Management of Chronic Hepatitis B: Why we care and how to treat?

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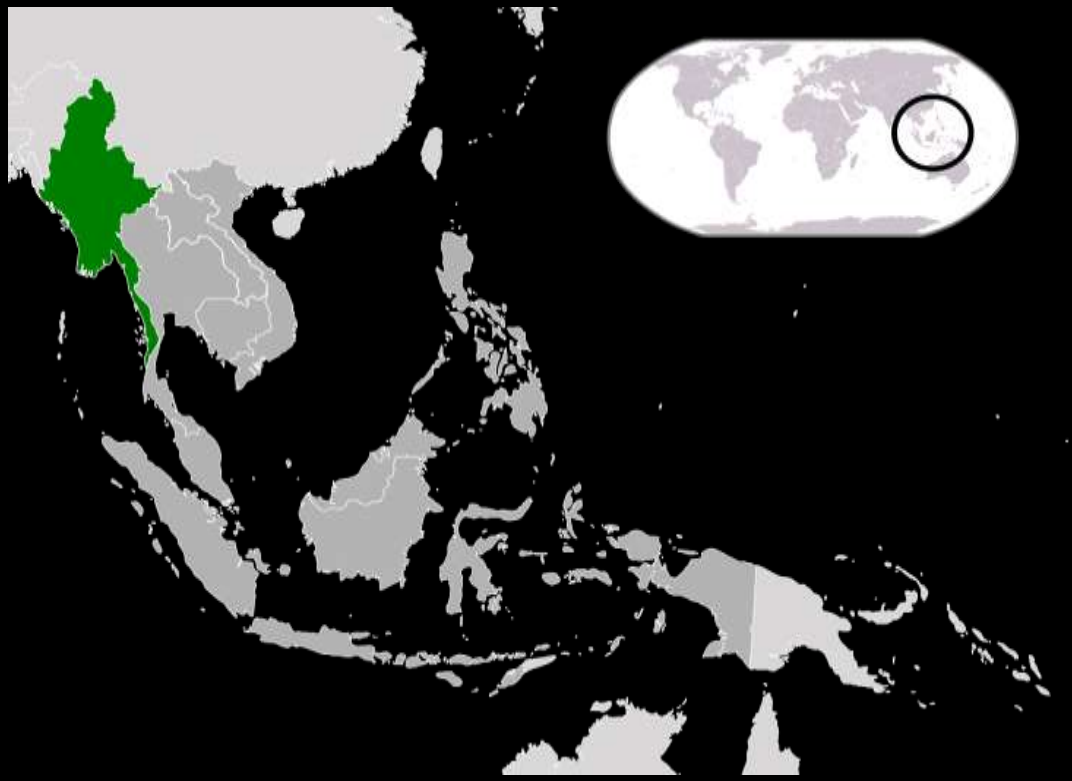
Myanmar

Disclosure

I have no financial relationships to disclose relevant to my presentation

Where is Myanmar?



About Myanmar

(Formerly called Burma)

Shwedagon pagoda

Hepatitis B; Why do we care?

- Because HBV is the main causal factor of HCC
- Direct correlation between HBV viral load and HCC
- Treatment of HBV can prevent HCC

What are the evidences?

HBV is the main causal factor of HCC

What are the Evidences?

HBV and HCC

- **Chronic HBV was noted to be associated with the development of HCC.**

[Sherlock S, et al. Lancet, 1970; i: 1243-1247] [Beasley RP, et al. Lancet. 1981: II: 1129-1133.]

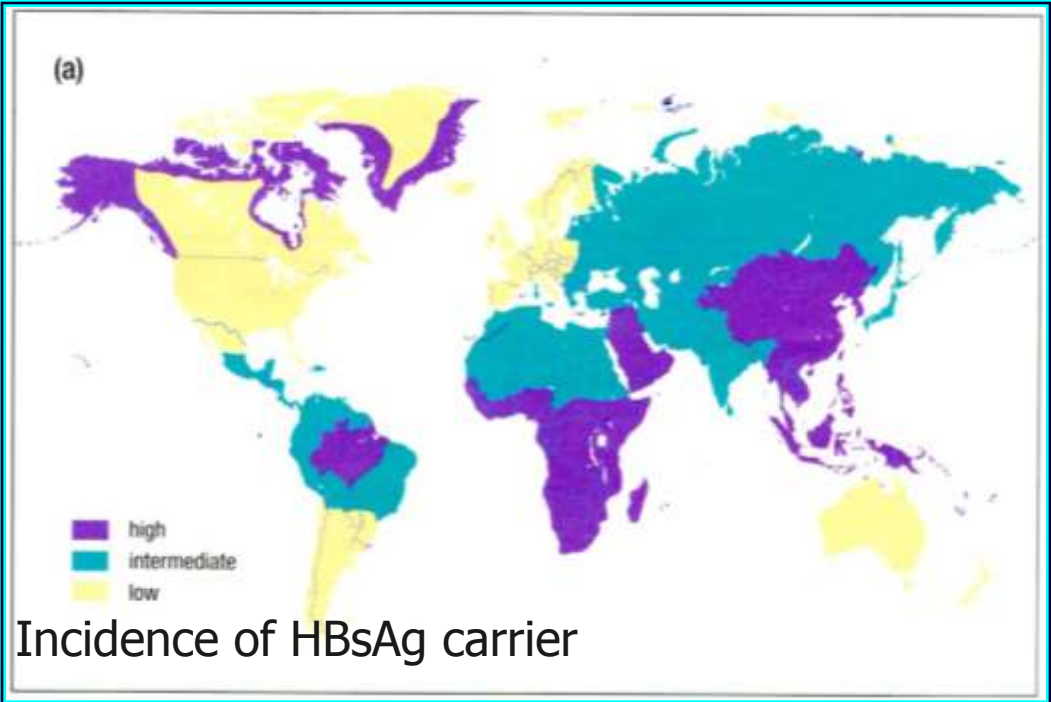
- **Chronic hepatitis B virus has been linked epidemiologically to the development of HCC for more than 30 years.**
  - **Epidemiological evidence**
  - **Evidence by reduction of HBV incidence by HB vaccination**
  - **Correlation between HBV viral load and HCC**

Bisceglie, Hepatology. 2009 May ; 49(5 Suppl): S56–S60. doi:10.1002/hep.22962.

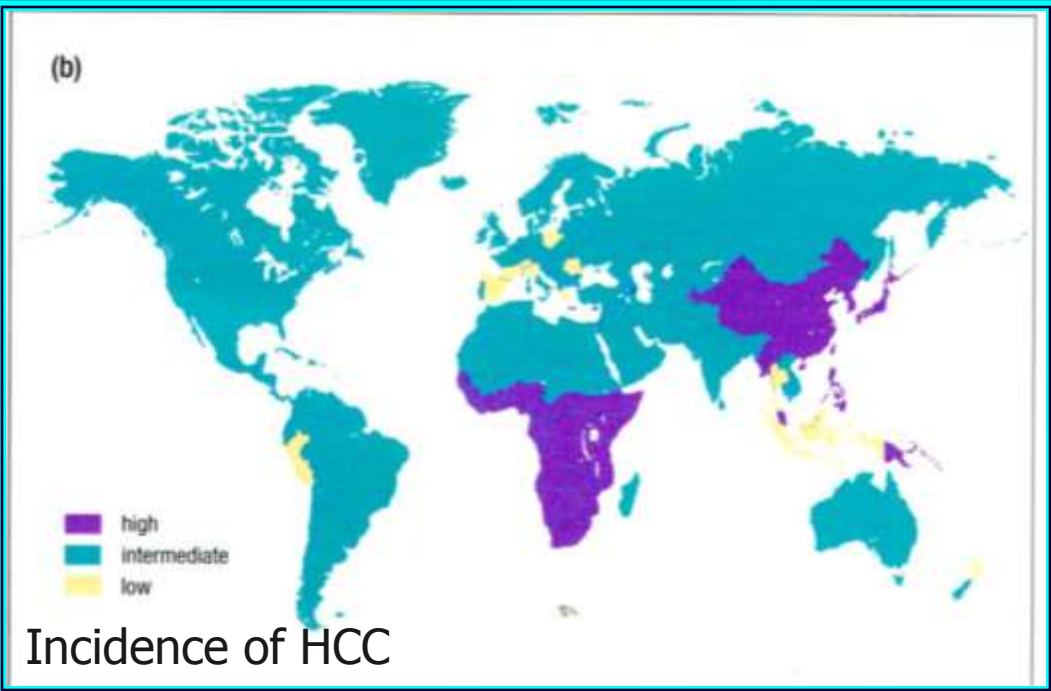
Geographical correlation between the global incidences of HBV carrier state (a) and hepatocellular carcinoma (b).

The incidence of HCC is directly related to the prevalence of chronic infections caused by HBV.

(Ref: Lai & Locanini, Hepatitis B Virus, International Medical Press Ltd, 2002)



Incidence of HBsAg carrier

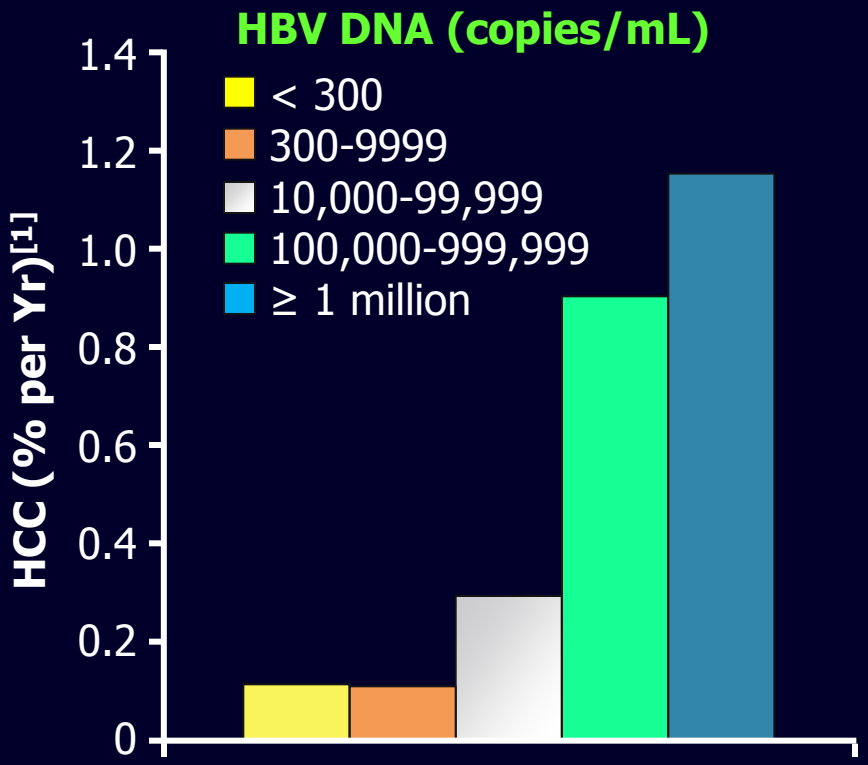


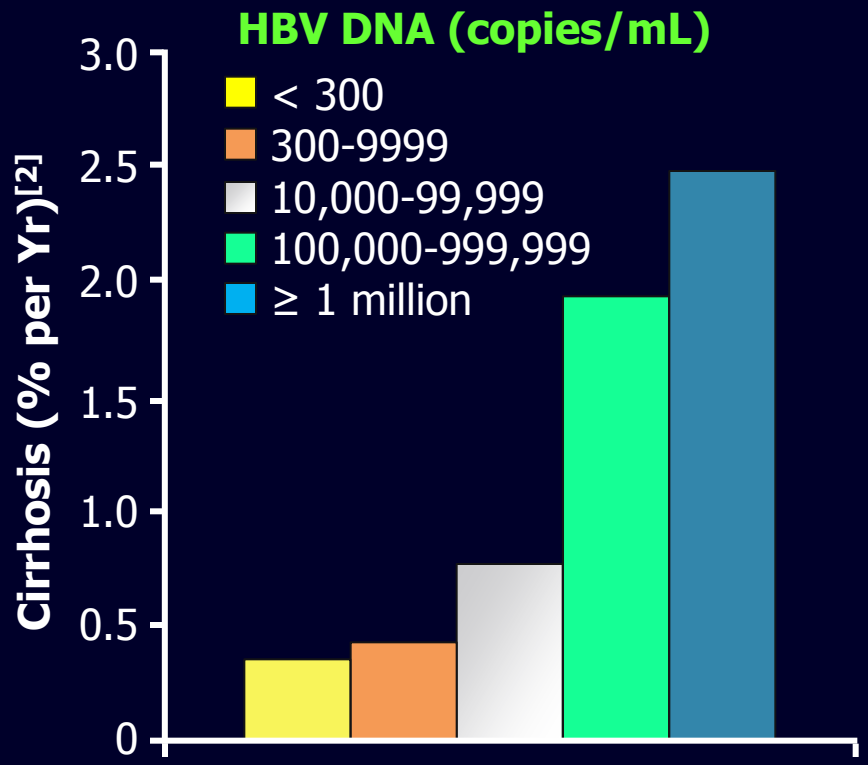
Incidence of HCC

Correlation between HBV viral load and HCC

What are the Evidences?

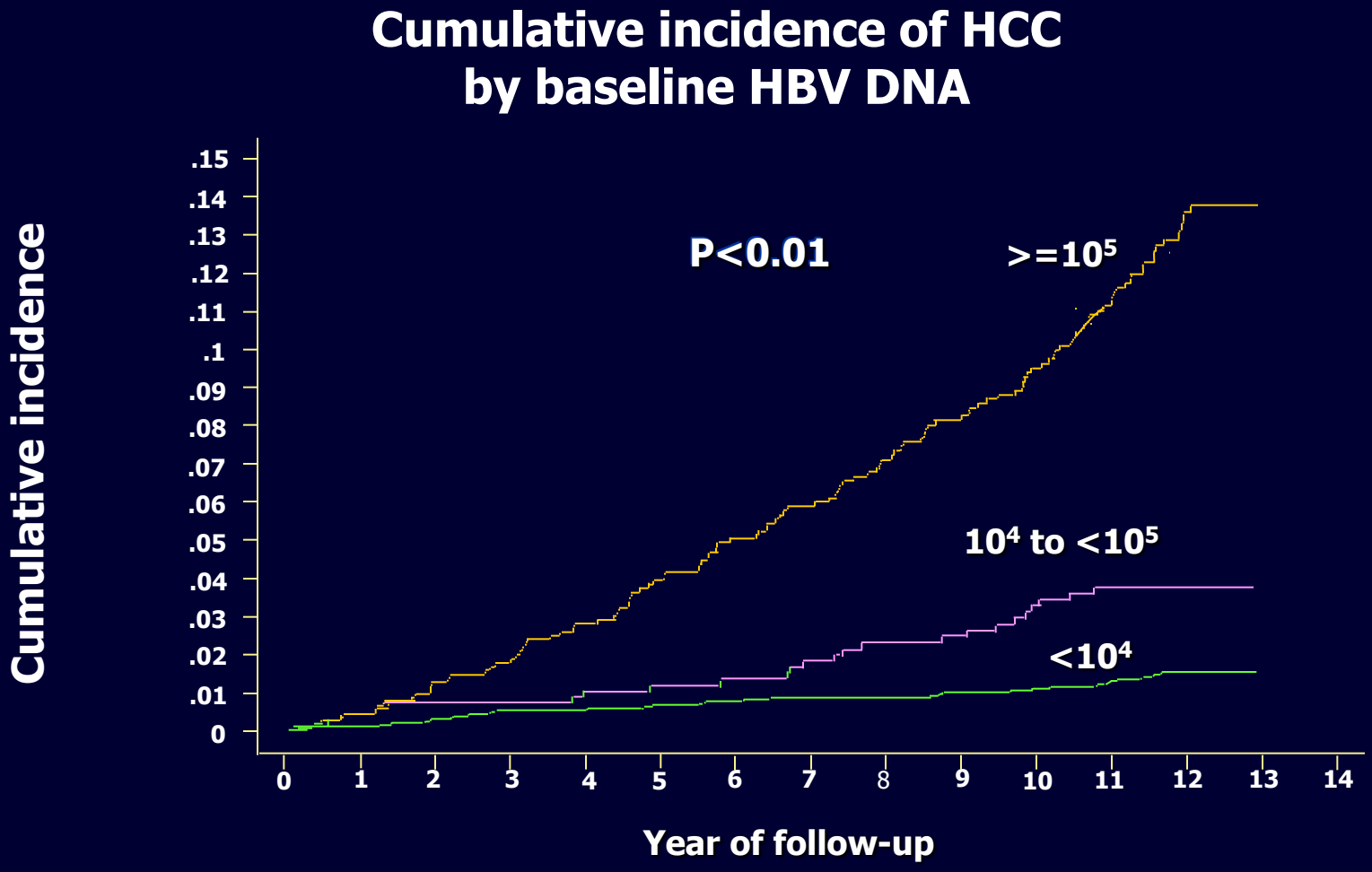
Risk of HCC and Cirrhosis According to Baseline HBV DNA





1. Chen CJ, et al. JAMA. 2006;295:65-73. 2. Iloeje UH, et al. Gastroenterology. 2006;130:678-686.

Viral Load Associated with Risk of HCC



Adjusted for gender, age, anti-HCV, habits of cigarette smoking and alcohol consumption.

Chen et al. 14th APASL. 2004. Poster

Persistent presence of HBeAg and persistently high serum HBV DNA levels are associated with increased risk of cirrhosis and HCC.

(**Ref: Liaw YF, et al. *N. Engl. J. Med.* 2002: 347;168-74**)

Treatment of HBV can prevent HCC

What are the Evidences?

Treatment of HBV can prevent HCC

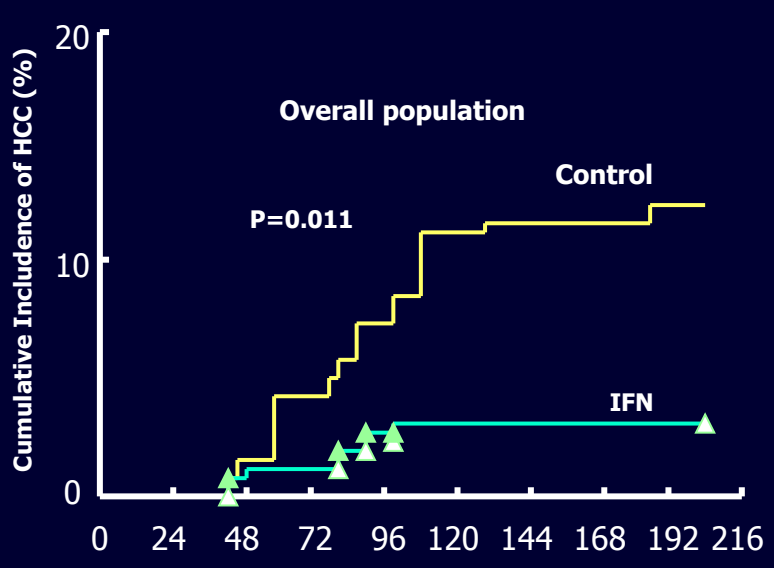
- Antiviral therapy
  - effective in causing prolonged lowering of serum levels of HBV DNA.
- Prolonged antiviral therapy
  - may reduce the risk of HCC among certain patients with chronic hepatitis B.

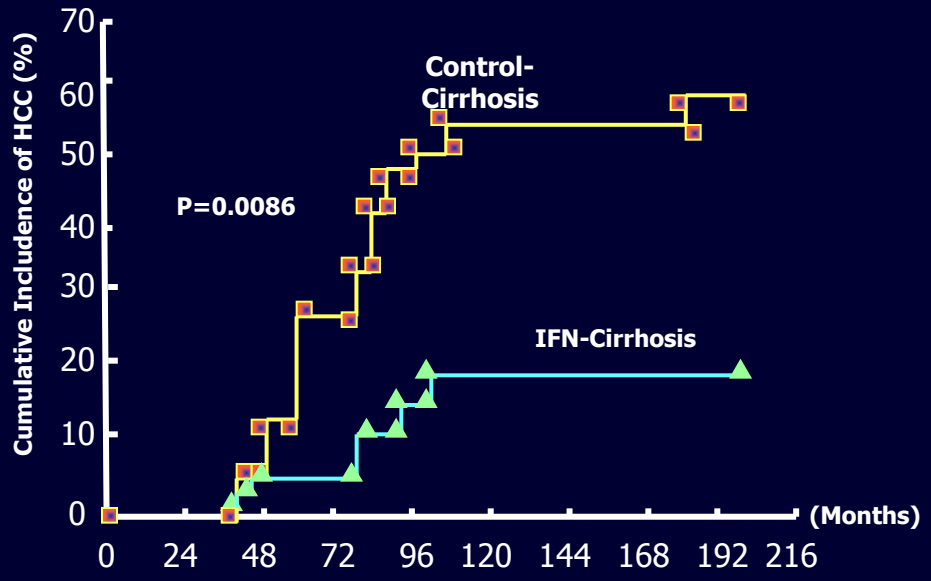
Evidence to support the notion that antiviral therapy can prevent HCC

- Prevention of HBV-related HCC with
  - Interferon
  - Nucleos/tide Analogue

Interferon Treatment

- 233 IFN –treated vs. 233 matched controls

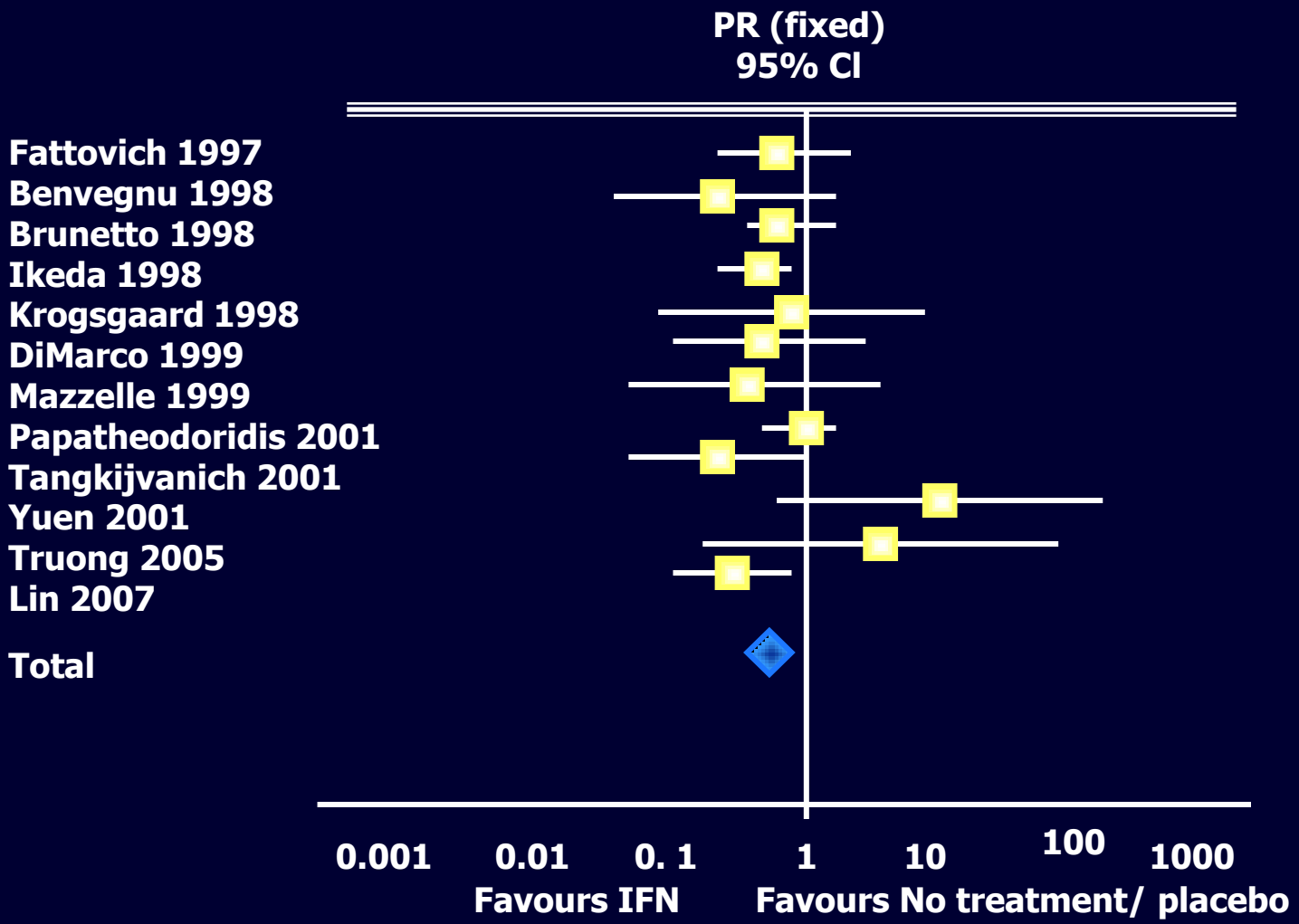




NB: HCC was reduced significantly only in patients with pre-existing cirrhosis (3/19 IFN vs 14/24 controls; p<0.01)

Lin et al, J Hepatol 2007; 40:45-52

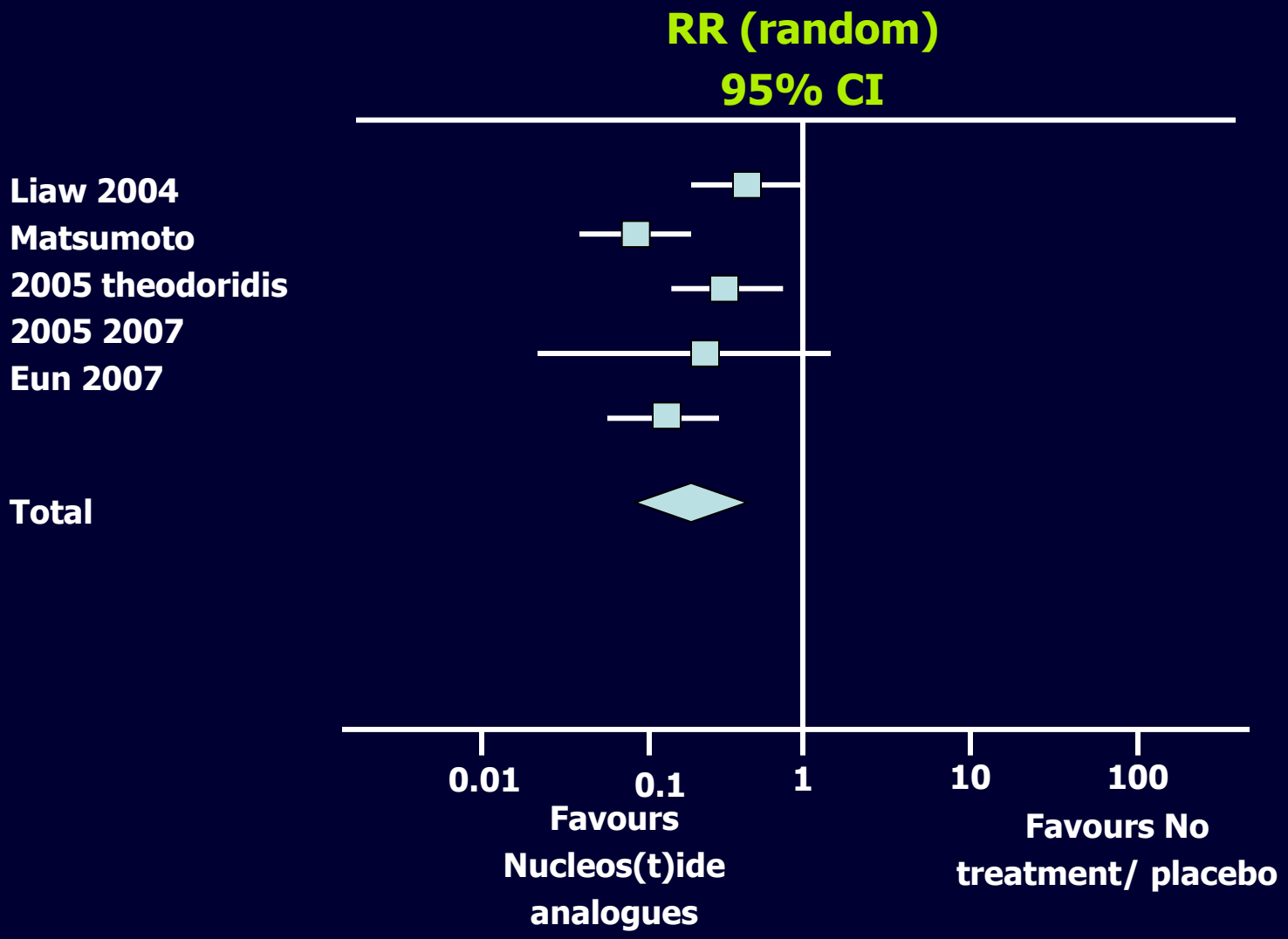
Prevention of HCC by IFN in CHB



Forest plot to compare interferon with placebo or no treatment in the development of HCC.

Sung et al., Aliment Pharmacol Ther 2008; 28:1067-77

Prevention of HCC by Nucleos/tide Therapy



Forest plot to compare interferon with placebo or no treatment in the development of HCC.

Sung et al., Aliment Pharmacol Ther 2008;28:1067-77

Conclusions

- **Successful treatment of CHB can decrease the incidence of HCC.**

- **Nucleos/tide analogues probably more effective than IFN**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YANGON G I & LIVER CENTRE

Treatment of Chronic Hepatitis B

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Today's Topics

- Goal of Therapy
- 4 Phases of Chronic HBV Infection
- When To Treat?
- Beyond the Guidelines: Treatment of Normal ALT Patients
- How to treat? With what drug?
- NAs When to stop?
- Combination Therapy
- HBsAg Quantification
- Newer Antiviral Therapy
- Summary: What is new in 2013?

Goal of Therapy

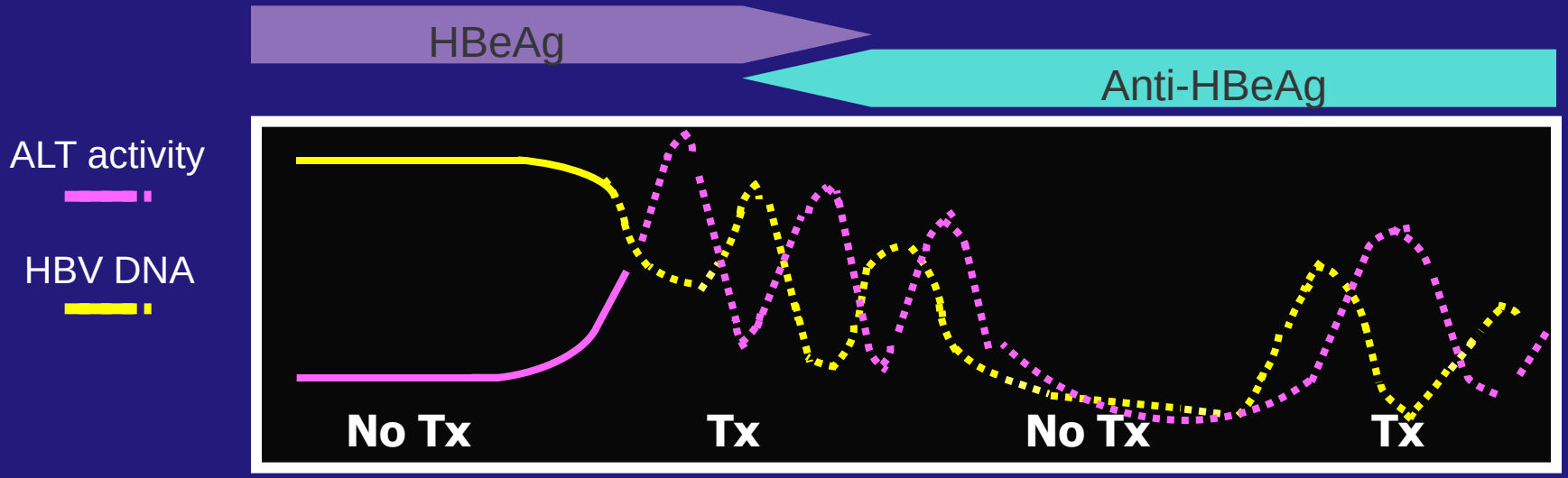
- **To improve quality of life and survival by preventing progression of the disease to**
  - **Cirrhosis**
  - **Decompensated cirrhosis**
  - **End-stage liver disease (ESLD)**
  - **HCC**
  - **Death**

- **This goal can be achieved**
  - **If HBV replication can be suppressed in a sustained manner**

(EASL CPGs: Management of chronic hepatitis B; J Hepatol 2009;50:227-42)

4 Phases of Chronic HBV Infection

Current Understanding of HBV Infection



Phase	Immune Tolerant	Immune Clearance	Inactive Carrier State	Reactivation
Liver	Minimal inflammation and fibrosis	Chronic active inflammation	Mild hepatitis and minimal fibrosis	Active inflammation

Optimal treatment times

Graham R. Foster. Clinical dilemmas in viral liver disease, 2010

When To Treat?

- **Traditional concept**
  - ALT based {< 2ULN → no Tx}
  - Biopsy based {< 3 HAI score (Ishak) → no Tx}
  - Not to treat if in immune-tolerant phase
- **Current and Controversial concept**
  - High viral load irrespective of ALT level
  - To treat even if in immune-tolerant phase

Guidelines for Starting Treatment

- **APASL (2012)**
  - **HBeAg positive**
    - **ALT >2 ULN and HBV DNA > 20000 IU/mL**
  - **HBeAg negative**
    - **ALT >2 ULN and HBV DNA > 2000 IU/mL**
  - **Advanced fibrosis or CL with any ALT level**
- **EASL (2012)**
  - **ALT >2 ULN and HBV DNA > 2000 IU/mL**
  - **ALT normal or high end**
    - **moderate to severe fibrosis even if ALT is normal.**
    - **Age, health status, family history of HCC or CL are also considered**

APASL, 2012 Update
EASL , Journal of Hepatology 2012, 57: 167-185

Beyond the Guidelines: Treatment of Normal ALT Patients

Antiviral Therapy in HBeAg (+) patients with ALT < 2x ULN

CON

- Belief that there's no disease progression, minimal histological lesions
- Immune tolerance – low probability of anti-HBe seroconversion
- (PEG-) IFN α : not effective
- NAs : inhibition of HBV replication
    - Probably life-long therapy in young patients : long-term safetly, patient reluctance , family planning?

Zouim F. Mason WS. Gut 2012,61 333-336,
EASL Clinical Practice Guidelines Management of Chronic Hepatitis B Virus Infection J Hepatol 2012,57:167-185

(PEG-)IFNα (pegylated)- interferon alpha:
NA: uncleos (t)ide analogue, HBV hepatitis Bvirus

Antiviral Therapy in HBeAg (+) patients with ALT < 2x ULN

PRO

- Maintenance of high HBV replication – increasing number of infected hepatocytes
- High risk of HBV transmission
- Patients with high HBV DNA levels are at risk of HCC regardless of ALT level

Zouim F. Mason WS. Gut 2012,61 333-336,
EASL Clinical Practice Guidelines Management of Chronic Hepatitis B Virus Infection J Hepatol 2012,57:167-185

(PEG-)IFNα (pegylated)- interferon alpha:
NA: uncleos (t)ide analogue, HBV hepatitis Bvirus

Clinical dilemma

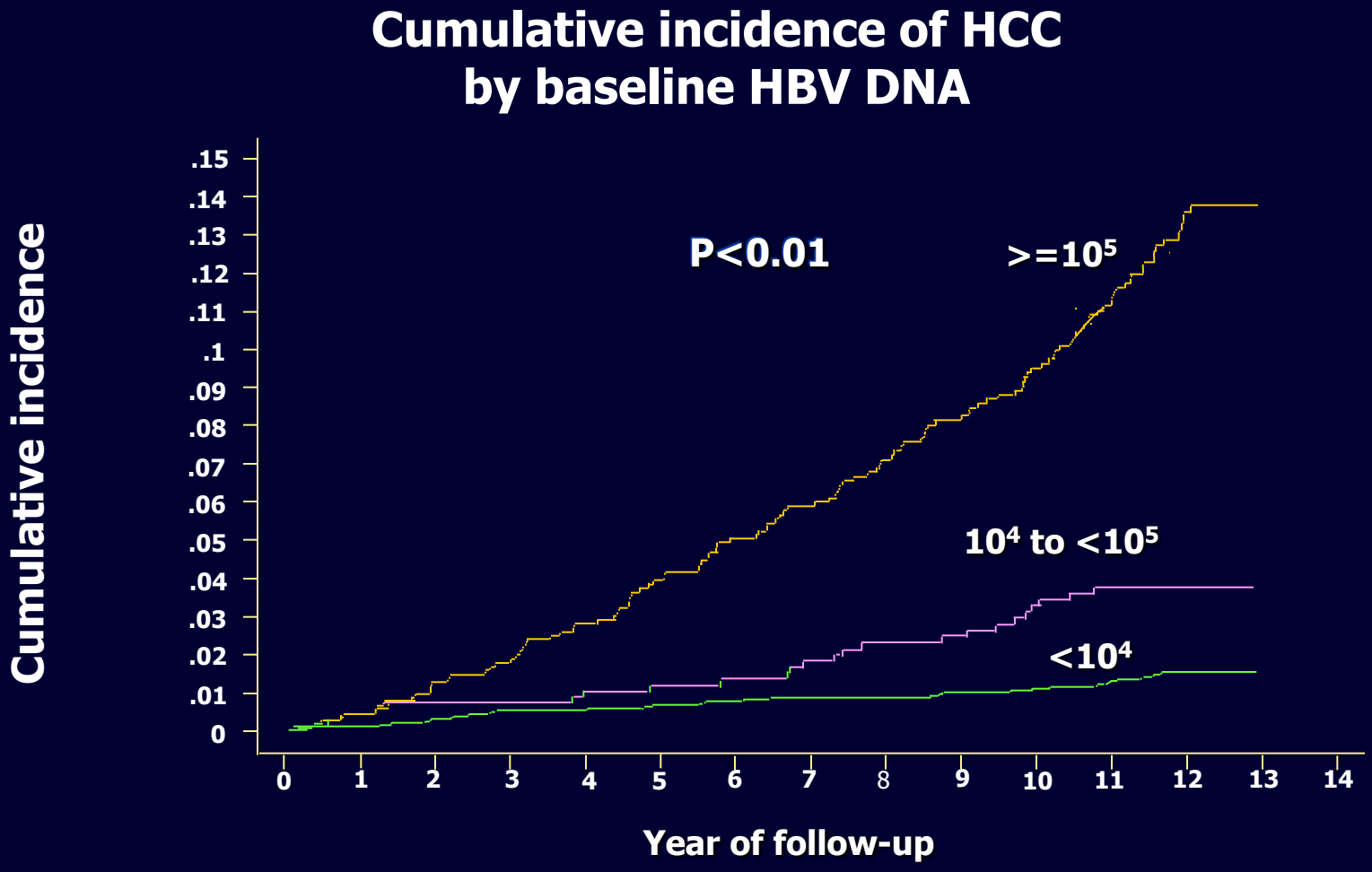
Should we treat immune tolerant patients to prevent HCC?

What is immune tolerance?

- Maternal HBeAg induces tolerance in neonate immune system to HBsAg and HBeAg
- Hepatitis B specific T cells are hyporesponsive
- Ineffective antigen processing
- Anergy, deletion, altered maturation of virus specific effector cells and expansion of regulatory T cells

Carey I et al J Virol 2011;85:2416

Viral Load Associated with Risk of HCC



Adjusted for gender, age, anti-HCV, habits of cigarette smoking and alcohol consumption.

Chen et al. 14th APASL. 2004. Poster

Immune Tolerance and HCC

- **Viral replication in immune tolerant expected to be very high 10^9-10^{10}**

- **Clonal hepatocyte repopulation: higher risk of HCC[4]**

1 Wang HY, J Virol 2010;84: 3454-63
2 Carey I et al J Virol 2011;85:2416
3 Xu C Virology 2007;359:283e94.
4 Marongiu F, et al Am J Pathol 2008;172:857

Hypothesis: clonal hepatocyte repopulation

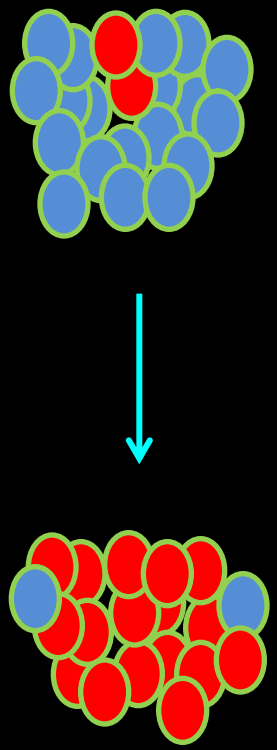
Chronic hepatocellular injury and/or impaired regeneration

↓

Emergence of phenotypically altered cells resistant to cytotoxicity and/or to growth arrest

↓

Selective clonal growth and development of dysplasia with altered growth pattern



Maroglu F, et al Am J Pathol 2008;172:857

Tx of Normal ALT Patients

- Two pediatric studies
  - Sequential therapy with LAM → IFN
  - HBsAg loss/seroconversion 17-21%

- LAM reduction in viral levels allowed
  - HBV specific cell mediated immunity,
  - reversal of hyporesponsiveness
  - sets platform for immune response to IFN

Carey I et al JOURNAL OF VIROLOGY, Mar. 2011, p. 2416-2428
Poddar U et al Journal of Viral Hepatitis, 2013, 20, 311-316

How to treat?
With what drugs?

Drugs available

- Immunomodulators
  - Interferons
  - Pegylated Interferon
- Nucleoside/tide analogues (NA)
  - Lamivudine
  - Adefovir
  - Entecavir
  - Tenofovir

Interferons

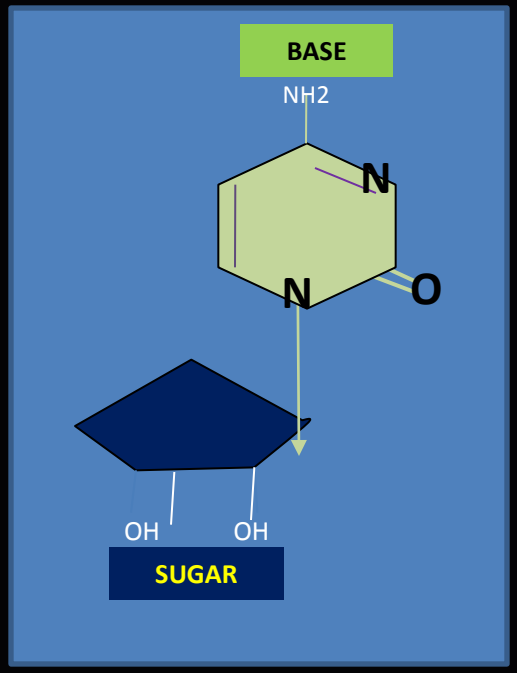
- Injection Pegylated Interferon
  - IFN α2a
    - Injection Pegasys (Roche)
      - 180 μg fixed dose
    - **The only IFN approved by US FDA for the Tx of CHB**
  - IFN α2b
    - Injection PegIntron (MSD)
      - Weight based
      - BW in kg x 1.5 = dosage
      - 50 μg, 80 μg, 100 μg

Available Nucleoside/tide Analogues

- Lamivudine
- Adefovir
- Entecavir
- Tenofovir

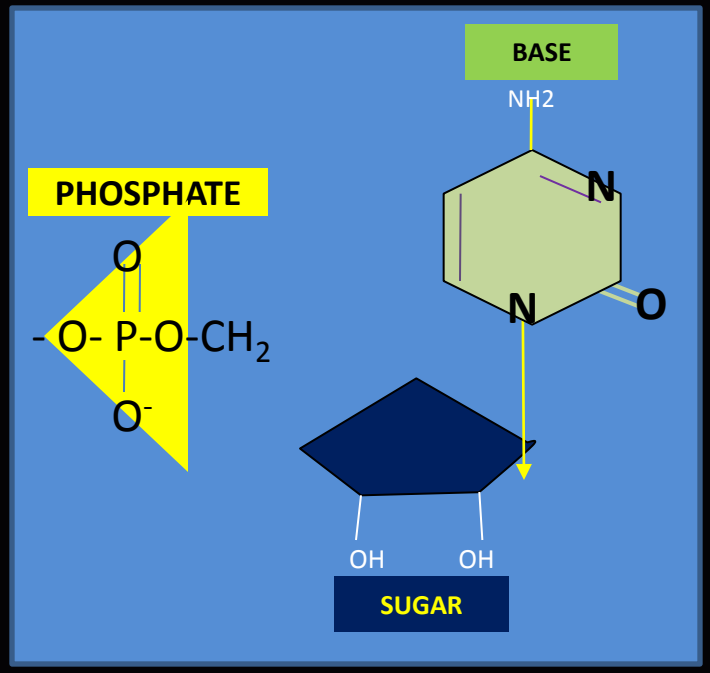
Nucleoside

Nitrogen-containing ring structures attached to a sugar.



Nucleotide

Addition of a phosphate produces a nucleotide.



HBV Treatment Goals

Sustained Remission

PEG-IFN

Low viremia

ALT normalization

Immune control, no further need to continue the drug

Maintained Remission

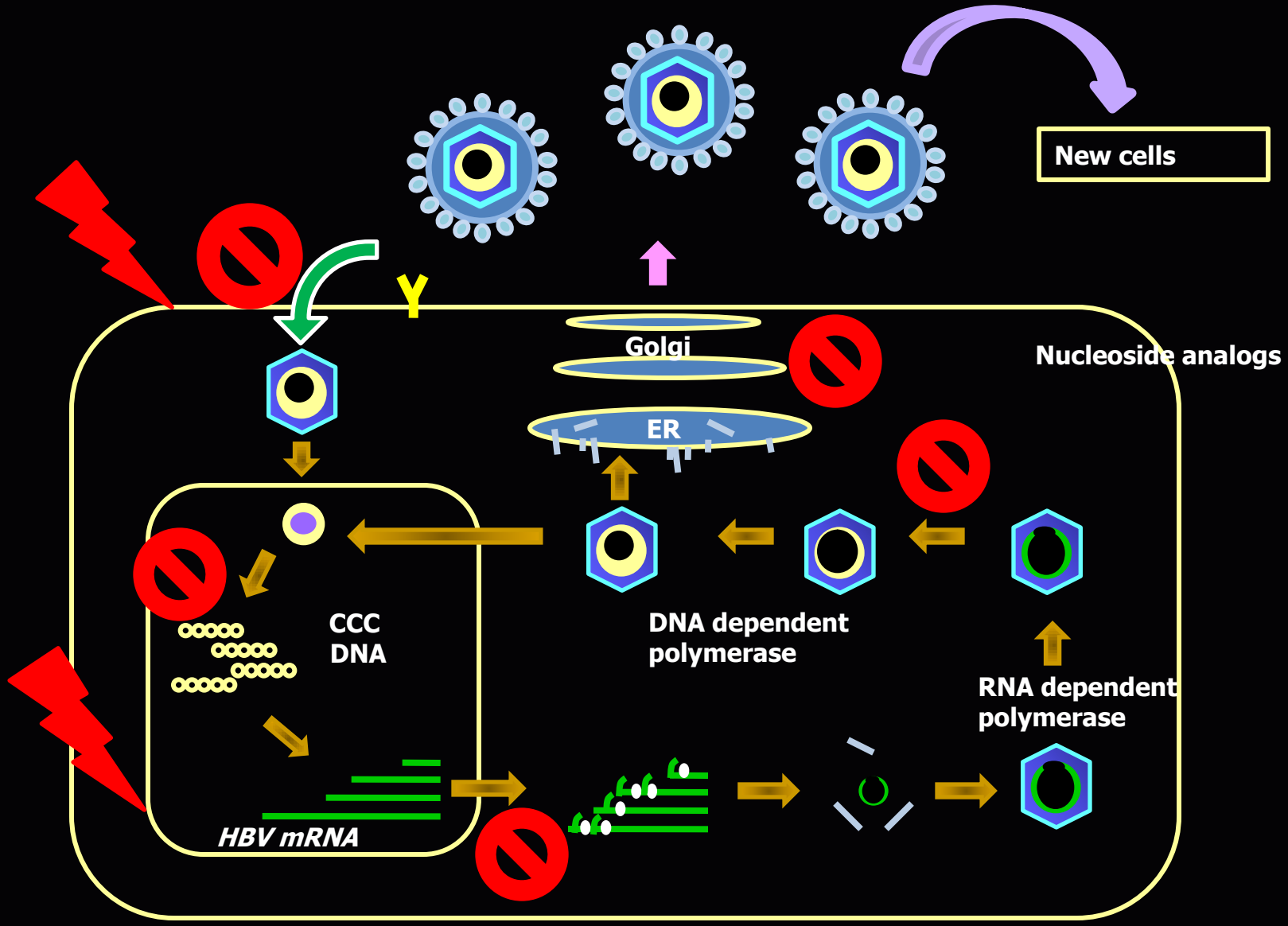
NA

Low viremia

ALT normalization

No immune control, continued need for antiviral drugs

Can treatment with NA be stopped?



Can therapy with NAs be stopped?

- **Long-term viral suppression**
- **Off-therapy response**
  - **unclear – limited sustained immune control**
- **‘When can therapy be stopped?’**
- **Monitoring qHBsAg may help us identify patients who can stop NAs with a low chance of relapse**

When to stop?

Current guidelines about NA cessation
Current suggestions

	AASLD 2009[1]	APASL 2012[2]	EASL 2012[3]
HBeAg-positive patients	6 months HBeAg seroconversion & undetectable HBV DNA	6 month HBeAg seroconversion & undetectable HBV DNA	12 months HBeAg seroconversion & undetectable HBV DNA
HBeAg-negative patients	HBsAg seroclearance	12 months undetectable HBV DNA	-

[1]Lok, Hepatology 2009; [2]Liaw APASL 2012, [3]EASL, J Hepatol 2012

Can therapy with analogues be stopped?

- HBeAg (+)
  - After HBe sero-conversion
  - After 6 months of additional therapy
  - In non cirrhotic
- HBeAg (-)
  - Never
  - HBs seroconversion nearly never happens
- COL
  - Never

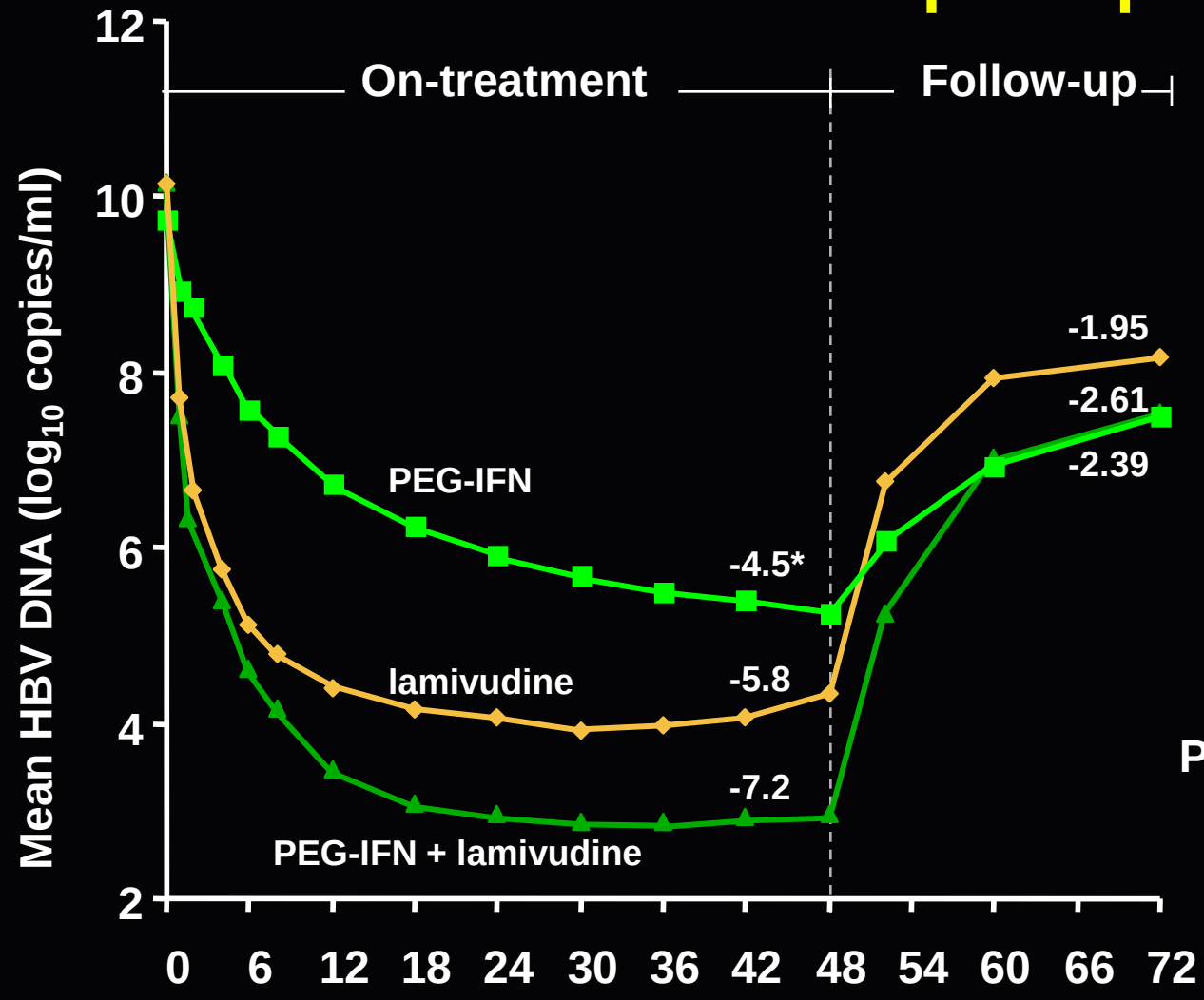
Long-term NA Treatment Conclusions

- Good virological response
  - potent last generation NA with high genetic barrier
- Profound improvement in inflammation & fibrosis score
- Reduction of liver failure and most probably also of HCC and all cause mortality
- NA therapy cannot be stopped in vast majority of patients

Combination therapy

The future for HBV treatment: combination of a potent NA and PEG-IFN

On-therapy HBV DNA Suppression and End of Follow-up Responses



PEG-IFN

HBeAg seroconversion at EOF = 32%

Lamivudine

HBeAg seroconversion at EOF = 19%

PEG-IFN + lamivudine

HBeAg seroconversion at EOF = 27%

*all numbers shown are $\log_{10}$ reduction from baseline

Lau G. et al. N Engl J Med 2005;352:2682-95.

Combination Therapy

- Two pediatric studies
  - Sequential therapy with LAM → IFN
  - HBsAg loss/seroconversion 17-21%

- LAM reduction in viral levels allowed
  - HBV specific cell mediated immunity,
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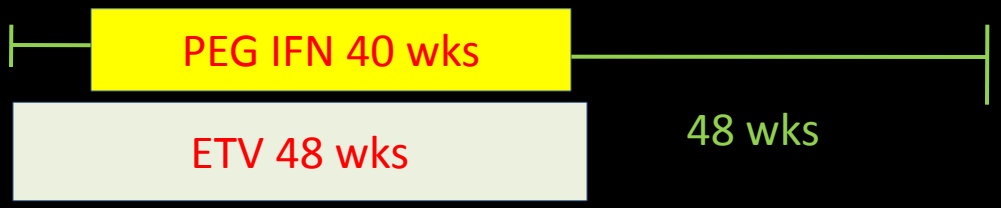
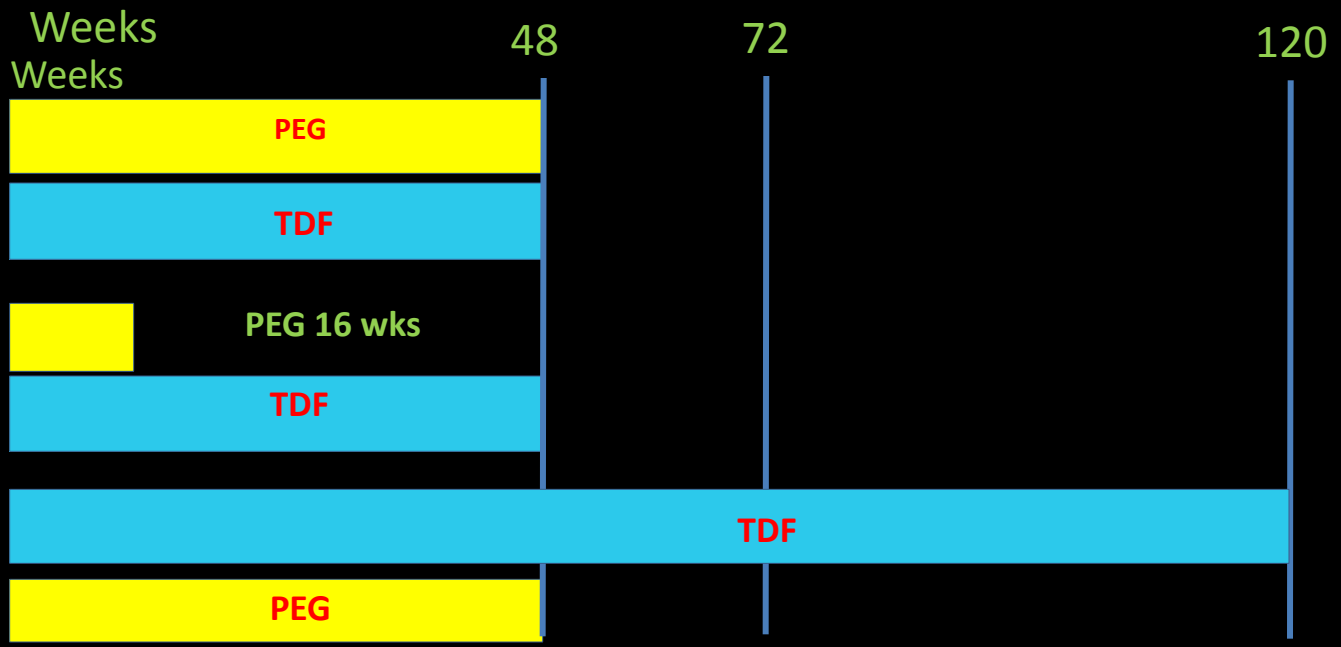
Carey I et al JOURNAL OF VIROLOGY, Mar. 2011, p. 2416-2428
Poddar U et al Journal of Viral Hepatitis, 2013, 20, 311-316

Coming back to immune modulation…

NIDDK HBRN:

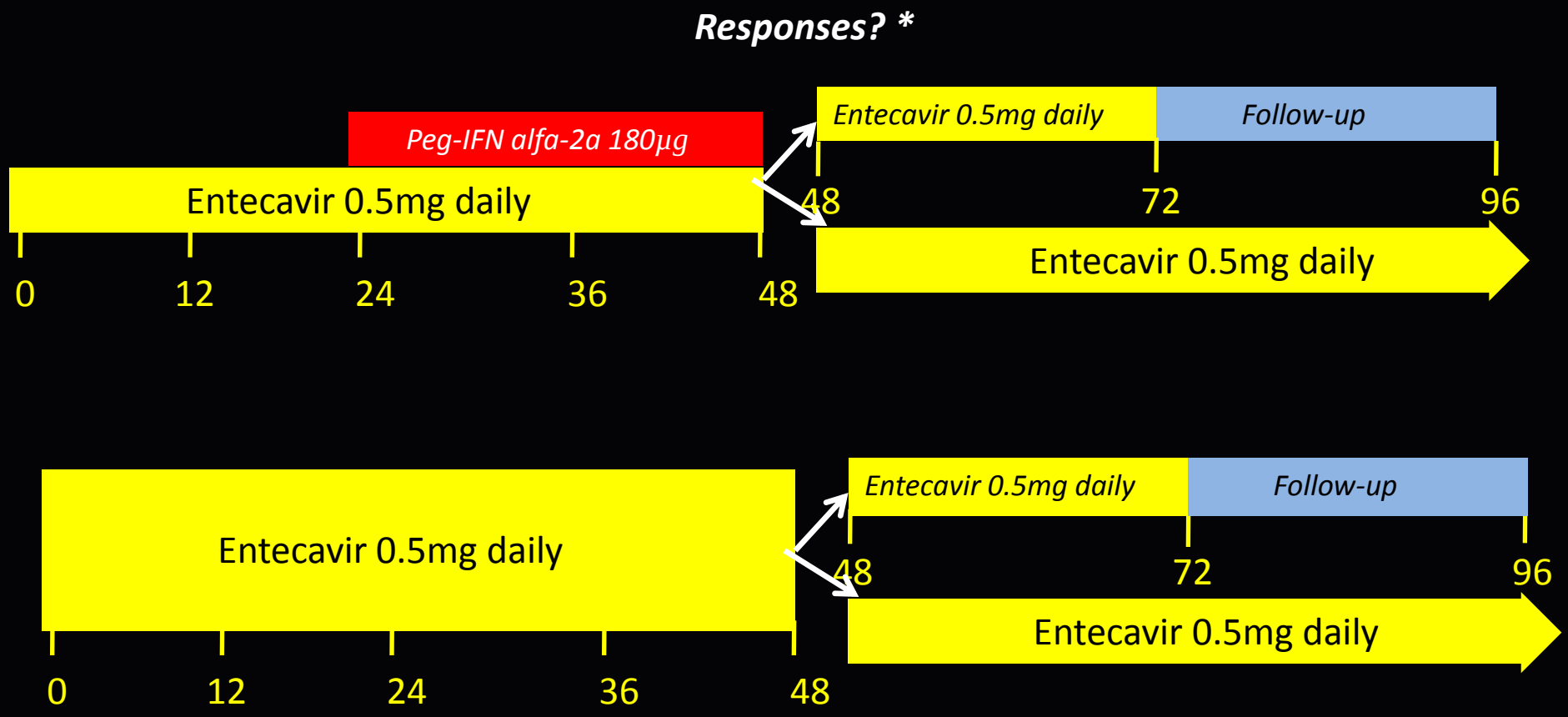


Tenofovir +/- PEG IFN



ETV and PEG-IFN (ARES Study)

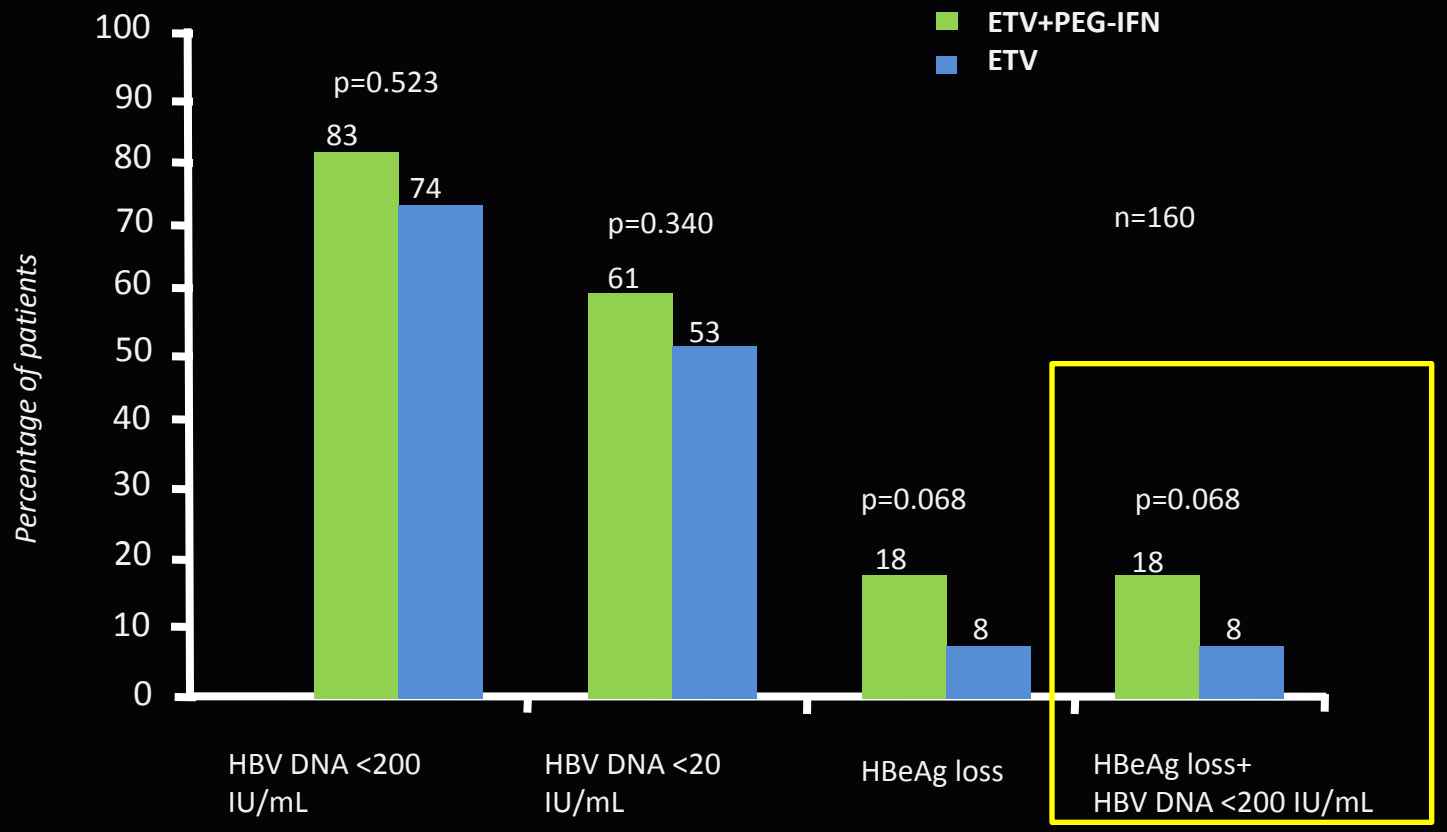
- HBe Ag positive study
- Multicenter, open-label, randomized controlled trial



Response: combined presence of HBeAg loss and HBV DNA level <200 IU/ml at week 48

Sonneveld et al. AASLD 2012

ETV and PEG-IFN (ARES Study)
Virological outcomes at week 48

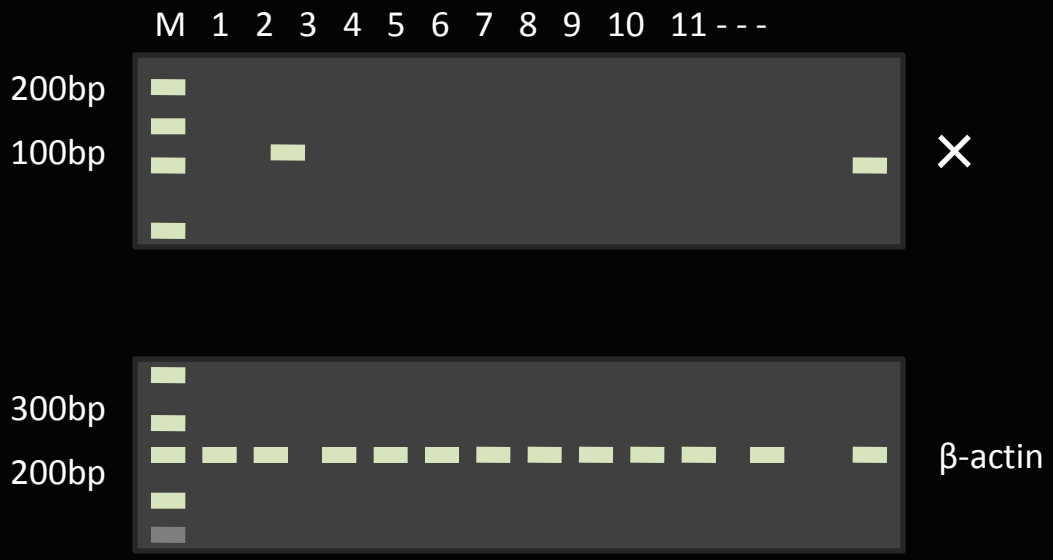


Sonneveld et al. AASLD 2012

New On-treatment Monitoring Test: HBsAg Quantification

HBsAg loss=cccDNA very low

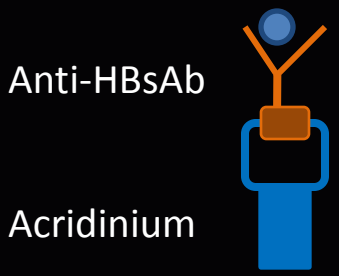
- 29 biopsies : HBsAg loss
- HBV DNA(+): 100%(1,68 cop/cell)
- ccc DNA(+) : 79%(0,03 cop/cell)



Yuen et al., Gastroenterology 2008

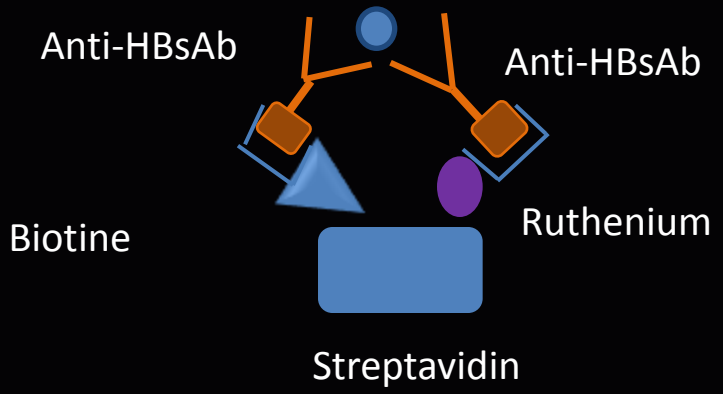
HBsAg quantification: technics

Architect plateform



(<0.05-250 UI/ml
Dilution manuelle 1/120 ou 1/500)

Elecsys HBsAg II



(<0.05-52 000 UI/ml
dilution automatique 1/100 ou 1/400)

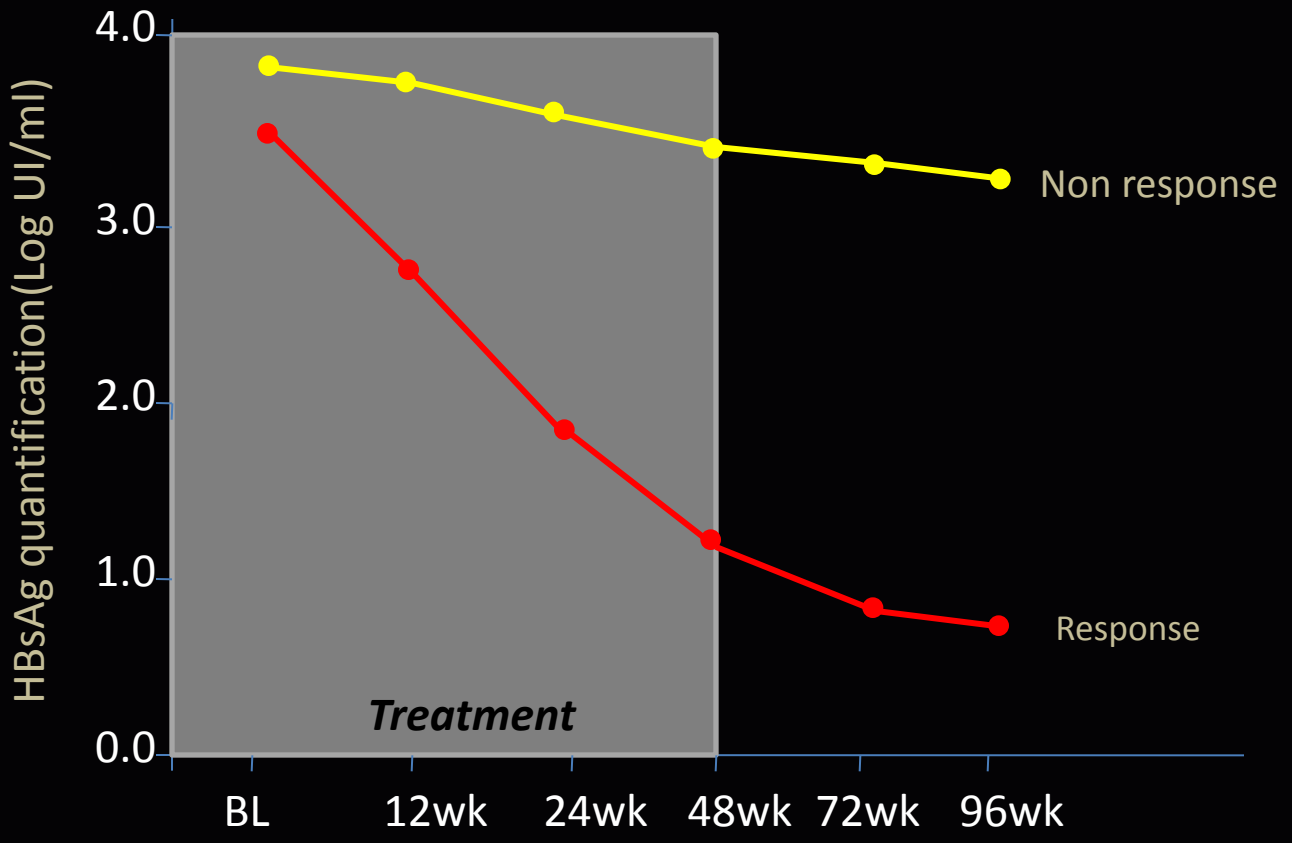
0.05 UI/ml HBsAg  4000 viral particules /ml

Different meanings of HBV DNA and HBsAg in CHB

	HBV DNA	HBsAg
Virology	Dane particle	Dane particle and subviral particles
Natural history	Reduced after HBeAg seroconversion but relapse on immune escape	Very slow reduction over time regardless of HBV DNA levels or disease activity
Implication	Viral replication	Immune clearance of infected hepatocytes

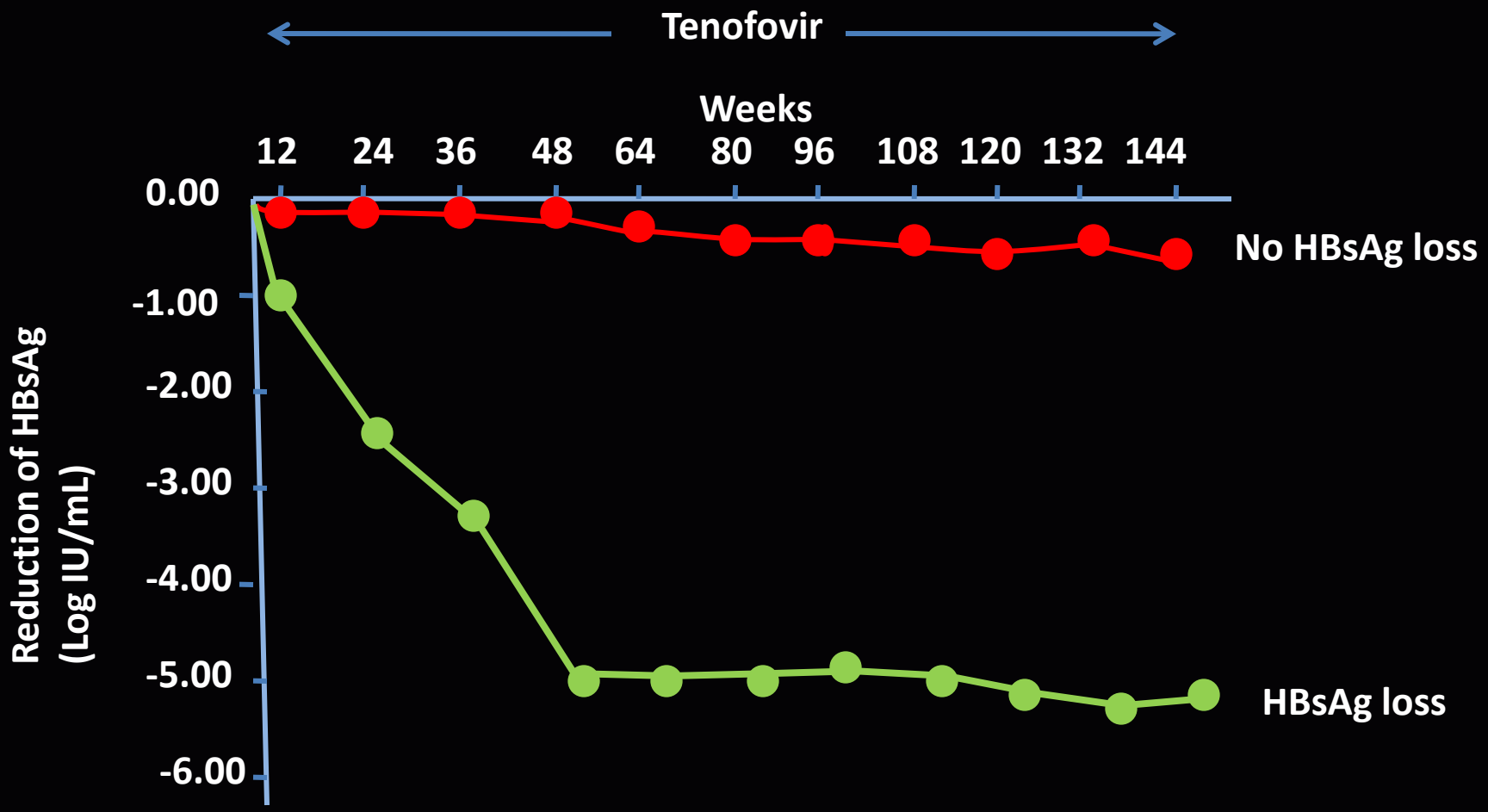
HBs Ag quantification

PegIFN-α2a,HBeAg-negative



Moucan R et al., Hepatology 2009, 49 1151-7

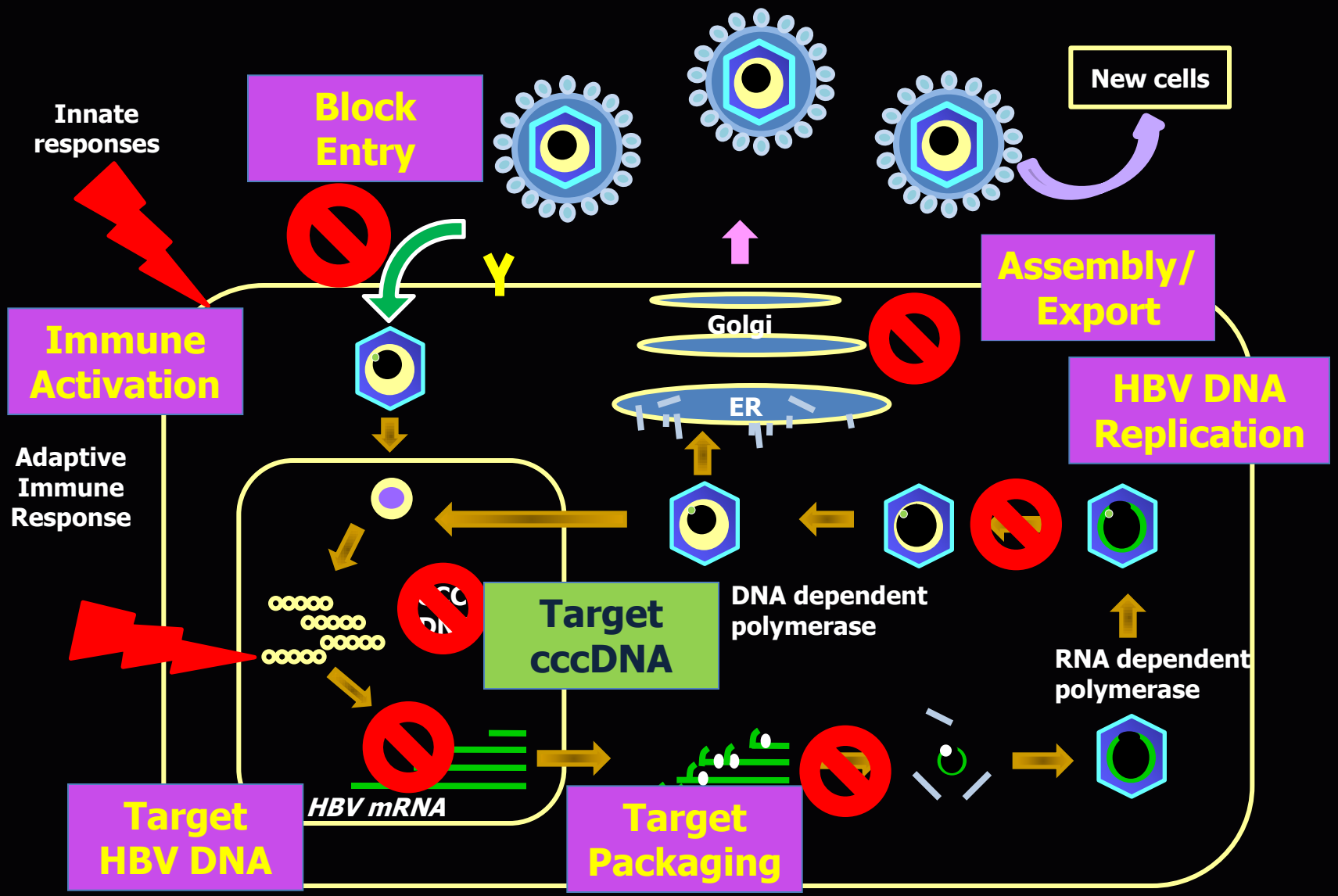
HBsAg kinetics
Tenofovir



(Heathcote E.J., et al., AASLD 2009, Gane E, et al, EASL 2010)

Newer Antiviral Therapies

Targeting Different Stages in the HBV Lifecycle



Summary: What is new in 2013 ?

- Lower threshold for determining transition to immune active phase or newer indications for HBV Tx
  - HBV DNA (slightly lower?)
  - ALT levels (slightly higher?)
  - Histologic evidence of inflammation (a little?)
  - "Old" young adult
- Combination therapy
- HBsAg quantification (qHBsAg) for on-treatment monitoring for the prediction of cure.
- Newer antivirals

Thank You