Recommendations regarding viral hepatitis care and treatment

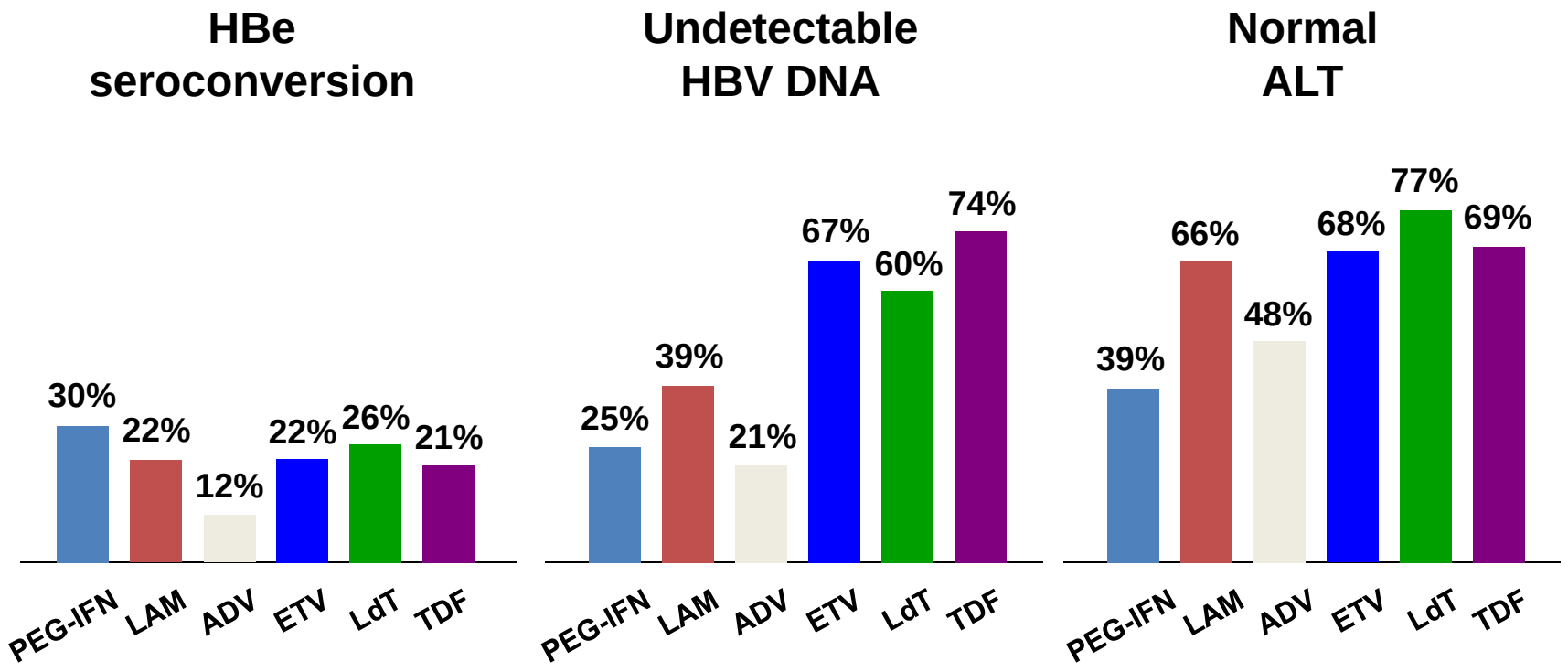
Whom to treat- when to treat

VHPB meeting 18 March 2010

Introduction: hepatitis B

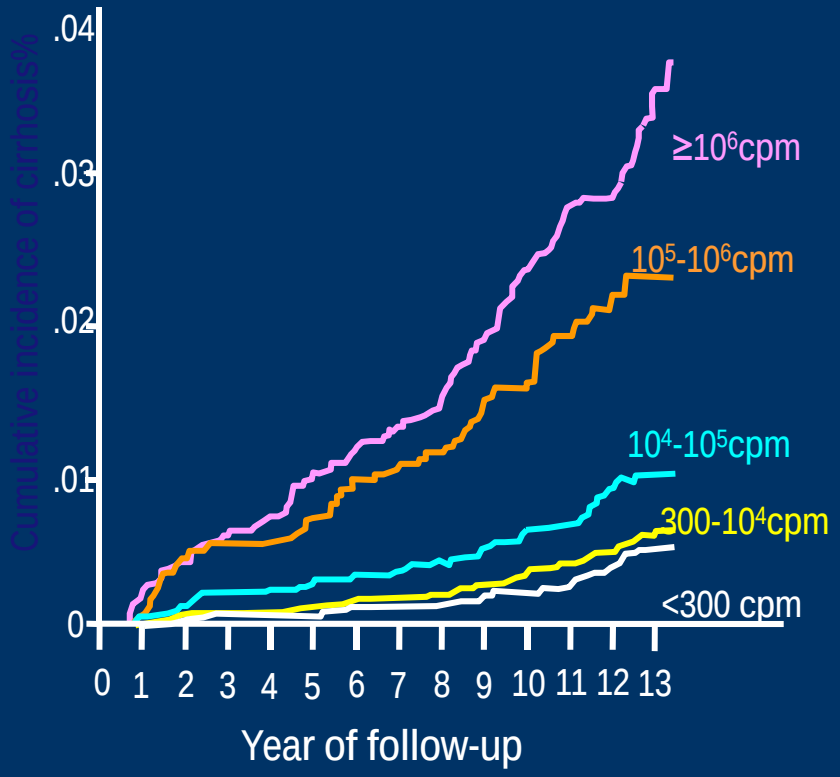
- Iinterferon alpha and recently, the introduction of nucleos(t)ides for therapy of hepatitis B transformed the therapeutic landscape.
- Treatment simpler and safer – but not curative
  - Continued treatment required for most
- Resistance a drawback
- Questions regarding indications for and timing of treatment

HBeAg-positive patients



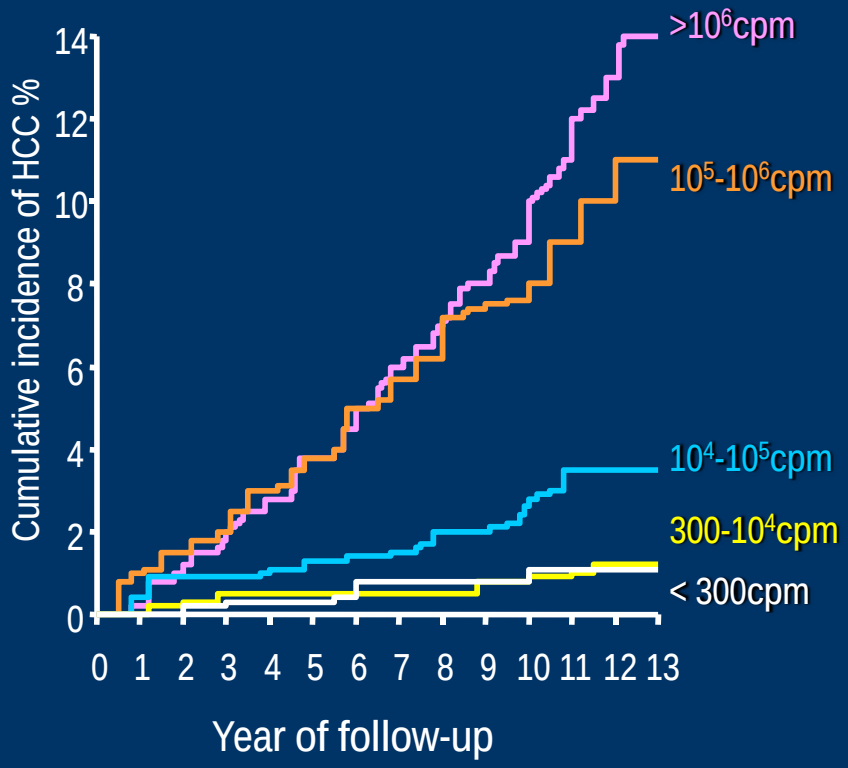
Higher viral loads are associated with long-term complications

Progression to Cirrhosis



Iloeje UH *et al*. *Gastroenterology* 2006; 130: 678–86.

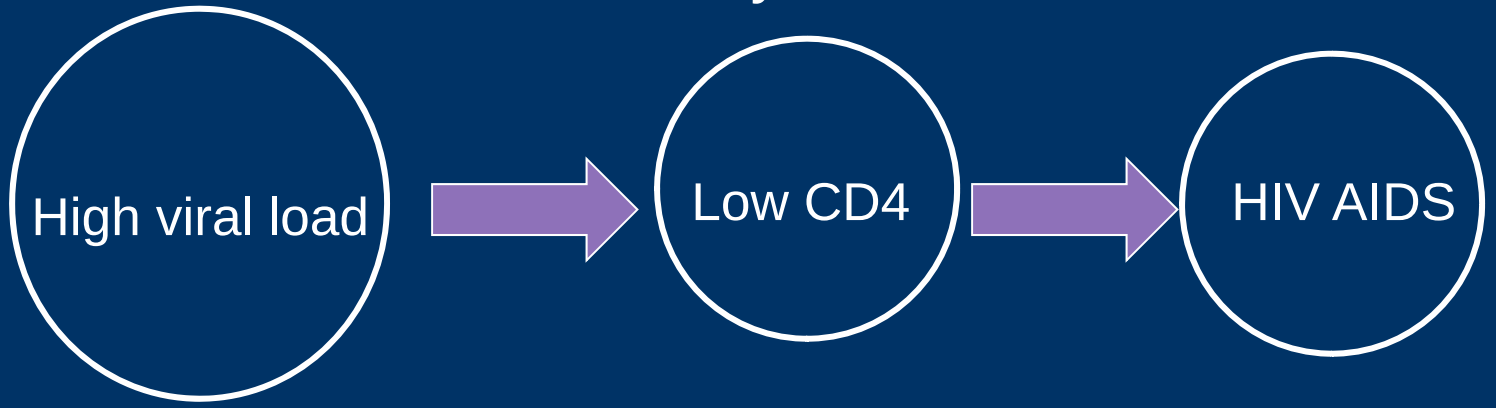
Progression to HCC



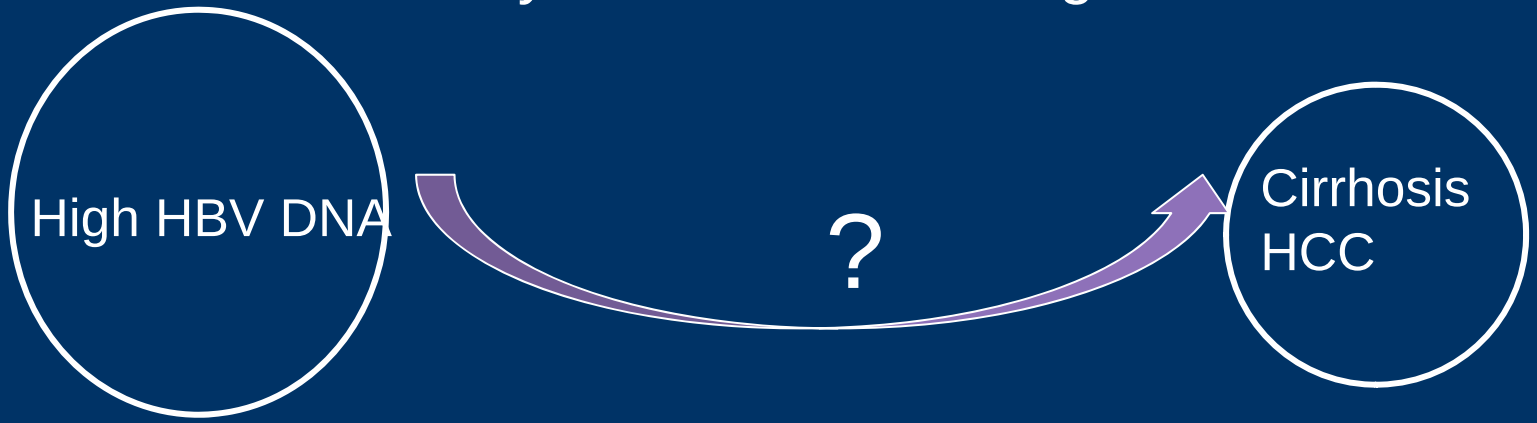
Chen CJ et al. *JAMA* 2006; 295: 65-73

Predictors of disease: HIV vs HBV

HIV Treatment necessary and benefit shown



HBV Necessity? Benefit? Health gain? Concerns



Chronic hepatitis B: treatment

- Chronic hepatitis B is a life-long disease
- A major health problem in endemic regions
- Treatment should be started with the long-term in mind
- Outcome may be jeopardised by suboptimal treatment

EASL Clinical Practice Guidelines. *J Hepatol* 2009; 50:227-242;
Sorrell M *et al*. *Annals of Internal Medicine* 2009; 150:104-112; Zoulim F *et al*. *J Hepatol* 2008; 48:S2-S19 .

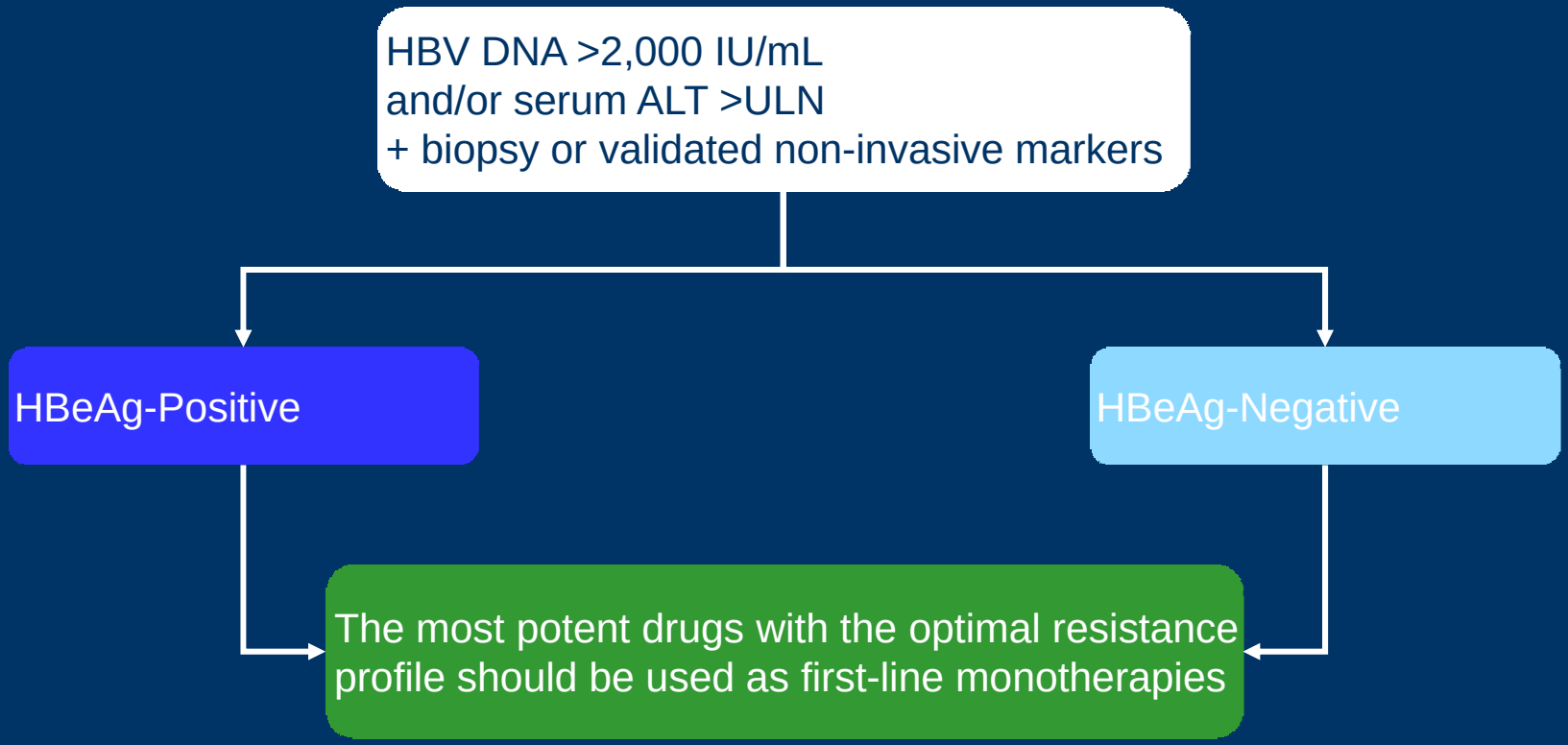
Goals of treatment HBV

- **Prevent progression of disease**
- **Can be achieved by reducing viral load?**
  - **Level of HBV DNA replication requiring therapy?**
  - **Optimal target DNA for suppression that alters histology and natural history?**

Indications for treatment HBV bon combination of

- Serum aminotransferases
- HBV DNA levels
- Histological stage and activity

Indications for therapy within the guidelines:



- Indications for treatment must also take into account age, health status, and availability of antiviral agents in individual countries

EASL Clinical Practice Guidelines. *J Hepatol* 2009; 50:227-242.

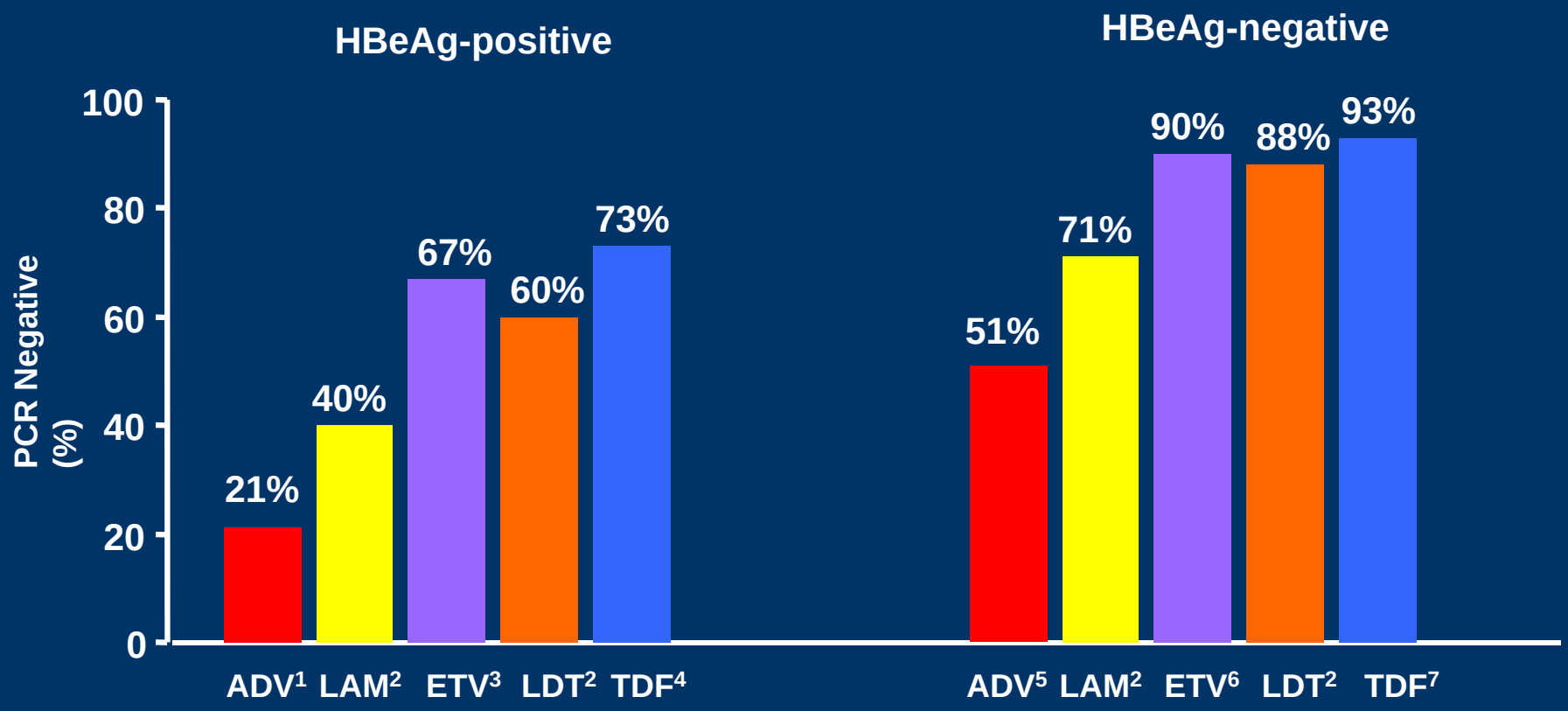
Indications for therapy
Patients for longitudinal monitoring

- HBeAg positive immunotolerant
  - Most under age 30, normal ALT and high HBV DNA levels without suspicion/family history liver disease
  - Do not require immediate treatment
  - Follow up mandatory
- Patients with mild chronic hepatitis B:
  - ALT < 2X ULN, < A2F2 histologically
  - Do not require immediate treatment.

EASL

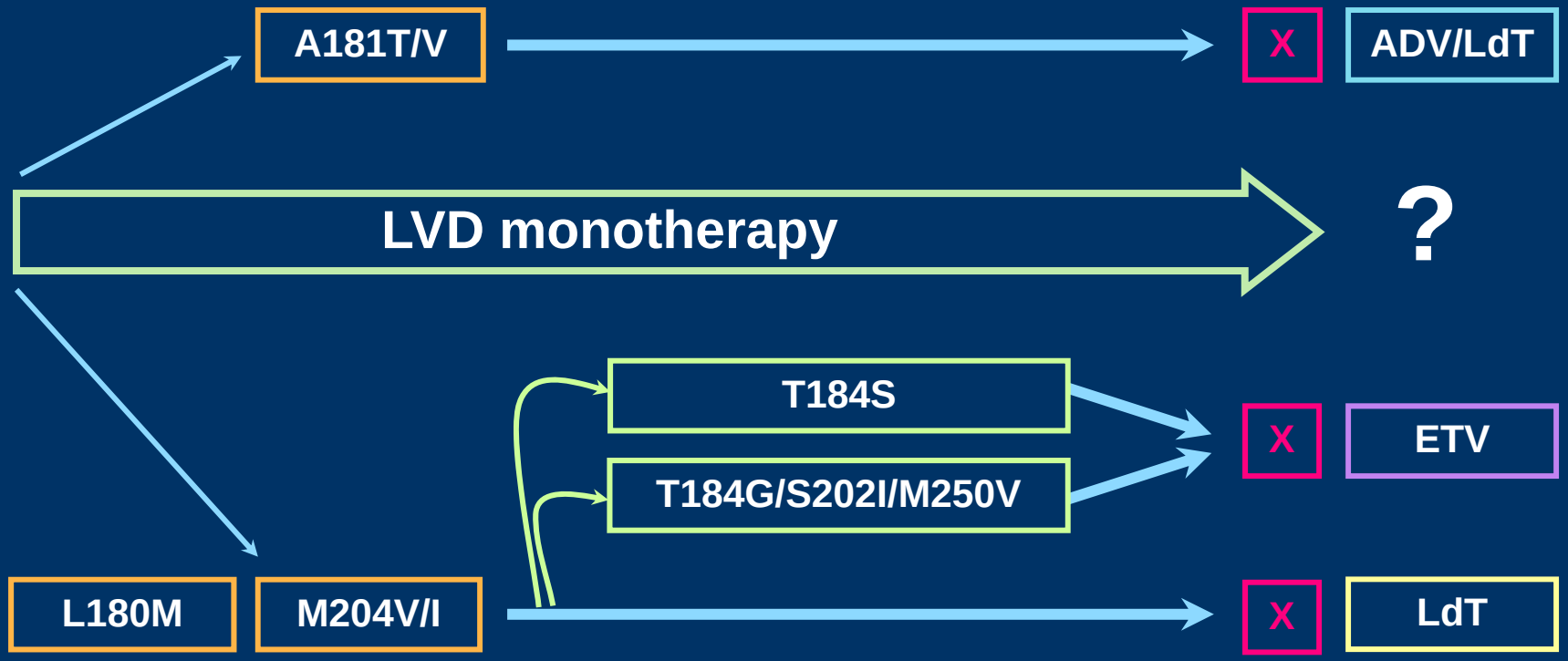
PCR Negativity At 1 Year

Data not from head-to-head studies



1. Marcellin P et al. N Engl J Med 2003;348(9):808-14
2. Lai CL. et al. N Engl J Med 2007; 357:2576-88
3. Chang TT et al. N Engl J Med. 2006;354:1001-1010.
4. Heathcote EJ et al. AASLD 2007
5. Hadziyannis S. et al. N Engl J Med 2003;348:800-7
6. Lai CL et al. N Engl J Med 2006;354:1011-20
7. Marcellin P et al. AASLD 2007

Lamivudine monotherapy and cross resistance



Locarnini S. Hepatol Int 2008;2:147–151

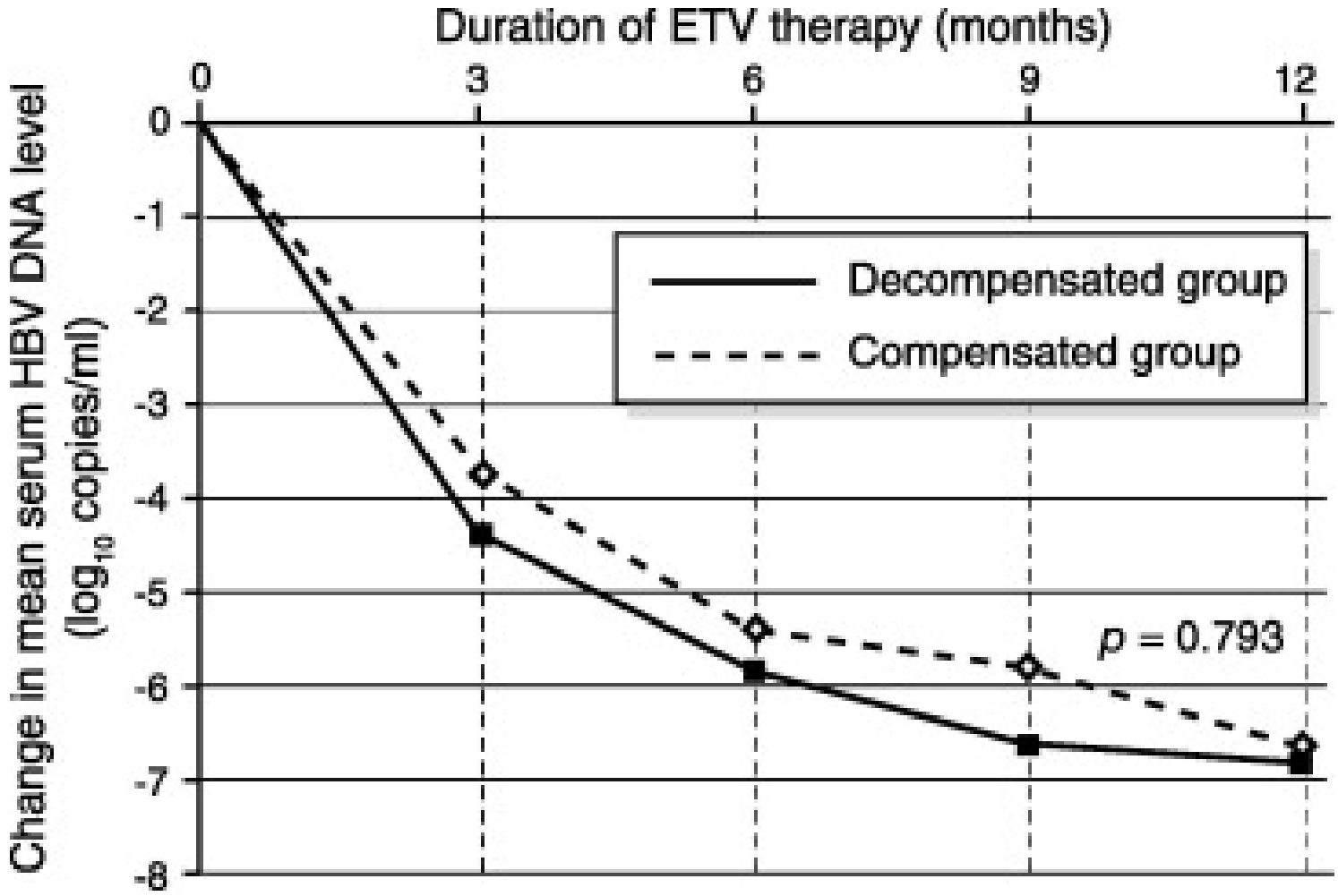
Preventing resistance nucleoside analogues HBV

- **Clear indication for starting therapy**
- **Encourage patient compliance**
- **Maximise antiviral activity**
- **Suppress HBV DNA to lowest possible level**
- **Maximise genetic barriers**
- **Avoid sequential treatment**
- **Avoid treatment interruptions**

Indications for treatment: cirrhosis

- Patients with compensated cirrhosis and detectable HBV DNA
  - Considered for treatment
- Patients with decompensated cirrhosis
  - Require urgent antiviral treatment
  - Should be considered for liver transplantation

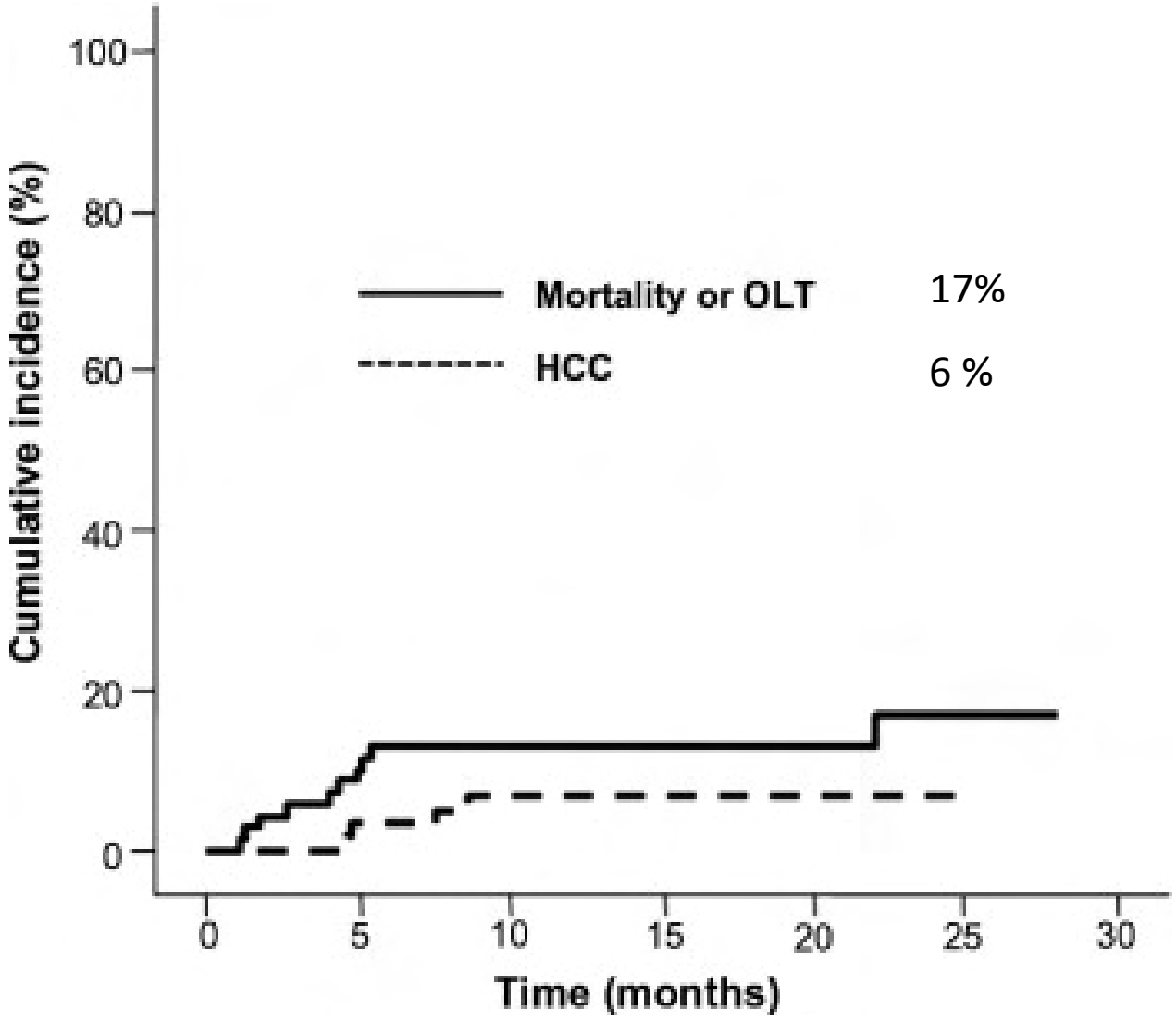
Changes in HBV DNA cirrhosis Entecavir



Shim et al J Hepatology 52: 176-182

2 year mortality cirrhosis Entecavir

Shim et al J Hepatology 52: 176-182



Utility of nucleosides

- Integral role liver transplantation
  - Combination of nucleosides and HBIG
  - In decompensated disease
  - anti-HBc donors

- Fulminant hepatitis
- Prophylaxis chemotherapy
- Extra-hepatic disease
- HIV co-infected patients
- In pregnancy?
- In HCC (post treatment)?

Nucleosides: Preventing mother infant transmission of hepatitis B

- Vaccination is the mainstay of prophylaxis.
- Utilise antiviral drugs for prophylaxis?
  - What viral level increases the risk of maternal infant transmission despite HBIG and vaccination?
- How early in pregnancy should treatment be initiated?
- Are all nucleos(t)ides safe in pregnancy?
- Which drug is most appropriate?
- What are the risks and benefits for the mother?

Potential Consequences of Antiviral Drug Resistance in Chronic HBV

Virologic	Virologic breakthrough and rebound
	Reduced HBeAg seroconversion rates HBeAg seroconversion relapse
Biochemical	Biochemical breakthrough
Histologic	Histologic progression of disease
Clinical	Hepatic flare and decompensation
	Increased recurrence post liver transplantation (viral load is strongest predictor of HBV recurrence post liver transplant)* ?Increased tumourigenicity
Public health	Alteration in HBsAg antigenicity
	Transmission of drug resistant HBV Development of multi-drug resistant HBV population

*Lai, C.L. et al 2003. Clin Infect Dis;36:687-96.; Leung, N.W. et al 2001. Hepatology;33:1527-32.; Liaw, Y.F. et al 1999. Hepatology;30:567-72.; Dienstag, J.L. et al 2003. Gastroenterology;124:105-17.; Mutimer, D. et al 2000. GUT;46:107-13. *Mutimer, D. et al 1999. J Hepatol;30:715-21.*

Treatment forms part of the control of the disease

- Progressive disease is associated with persistence of viral replication and ongoing necro-inflammation
- Remission is associated with loss of active viral replication.

Hepatitis C and liver pathology

- Fibrosis induced by the inflammatory process.

- Factors shown to accelerate the progression to cirrhosis include older age at HCV acquisition, male gender, heavy alcohol intake and co-infection with either HBV or HIV.
- Steatosis may lead to advancing fibrosis.
- No DNA intermediate or integration of viral nucleic acid
- Oncogenesis through cirrhosis and regeneration of liver cells.

Chronic hepatitis C: Evaluating treatment

- The chronic disease generally slowly progressive
- Cirrhosis develops within 20 years in about 10–20%
- Variability in rates of progression of the disease makes the prediction of ultimate outcome difficult.
- The disease is not necessarily benign, however
- The numerical prevalence of the disease has translated into a large pandemic worldwide of liver disease.

Acute hepatitis C

- Clinically mild, and typically unrecognised. Acute hepatitis C is thus only infrequently diagnosed.
- Incidence of acute hepatitis C is falling in several industrialised countries
- Higher rates of spontaneous recovery from acute hepatitis C have been observed in individuals with identified single nucleotide polymorphisms that lie in or near the IL28B on chromosome 19 which encodes IFN lambda3

Treatment of acute hepatitis C

- Early identification of acute hepatitis C is important, but may be difficult
- Early spontaneous convalescence can be difficult to confirm
- Recent studies have indicated that treatment benefits those patients who have been treated early.
- The optimal timing and form of treatment for acute hepatitis C is not yet determined but

General management Chronic hepatitis C

- *Evaluation of liver disease*
- HCV RNA should be quantitated
- Genotype determined
- HBsAg and HIV infection must also be tested
- *Liver biopsy or assessment of fibrosis*
- *Biomarkers: IL28b polymorphisms*
- General management
  - Careful clinical monitoring
  - Alcohol: synergistically aggravates hepatic injury.
  - Reversibile comorbidites: hepatitis B, HIV, obesity, hepatic steatosis diabetes, insulin resistance
- Advise on route of transmission and vaccination

Indications for treatment chronic hepatitis C

- All patients irrespective of the degree of fibrosis are potential candidates for treatment.
- Some patients with mild disease do not require immediate treatment
- Psychiatric co-morbidities may be worsened with IFN treatment: should be stabilised
- Patients with compensated cirrhosis are candidates for treatment
- Alpha IFN is difficult to apply in decompensated cirrhosis and may precipitate deterioration
  - Liver transplantation

Serum aminotransferases and treatment

- Most patients with raised serum ALT are HCV RNA-positive
- The converse not true.
- Perhaps 25-50% may have persistently normal serum ALT.
- “Normal serum aminotransferases" in patients with hepatitis C, frequently actually high relative to healthy individuals.
- Low-grade hepatitis, and even low-grade fibrosis may be present
- Fibrosis progression may be less rapid in females with low or normal ALT.

Table: Factors adversely determining response

- Genetic polymorphism: tt IL28b polymorphism
- High baseline viral load
- Age greater than 50 years
- High body mass index
- Poor adherence to therapy
- Excess alcohol
- Genotype 1 versus genotype 2 or 3
- Genotype 4, and probably 5 and 6
- Advanced fibrosis, cirrhosis or advanced liver disease
- Hepatic steatosis
- Low platelet count
- High homeostasis model assessment index (HOMA)
- Failure to achieve RVR
- African American ethnicity
- HIV and HCV coinfection

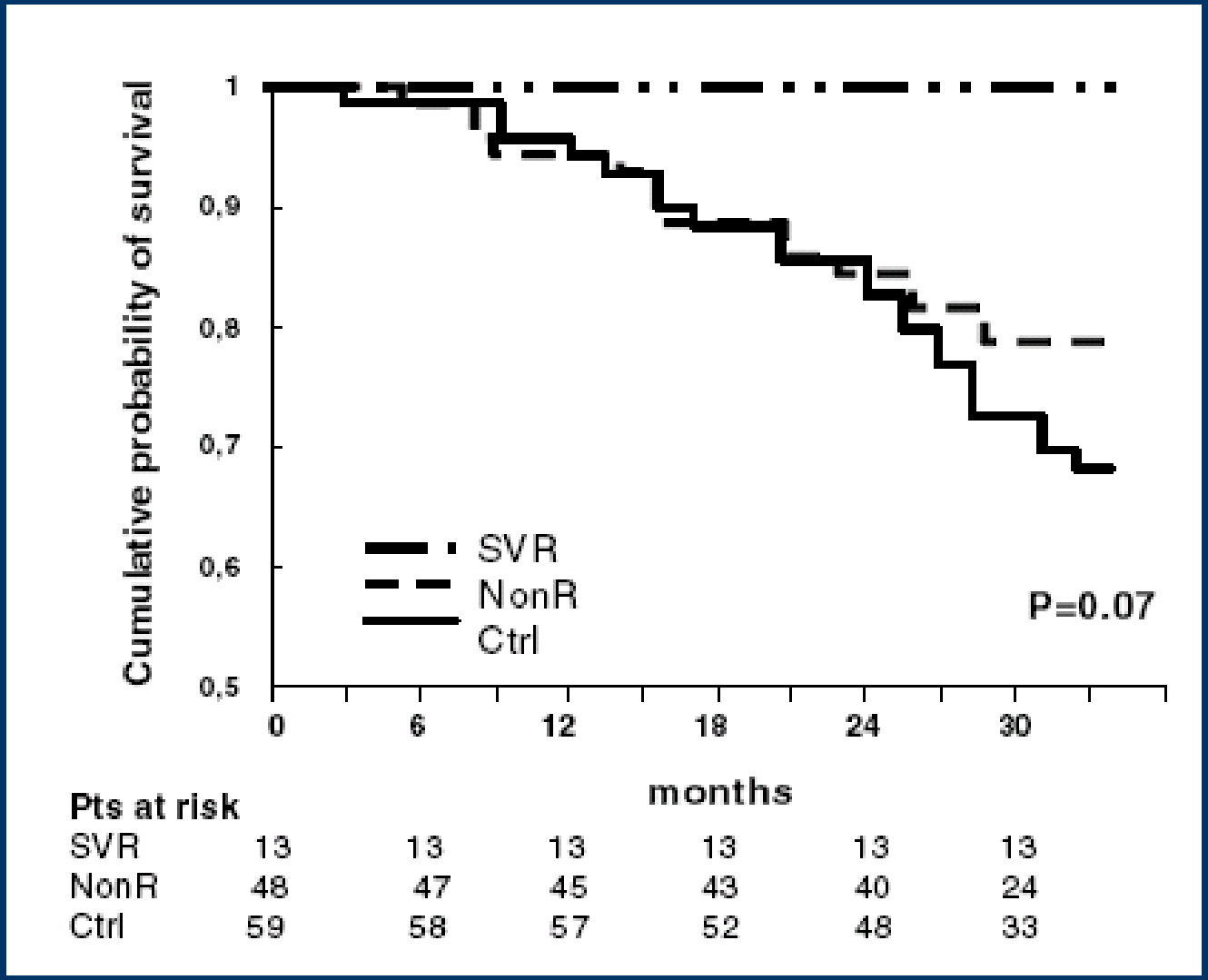
Impact of disease severity on therapy

- Virological response to re-treatment
- 1046 patients HALT C

Group	A	B	C	D
Fibrosis	Ishak 3-4 platelets >125	Ishak 3-4 platelets <125	Ishak 5-6 platelets >125	Ishak 5-6 platelets <125
SVR	23%	17%	10%	9%

Everson Hepatology 44:1675 2006

Overall survival in responders non responders and untreated patients
Decompensated cirrhoris



Iacobellis A et al J Hepatol 46: 206 20007

Other groups for treatment

- **IVDU**
- **HIV coinfected**
- **Decompensated cirrhosis**
- **Recurrence post liver transplant**
- **Non responders**

New agents for hepatitis C

Anticipated advantages

- Improved response rates
  - Naive and Non responders
- Rapid reduction in HCV RNA
- Shorter duration therapy
- Better tolerated therapy?
- Treatments equally efficacious across all genotypes and subtypes?
- Ribavirin sparing effect?
- Eventual IFN sparing effect?
- Cost effective and cost benefits?

Potential disadvantages

- New concerns raised
- Unequal effect genotypes and subtypes
- Triple or even quadruple combinations
- Antiviral resistance
- New drug interactions
- Dosing frequency
- Additive or new side effects
- Cost effectiveness

Treatment going forward with new agents

- Mild fibrosis
  - Interferon and RBV
    - Regard these patients as potential candidates
    - Does this hold for new combination therapies?
    - Threat of resistance not previously encountered
- New protocols
  - Standard of care control arms?

Going forward

- Considerable progress has been made in our understanding of hepatitis C infection since its discovery
- Treatments have also improved, so that more than half of patients with chronic hepatitis C can be cured.
- Newer direct acting antiviral therapies will further improve response rates: Genotype 1: 70% or higher.