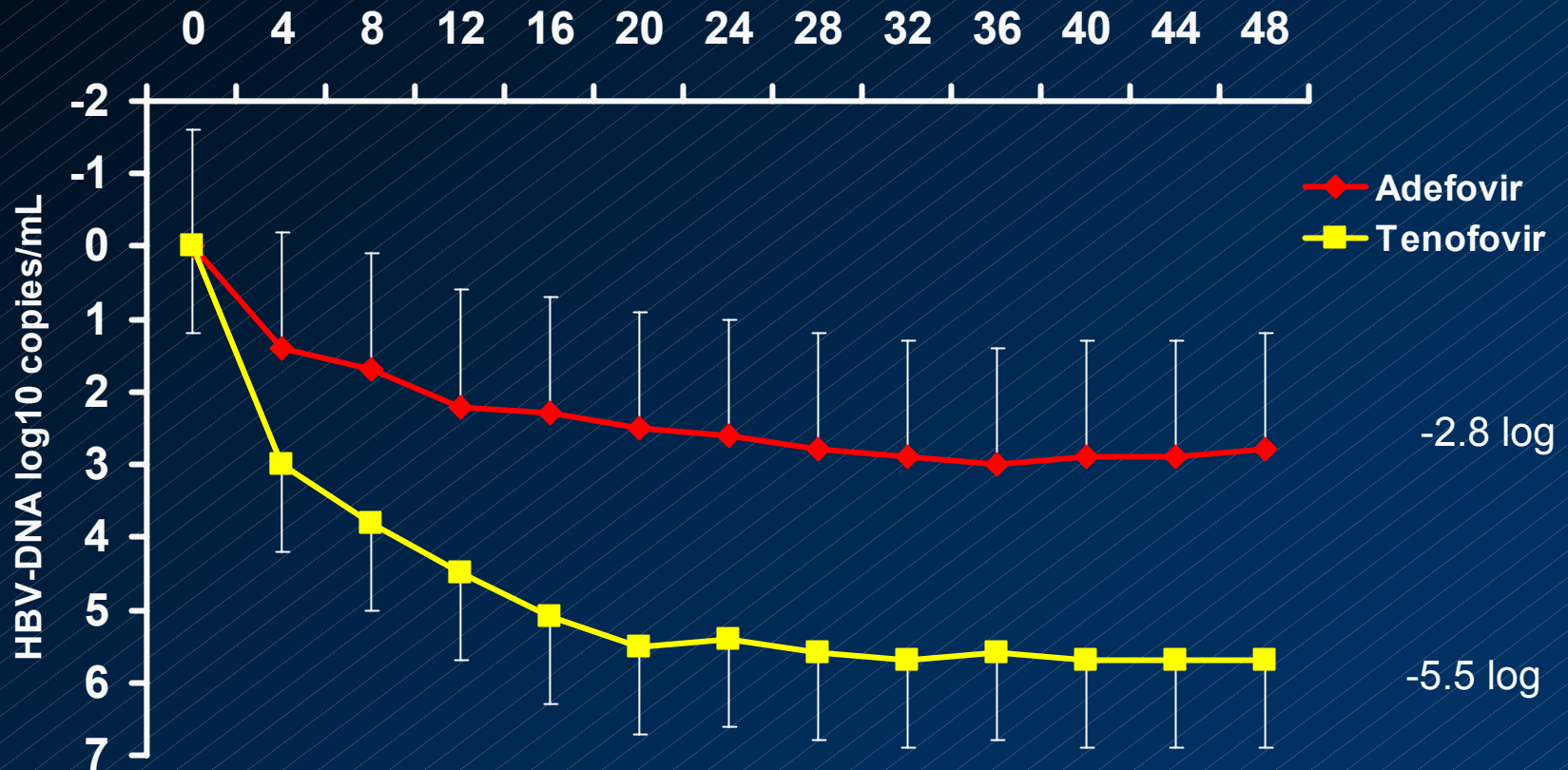
\* < 200 c/ml LdT, Resistance various defn, Histol response various

# 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

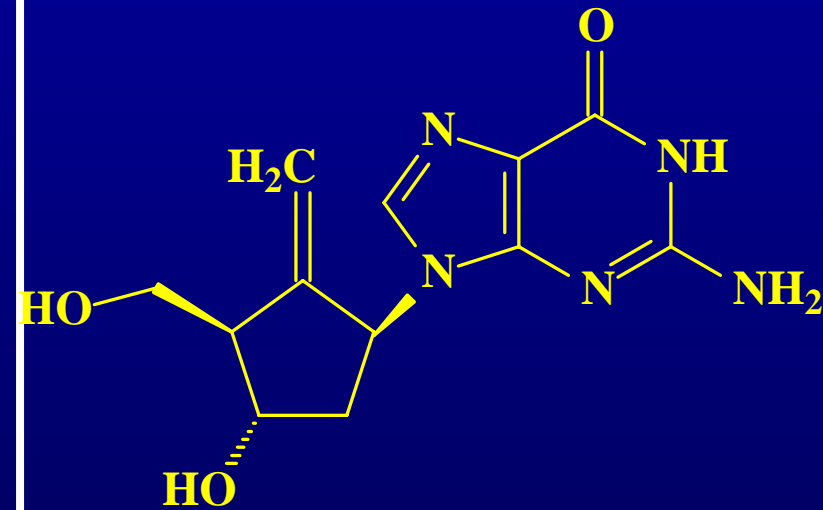


# Entecavir (ETV)

- Inhibits priming, reverse transcription of (-) strand and synthesis of (+) strand

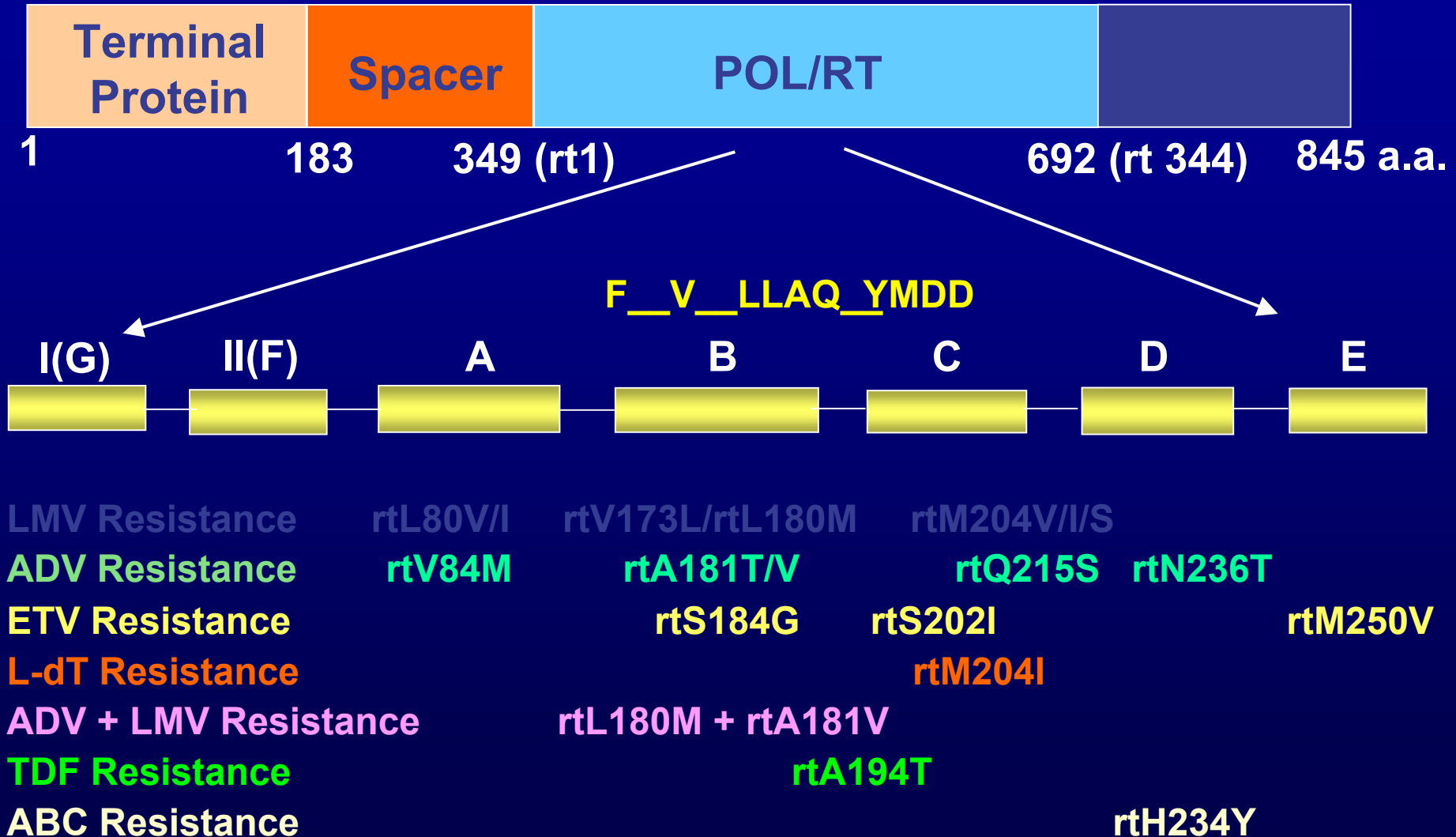
- Active against LAM-R in vivo but less pronounced against L180M +M204V/I

- 2 dosages developed:
  - 0.5mg in naïve patients
  - 1.0mg in LAM-R patients



1S-(1 $\alpha$ ,3 $\alpha$ ,4 $\beta$ )]-2-amino-1,9-dihydro-  
9-[4-hydroxy-3-(hydroxymethyl)-2-  
methylenecyclopentyl]-  
-6H-purin-6-one

# HBV Pol Resistance Mutations



# 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

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- 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

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- 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