New therapeutic strategies in HBV patients

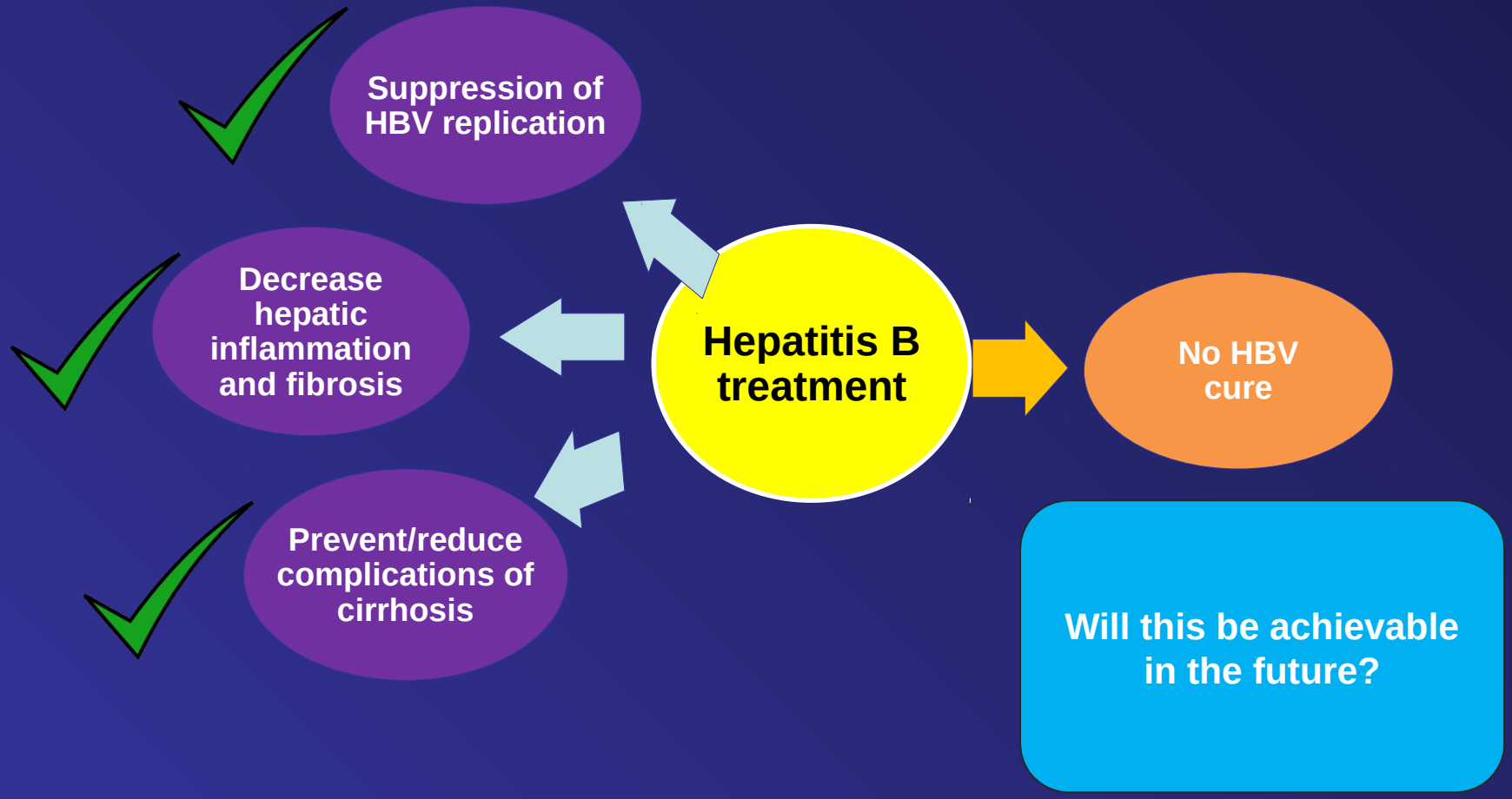
Philippe HALFON
MD, PhD

Associate Professor of Medecine

Internal Medecine and Infectious Diseases,
Hopital Europeen,
Marseille, France.

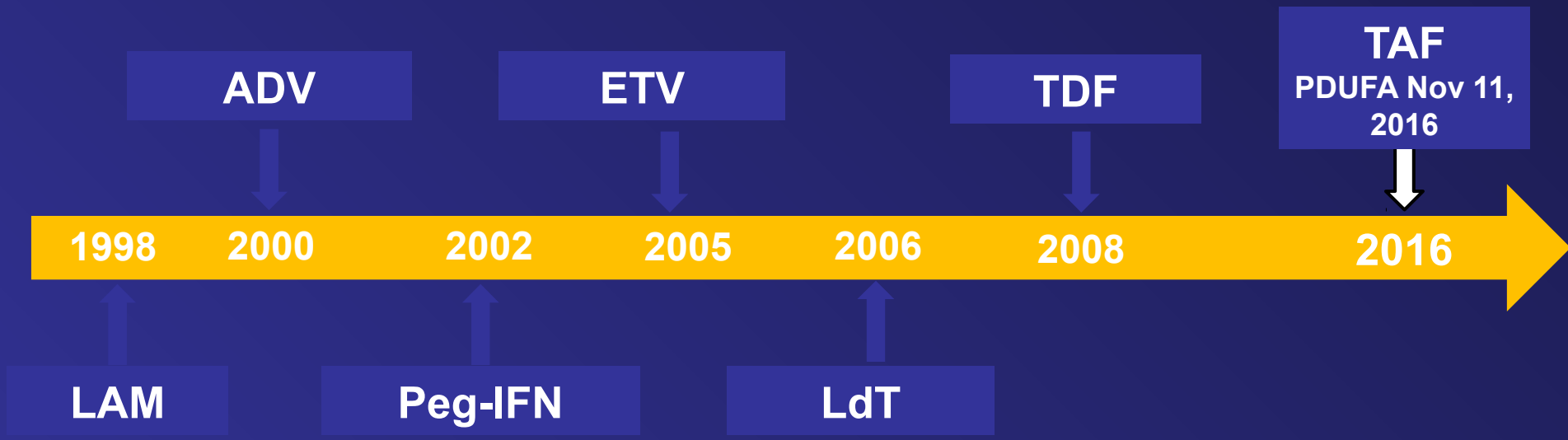
NUC + PEG IFN, HBsAg Clearance

HBV Treatment: achievements and ongoing challenges



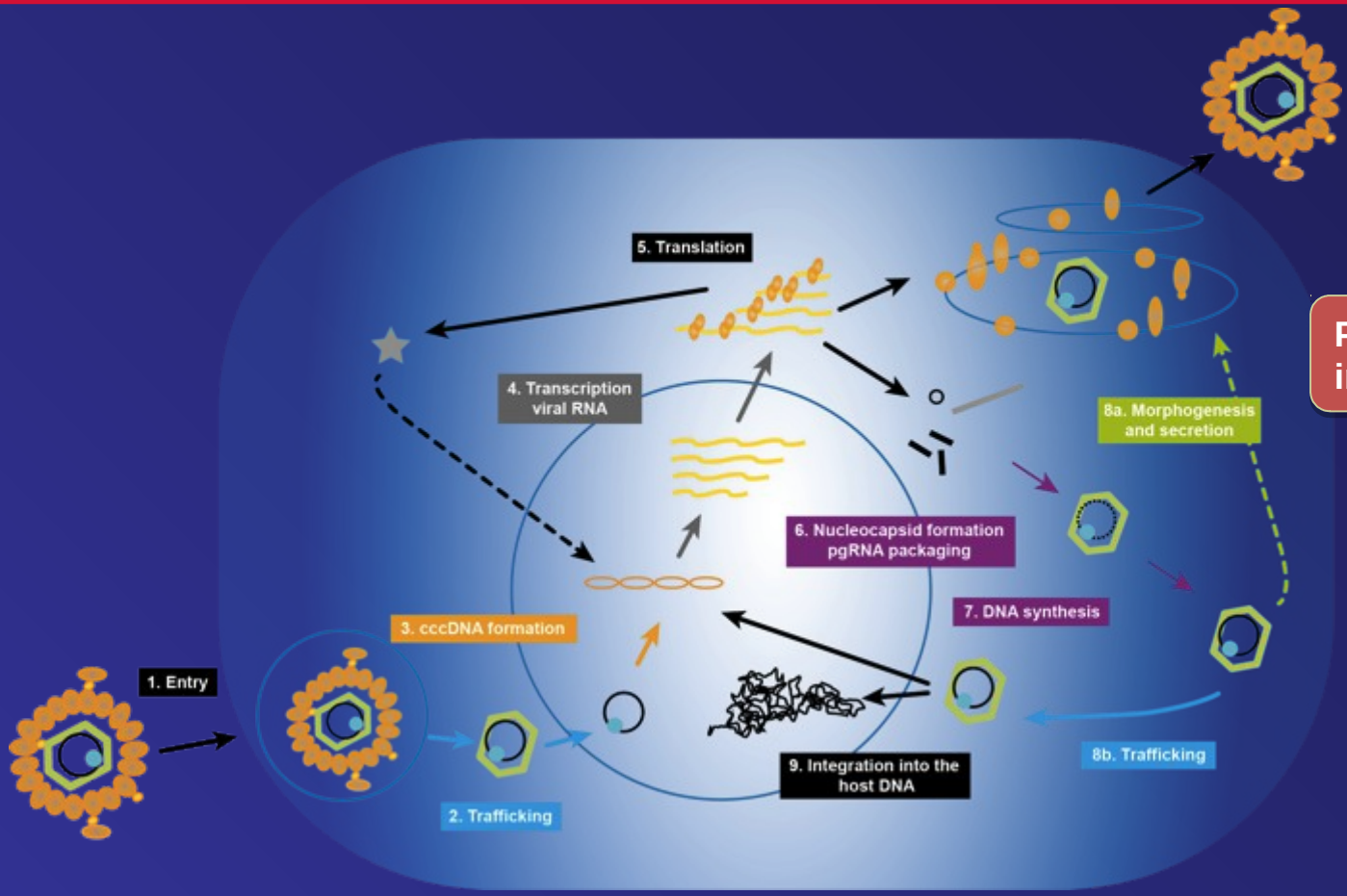
Liaw YF, et al. N Engl J Med 2004;351:1521–31;
Marcellin P, et al. Lancet 2013;381:468–75

Evolution of Current CHB Therapies



Terrault NB et al. Hepatology 2015; Published online November 13, 2015: doi:10.1002/hep.28156.
Martin P, et al. Clinical Gastroenterology and Hepatology 2015; Published online July 15, 2015: http://dx.doi.org/10.1016/j.cgh.2015.07.007
Lo AO et al. Expert Rev Gastroenterol Hepatol. 2014
Hepatitis B Foundation. Approved drugs for adult. Available at: http://www.hepb.org/patients/hepatitis_b_treatment.htm (accessed February 2016)

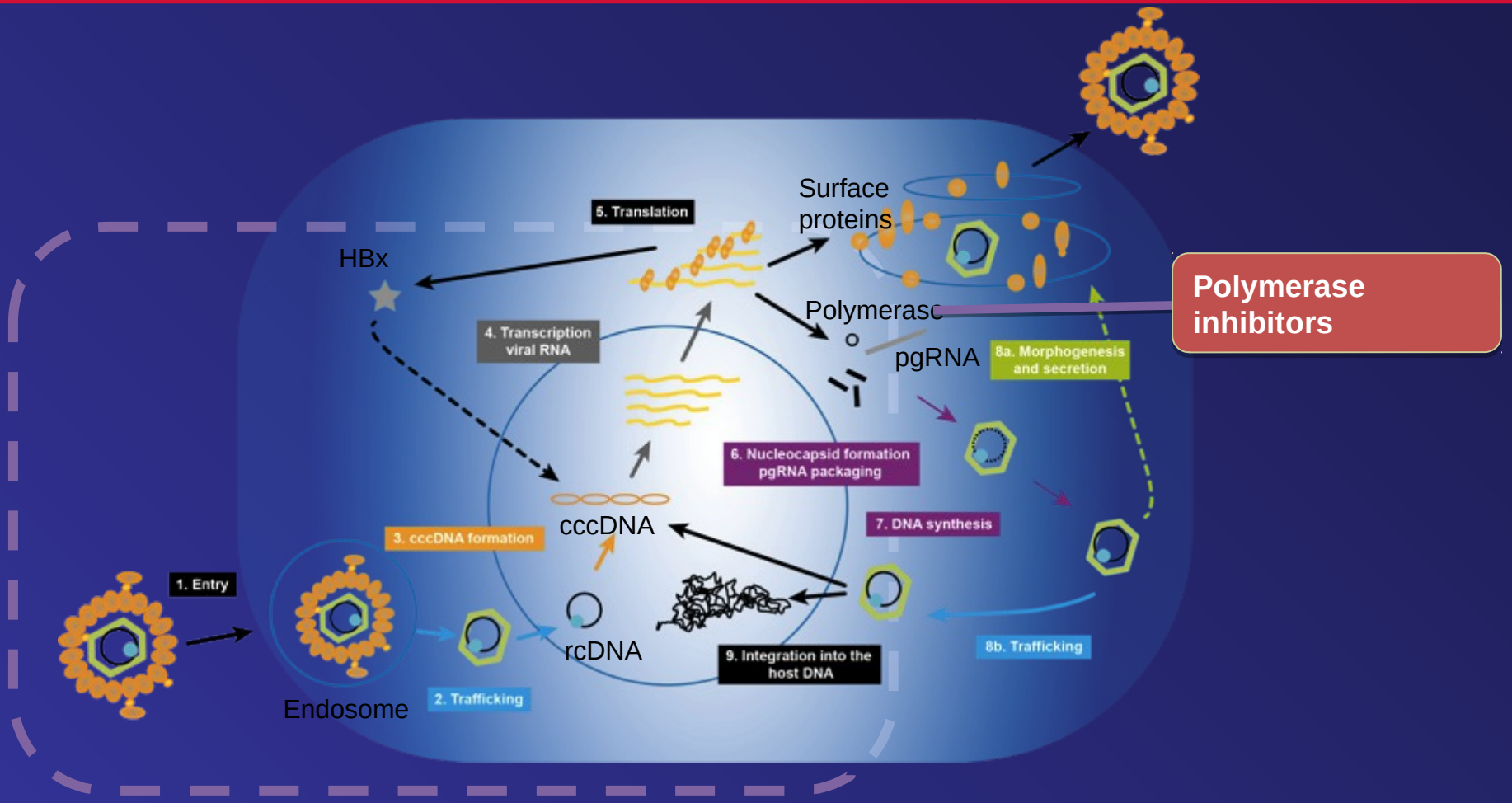
Currently available agents act via polymerase inhibition…



Polymerase inhibitors

pgRNA: pregenomic RNA

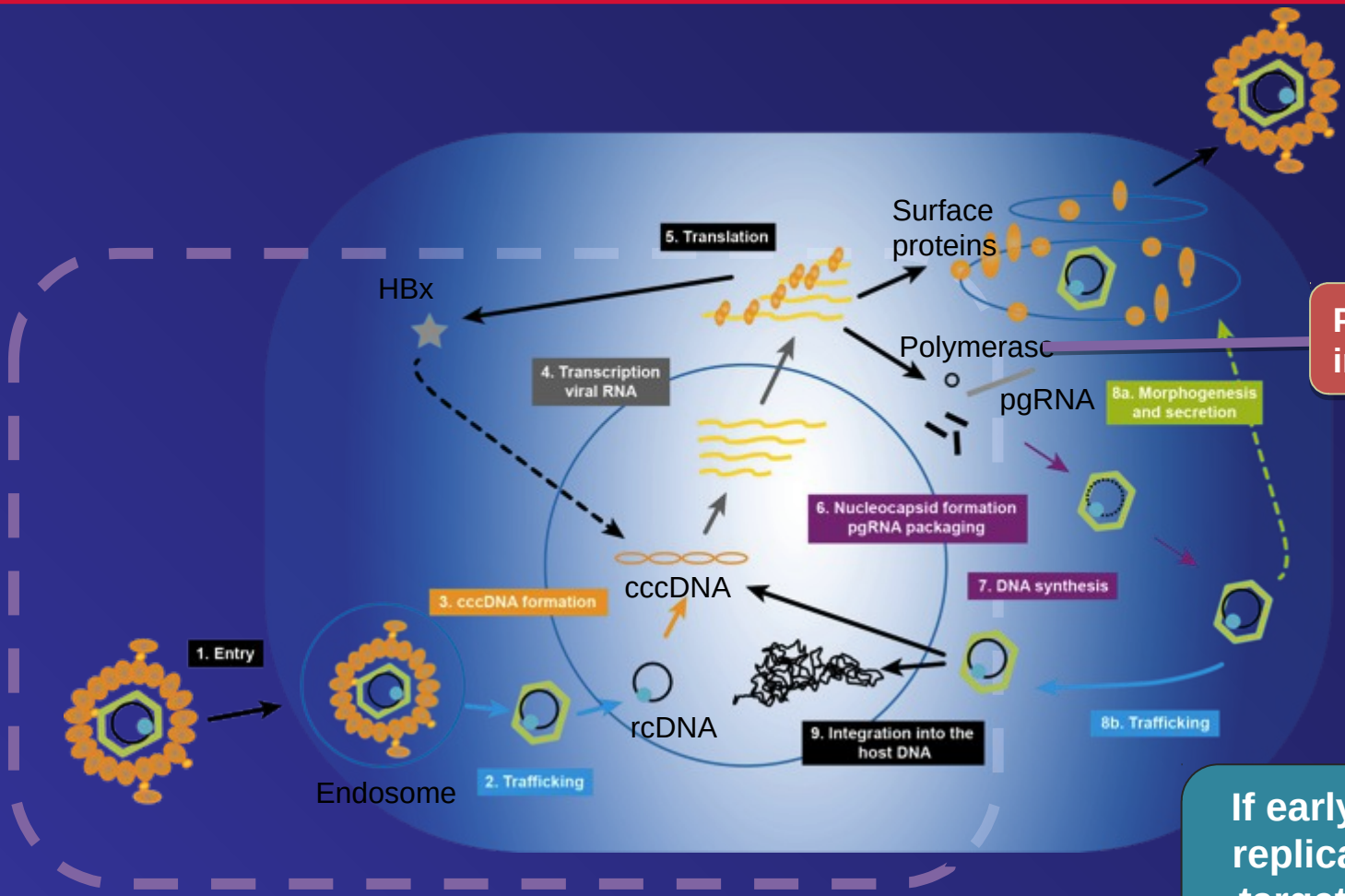
…and do not affect most of the HBV replication cycle



Zoulim F, et al. Antiviral Res 2012;96:256–9
Available at: www.hepb.org/professionals/hbf_drug_watch.htm (accessed April 2016)

HBx: HBV X protein; rcDNA: relaxed circular DNA

…and do not affect most of the HBV replication cycle



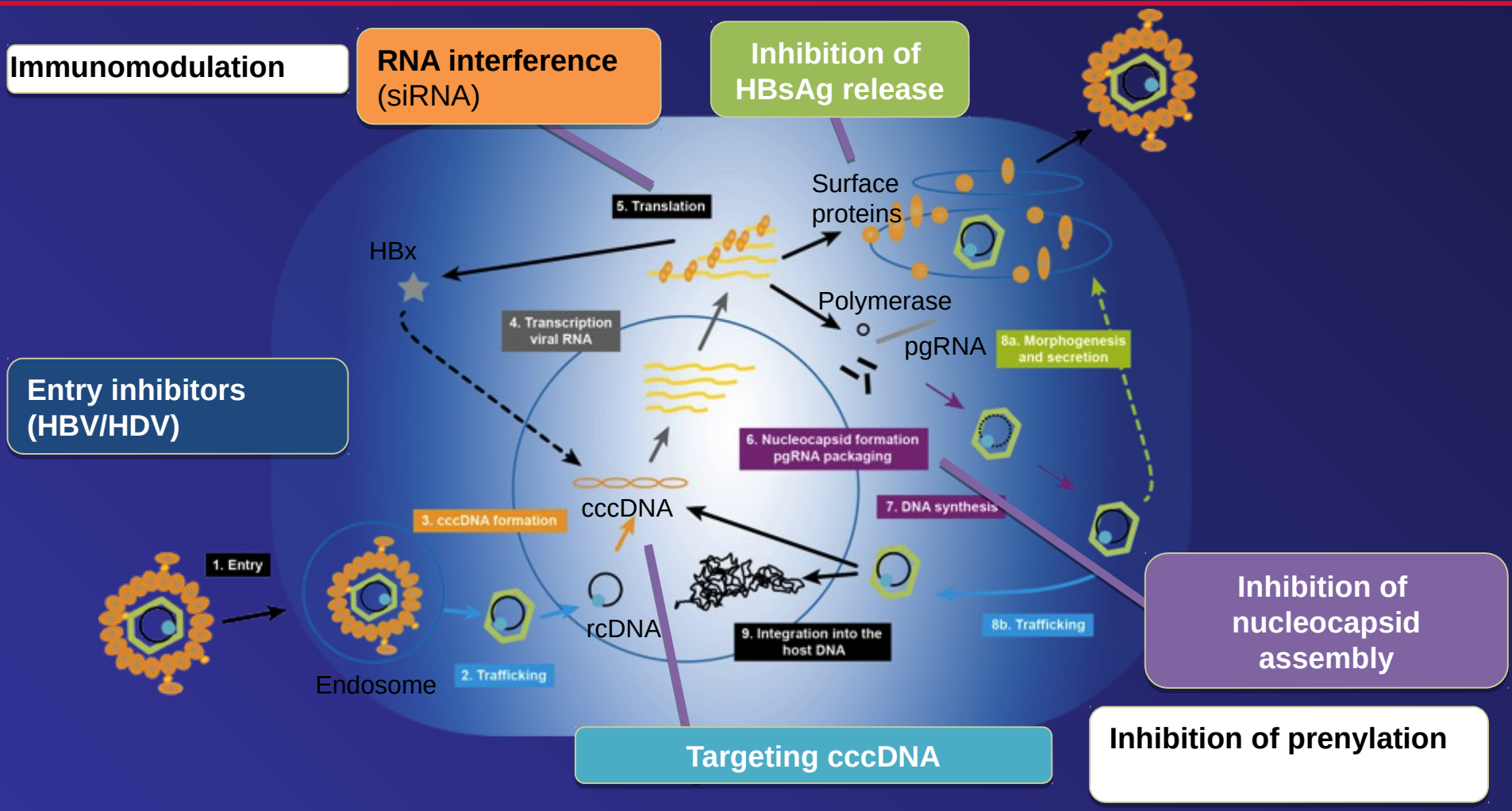
Polymerase inhibitors

If early stages of the replication cycle are targeted could HBV be eradicated?

Zoulim F, et al. Antiviral Res 2012;96:256–9
Available at: www.hepb.org/professionals/hbf_drug_watch.htm (accessed April 2016)

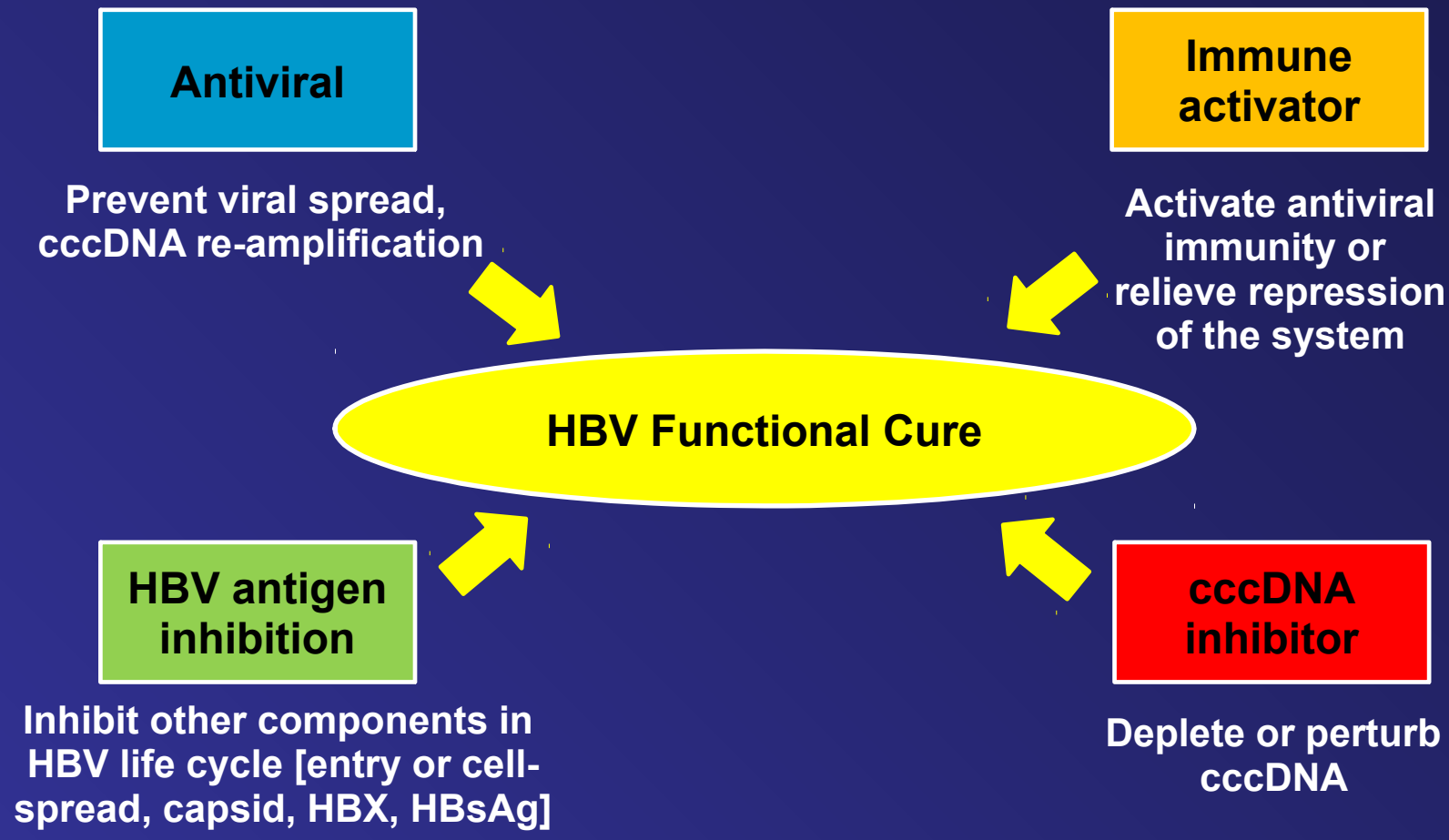
HBx: HBV x protein; rcDNA: relaxed circular DNA

Other targets may have the potential to cure HBV in the future



Zoulim F, et al. Antiviral Res 2012;96:256–9
Available at: www.hepb.org/professionals/hbf_drug_watch.htm (accessed Apr 2016)

How may a HBV curative regimen look in the future – a combination approach?



Courtesy of Prof Dr Harry Janssen

What does HBV cure mean?

Functional Cure

Clinical resolution sustained off therapy

- No inflammation: normal ALT and liver biopsy
- HBsAg loss
- HBsAb gain

Currently achievable in only a few patients

Complete Cure

Virological cure

- Clinical resolution sustained off therapy

+

- Loss of cccDNA

Not achievable… YET

ALT: alanine aminotransferase; cccDNA: covalently closed circular DNA; HBsAg: hepatitis B surface antigen; HBsAb: hepatitis B surface antibody

Outcome case

- Female, 35yo, Chinese
- ALT 126 IU/L (N=40)
- HBeAg (-)
- HBV DNA = 200 000 UI/mL
- HBsAg = 6050 UI/mL
- Liver biopsy: A2 F2
- Proposed treatment : NA = Entecavir

ARTICLE IN PRESS

Clinical Practice Guidelines

EASL | JOURNAL OF HEPATOLOGY

EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection☆

European Association for the Study of the Liver*

- **The loss of HBsAg is regarded as the optimal treatment endpoint**

termed '**functional cure**', but it is only rarely achieved with our current antiviral armamentarium.

- The main advantage of HBsAg loss is that it allows **a safe discontinuation of antiviral therapy.**

- As chronic HBV infection cannot be completely eradicated due to the persistence of cccDNA and integrated HBV DNA :

it remains unclear whether HBsAg loss adds to the prevention of the long-term complications of chronic HBV infection beyond what can be achieved by the suppression of HBV DNA replication alone

In order to reach an HBs Ag loss : which strategies would you want to implement?

- Long term NA treatment
- Add-on therapy using IFN
- Switch-on therapy
- Simultaneous combination
- Entecavir plus tenofovir combination therapy
- Switch to TAF
- Others?

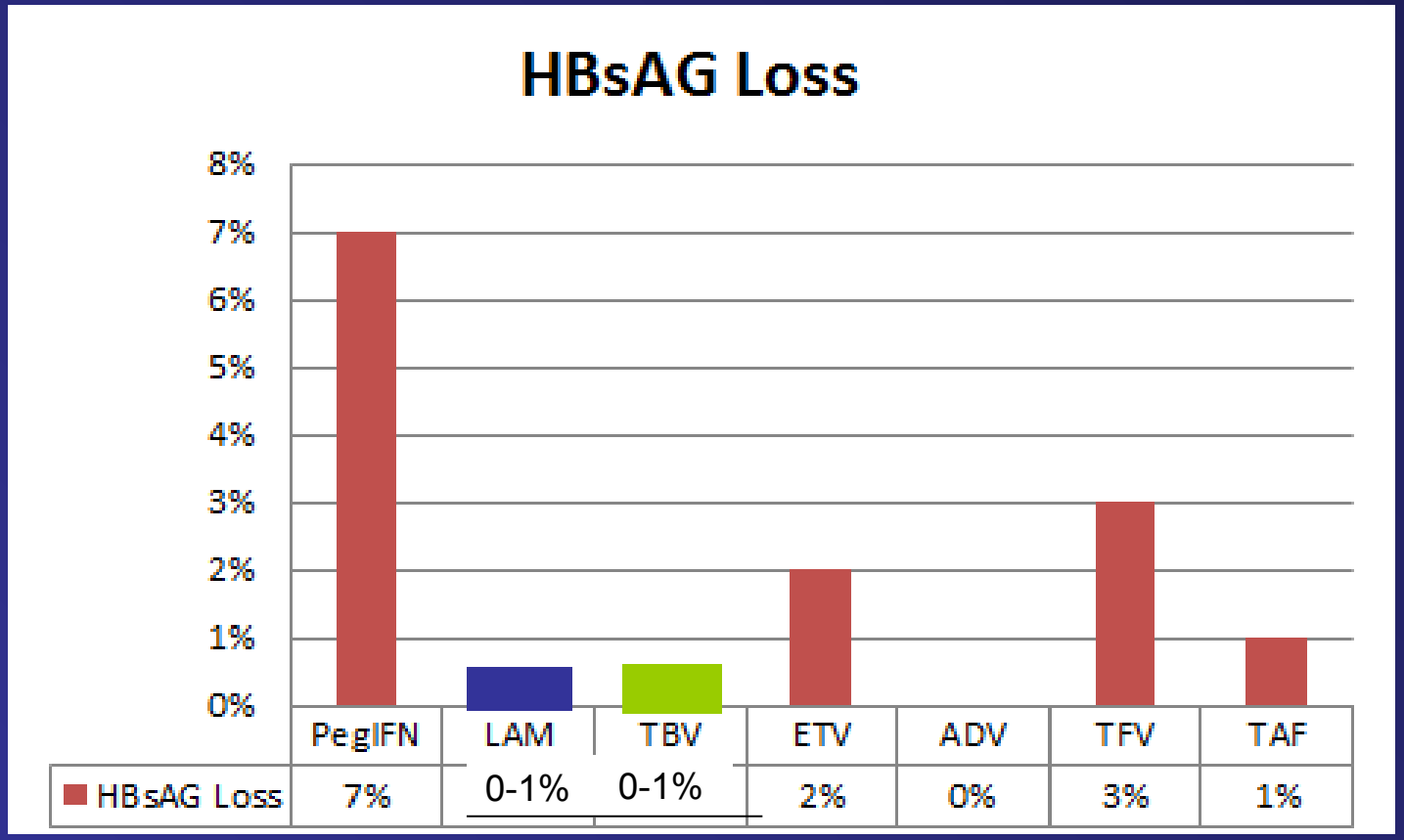
In order to reach an HBs Ag loss : which strategies would you want to implement?

- **Long term NA treatment**
- Add-on therapy using IFN
- Switch-on therapy
- Simultaneous combination
- Entecavir plus tenofovir combination therapy
- Switch to TAF
- Others?

RESULTS WITH Nucleosides Analogues :

HBsAg loss?

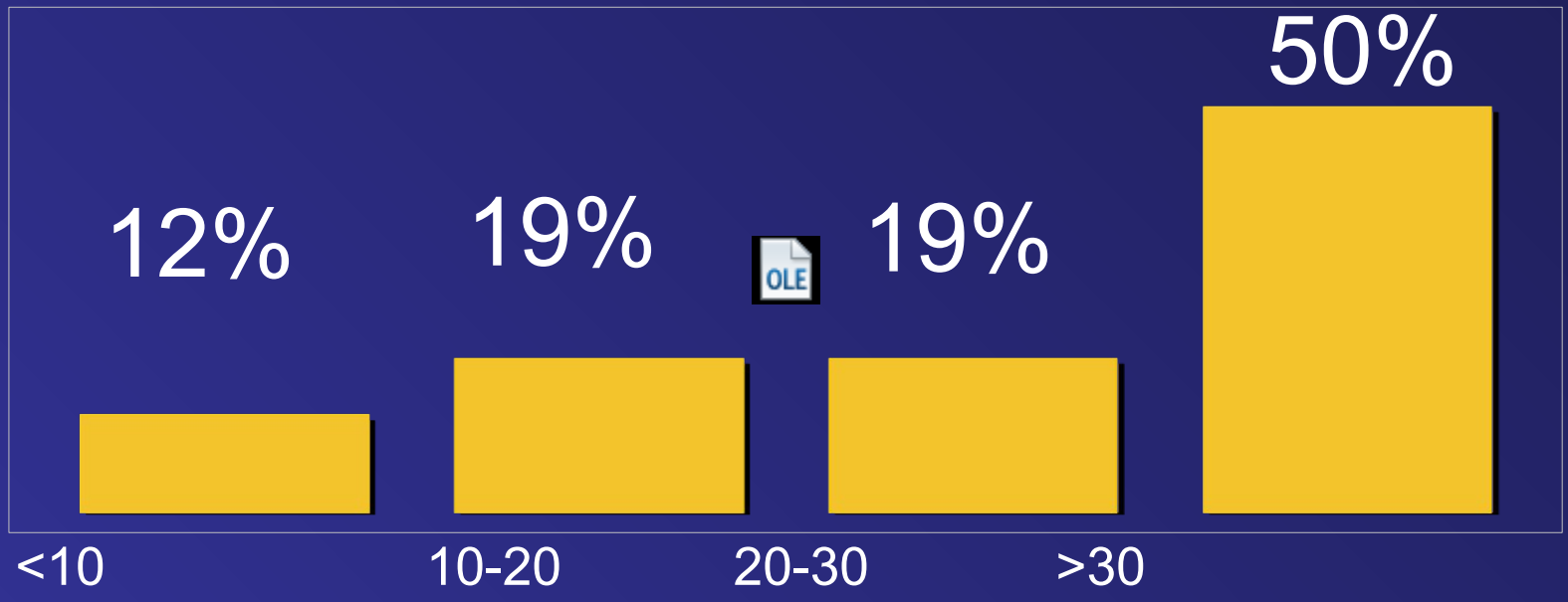
HBsAg loss after 2-3 years of treatment



EASL 2017 Clinical Guidelies

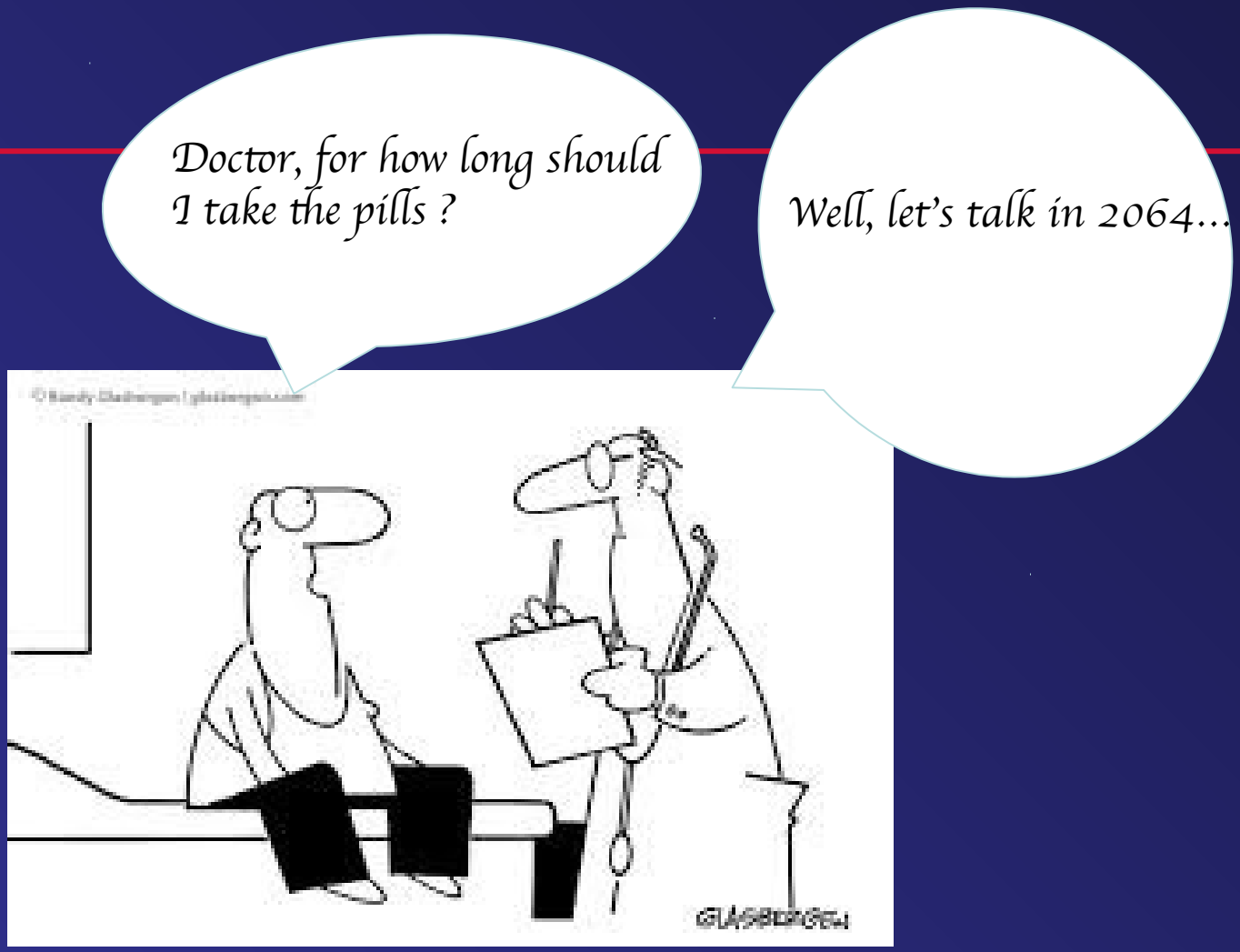
Finite treatment duration unlikely

Patients receiving long-term NUCs therapy
Prediction of HBs loss after achieving undetectable HBV DNA



Average decline/year 0.11 log10 (0.02-0.42)

Zoutendijk et al. JID 2011;204:415
Chevaliez et al. J Hepatol 2013

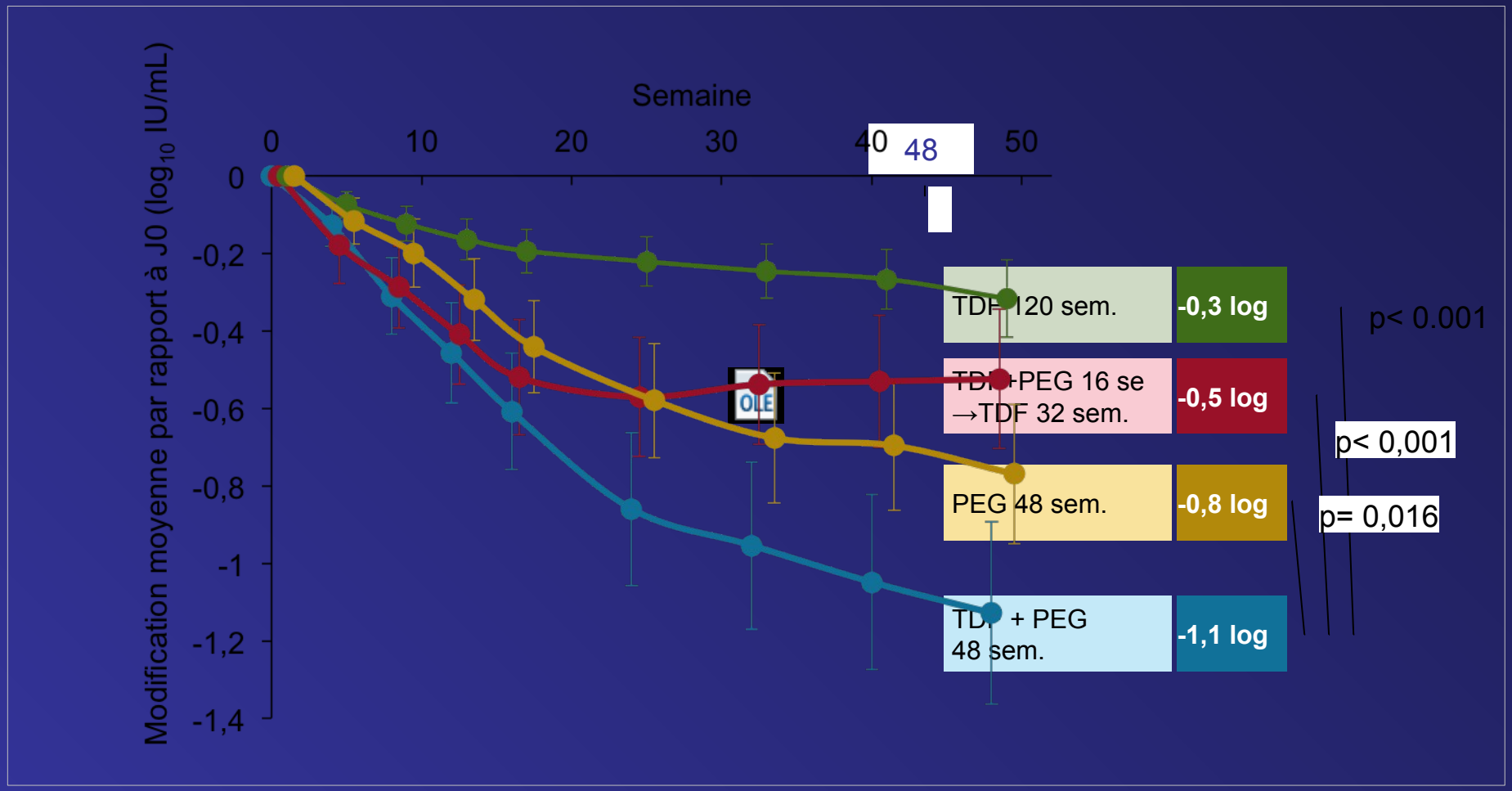

Doctor, for how long should I take the pills ?
Well, let's talk in 2064…

How find a solution for alternative to indefinite NA therapy in patients chronic hepatitis B : Alternative options

- Finite therapy studied after long-term virological suppression
- Combination therapy may provide an alternative treatment strategy

Combination TDF + PEG-IFNα-2a

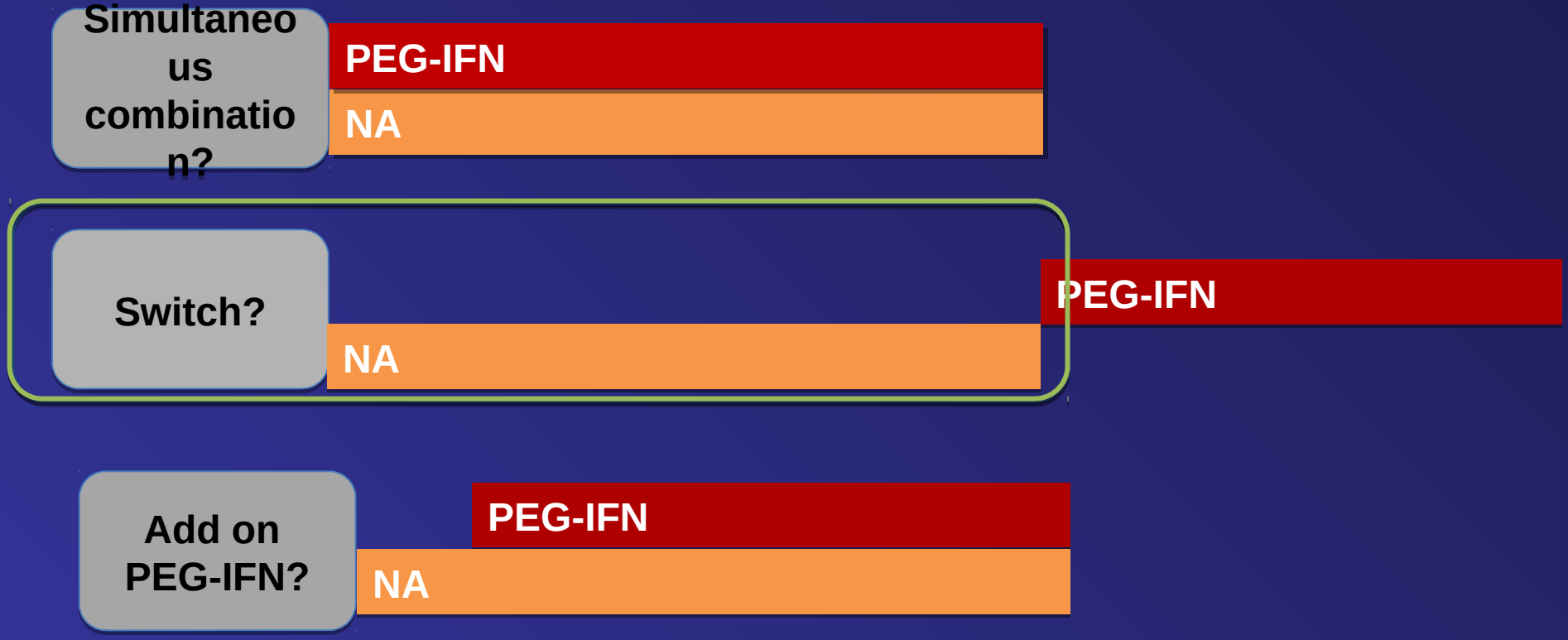
HBsAg at week 48



Marcellin P, Gastroenterology 2015

How find a solution for alternative to indefinite NA therapy in patients chronic hepatitis B : Alternative options

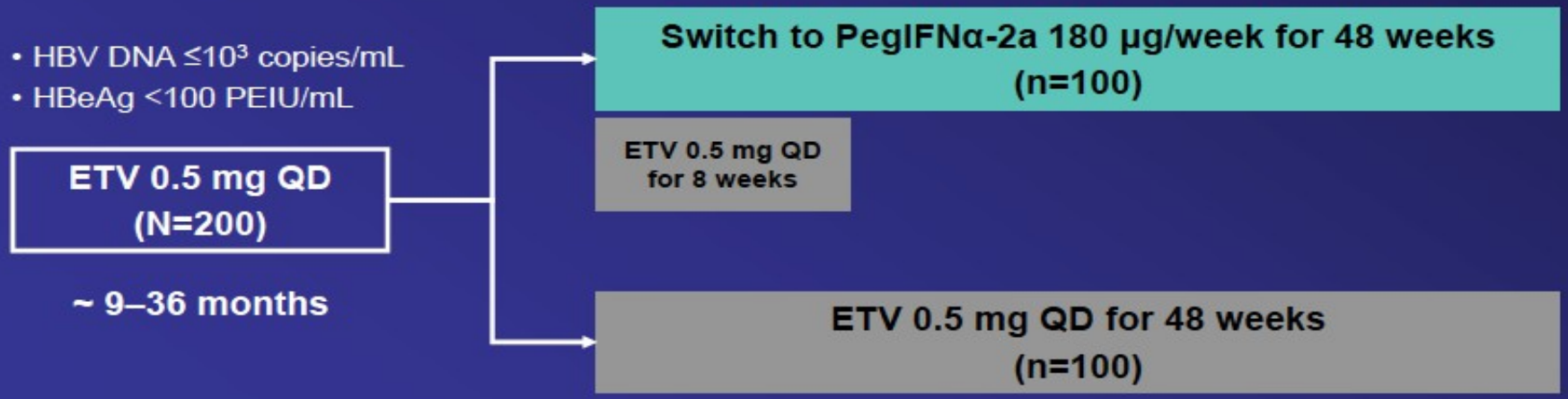
- Finite therapy studied after long-term virological suppression
- Switch therapy may provide an alternative treatment strategy



Switching from long-term entecavir to peginterferon alfa-2a (40 kD) induces HBeAg seroconversion/HBsAg loss in patients with HBeAg-positive chronic hepatitis B (The OSST study)

Study design

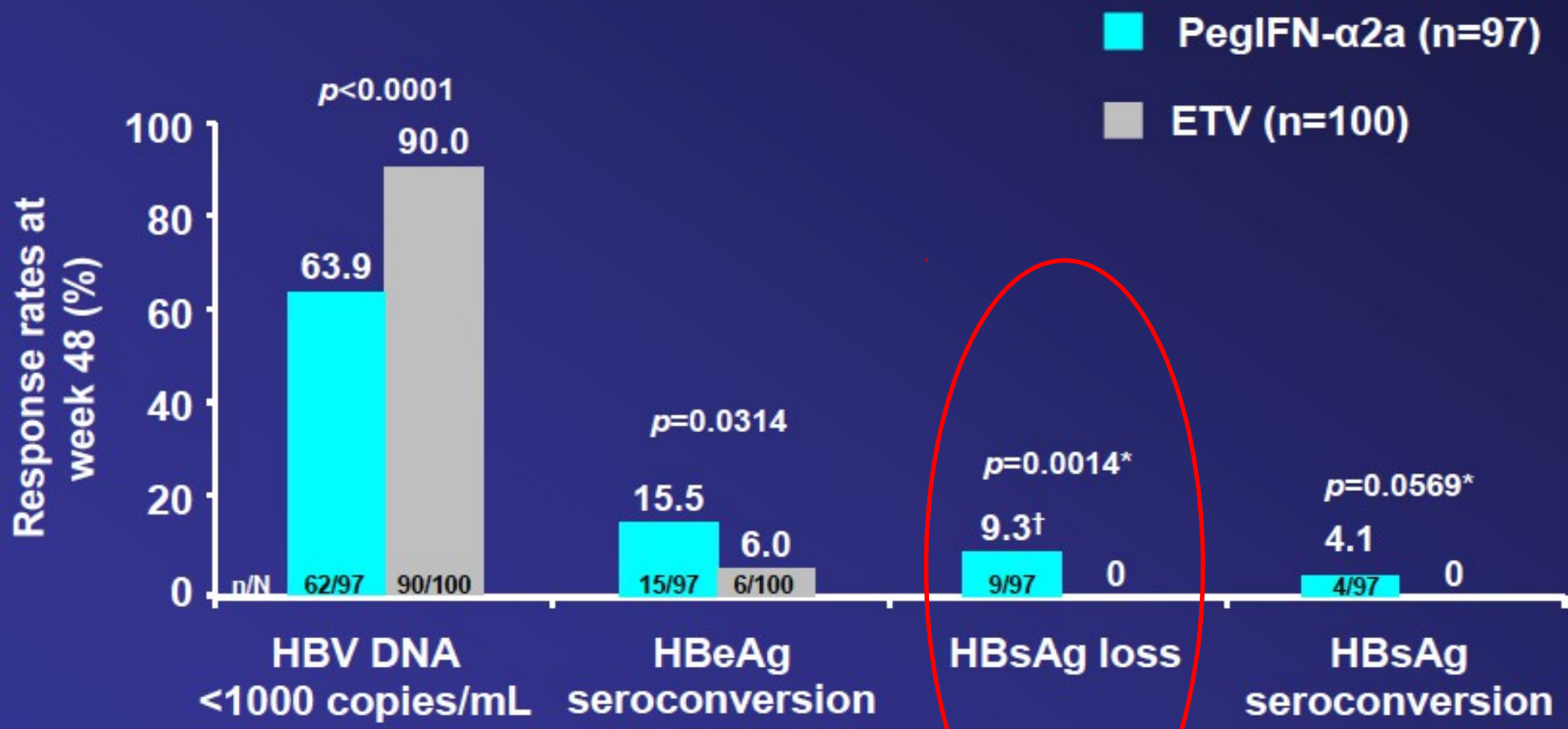
- Randomized, multicenter, open-label study
- Primary endpoint: HBeAg seroconversion at end of treatment (week 48)
- Secondary endpoint: HBsAg loss at week 48



QD = once daily; PEIU = validated with in-house reference standards obtained from Paul Ehrlich Institute

Ning et al J Hepatol 2014

Response rates at week 48 of treatment with PegIFNα-2a: ITT population

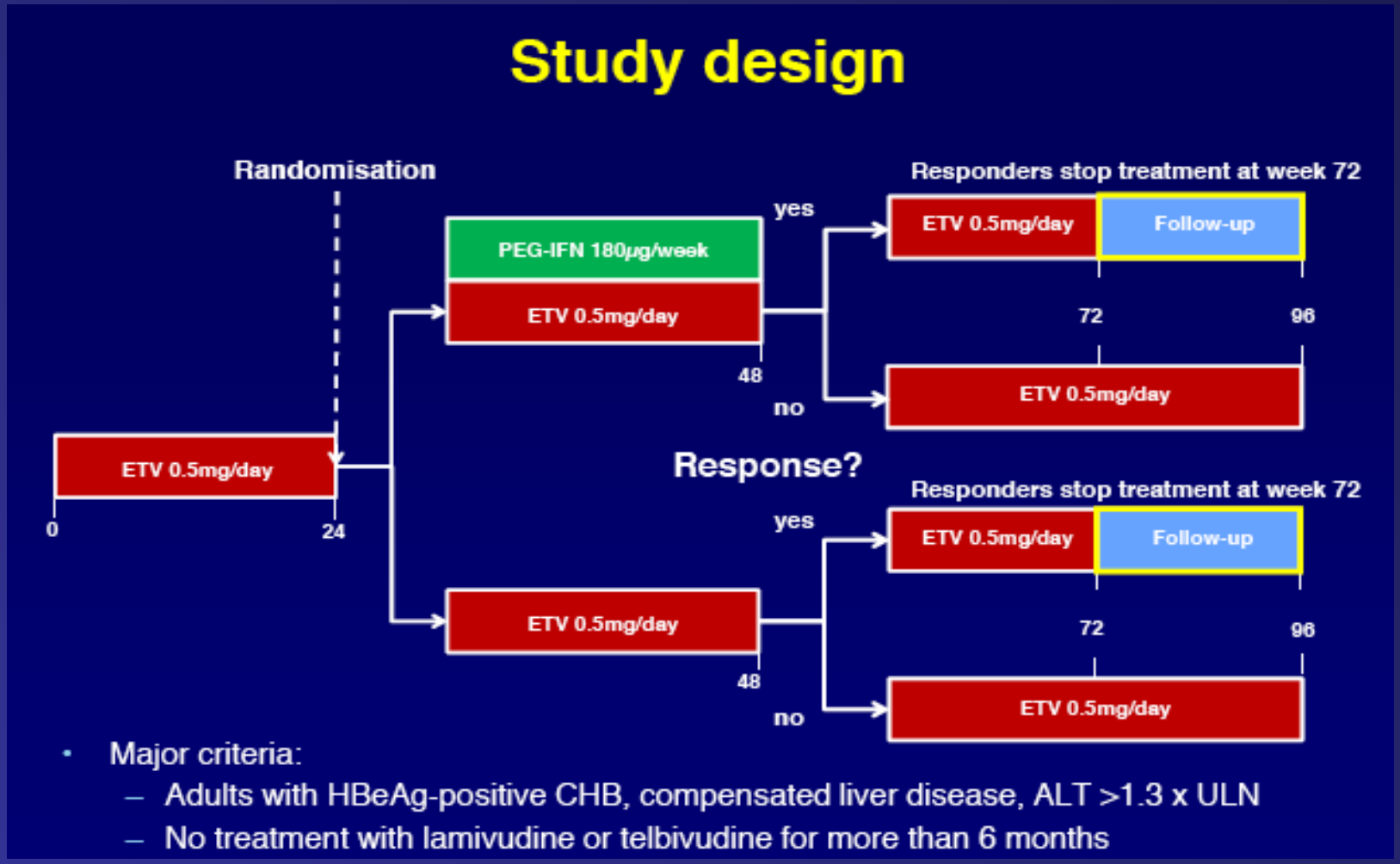


* Fisher Exact test, other p-values are using Chi-Squared Test
† Updated data from time of abstract submission
ITT = intention-to-treat

How find a solution for alternative to indefinite NA therapy in patients chronic hepatitis B : Alternative options

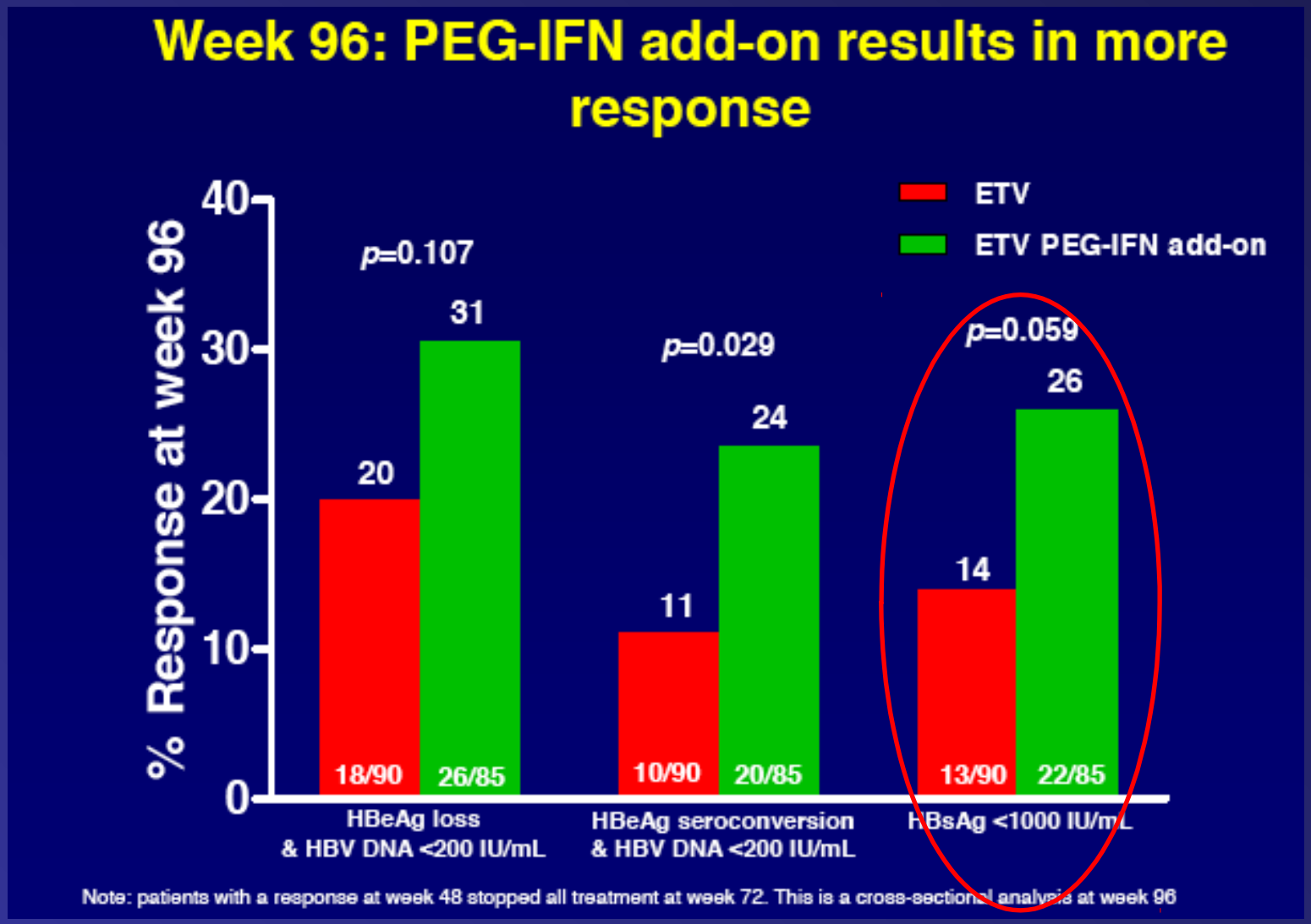
- Finite therapy studied after long-term virological suppression
- Add-on therapy may provide an alternative treatment strategy

ADDING PEGINTERFERON TO ENTECAVIR INCREASES RESPONSE RATES IN HBEAG-POSITIVE CHRONIC HEPATITIS B PATIENTS: WEEK 96 RESULTS OF A GLOBAL MULTICENTER RANDOMISED TRIAL (ARES STUDY)



Brouwer, WP Hepatology 2015

ADDING PEGINTERFERON TO ENTECAVIR INCREASES RESPONSE RATES IN HBEAG-POSITIVE CHRONIC HEPATITIS B PATIENTS: WEEK 96 RESULTS OF A GLOBAL MULTICENTER RANDOMISED TRIAL (ARES STUDY)



Add-on of peg interferon to a stable nucleoside regimen

30 centers

Assesment of HBsAg loss

Pegasys 180 µg 48 weeks

Analogues 48 weeks

Analogues 96 weeks

NUCs

Randomisation

Analogues 144 weeks

≥ 1 years

*HBV DNA undetectable

Bourliere M et al . Lancet Gastroenterology 2017

Add-on of peg interferon to a stable nucleoside regimen

Loss of HBsAg at week 48

	Analogues	PEG-IFN + analogues	p
loss AgHBs ITT	1/93 (1 %)	7/90 (8 %)	0,0327
Loss HBsAg in patients who achieved the treatment	1/91 (1 %)	7/82 (9 %)	0,0276

Baseline HBsAg titres of less than 3 log10 IU/mL might benefit from this add-on strategy to achieve HBsAg loss and anti-HBs seroconversion

Bourliere M et al . Lancet Gastroenterology 2017

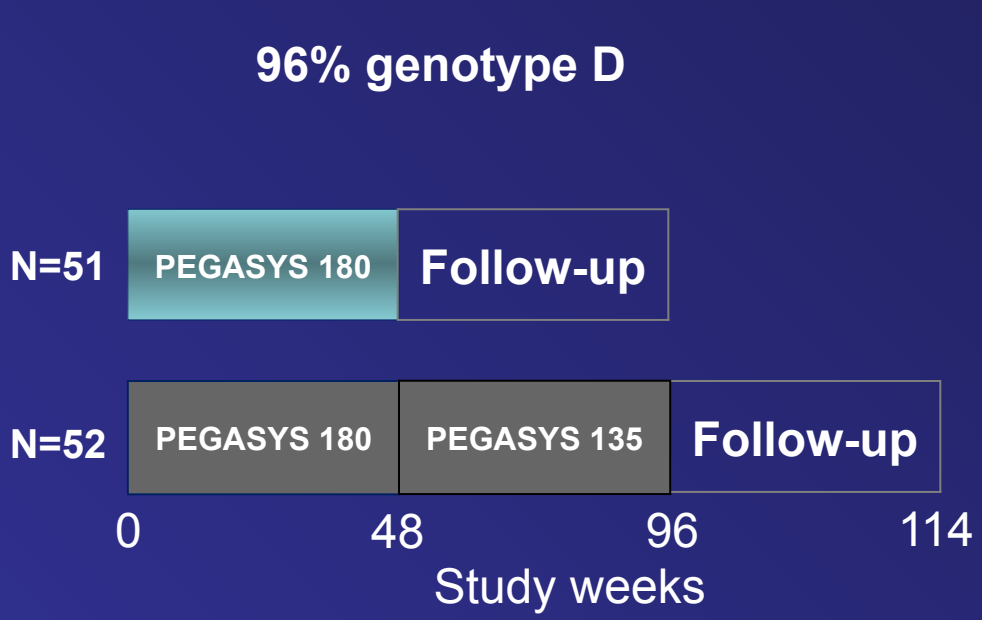
How find a solution for alternative to indefinite NA therapy in patients chronic hepatitis B : Alternative options

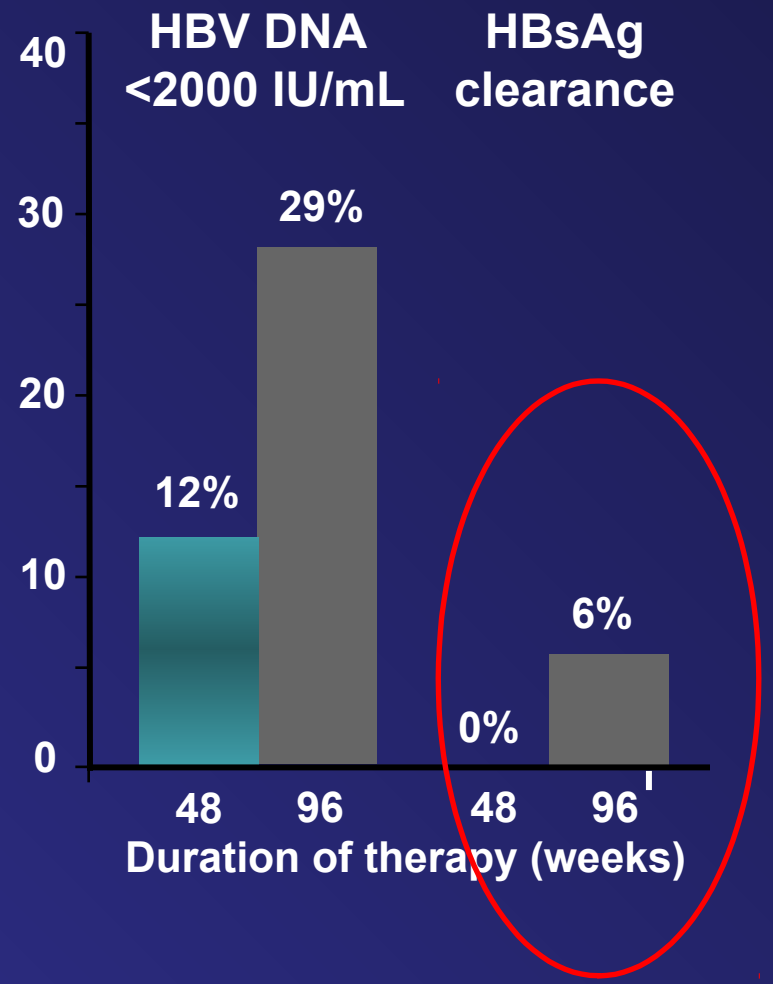
- Finite therapy studied after long-term virological suppression
- Add -on therapy may provide an alternative treatment strategy

How find a solution for alternative to indefinite NA therapy in patients chronic hepatitis B : Alternative options

- Swiching Therapy
- Add-on Therapy
- **Add-on therapy with Extention of duration based on HBsAg Kinetics**

Extending duration of Pegasys treatment increase response rate in HBe negative patients: PegBeLiver study

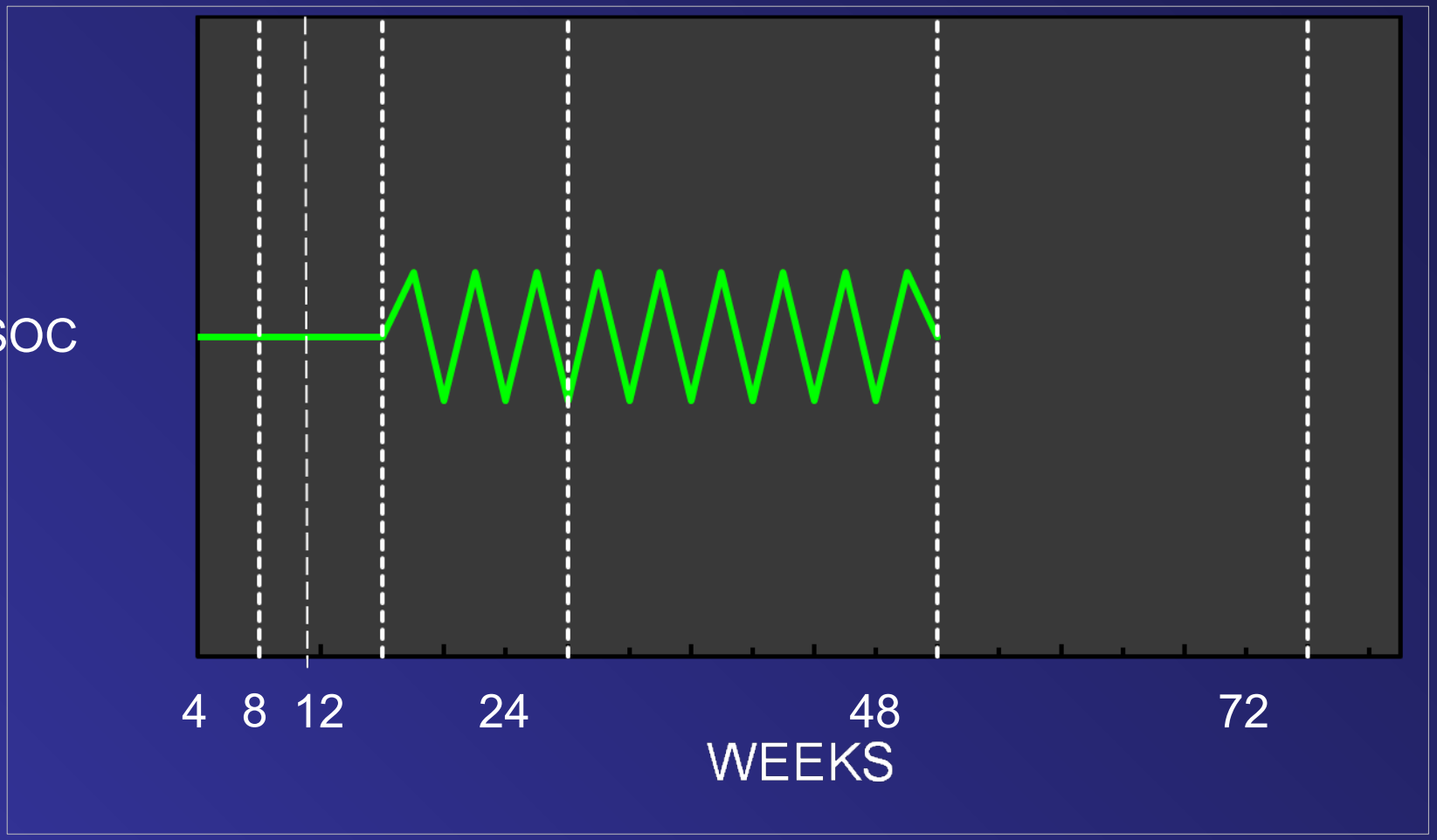




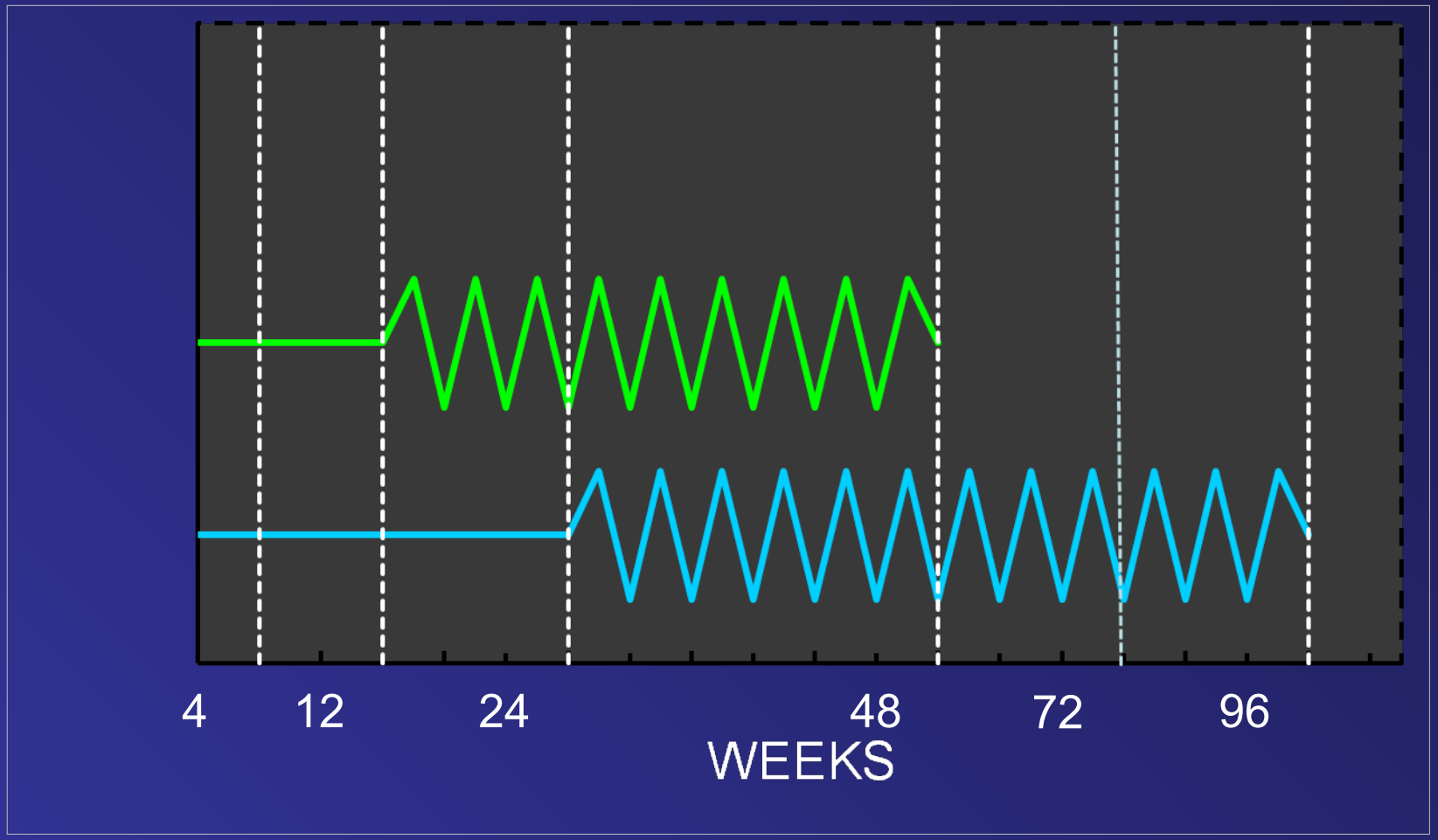
Patients with HBsAg <1000 IU/ml at week 48
had response rates of 25% vs 80%, depending on the treatment duration (48 vs. 96 weeks)

Lampertico et al. Gut. 2012; 62(2): 290-8.

The concept of "Time-individualized Peg-IFN treatment" according to the evolution of HBsAg titer



TIME TO BECOME HBsAG NEGATIVE EXTEND DURATION OF TREATMENT:



EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

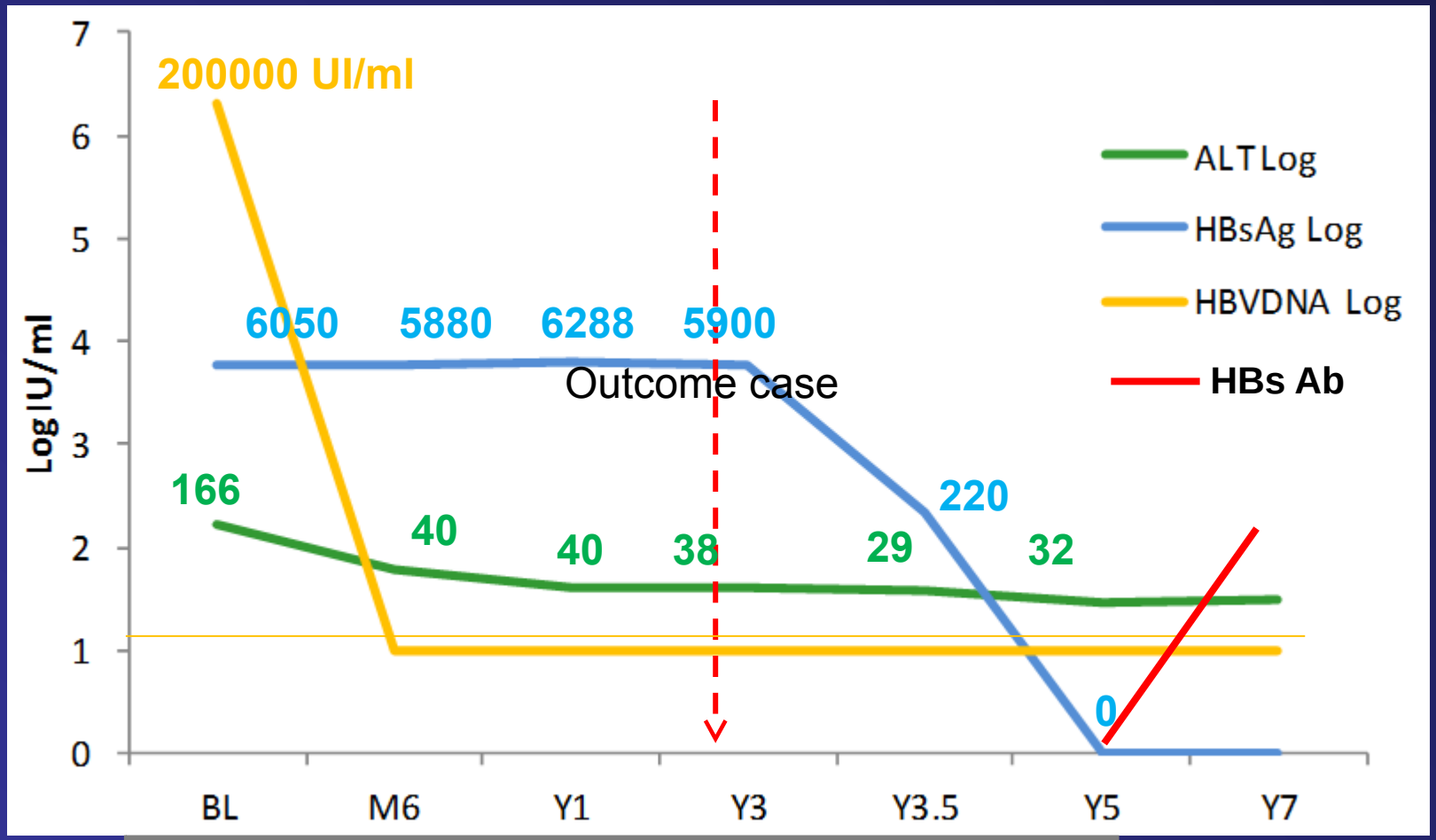
A Response-guided approach based on HBsAg kinetics may identify patients with the greatest chance of success

Halfon P. J Hepatol 2014

Outcome case

	D0	M6	Y1	Y3	Y3.5	Y5	Y7
ALT UI/ml	166	62	40	40	38	29	32
HBs Ag UI/ml	6050	5880	6288	5900	220	0	0
HBVDNA UI/ml	200000	<20	<20	<20	<20	<20	<20

Outcome case



ENTECAVIR 0.5mg/D

PEG-IFN 48 weeks

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

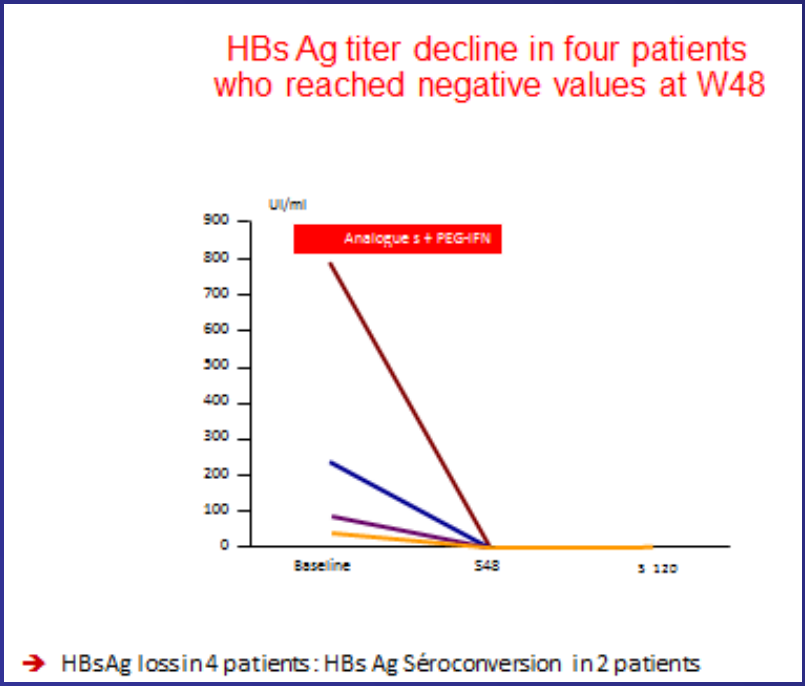
Short Communication

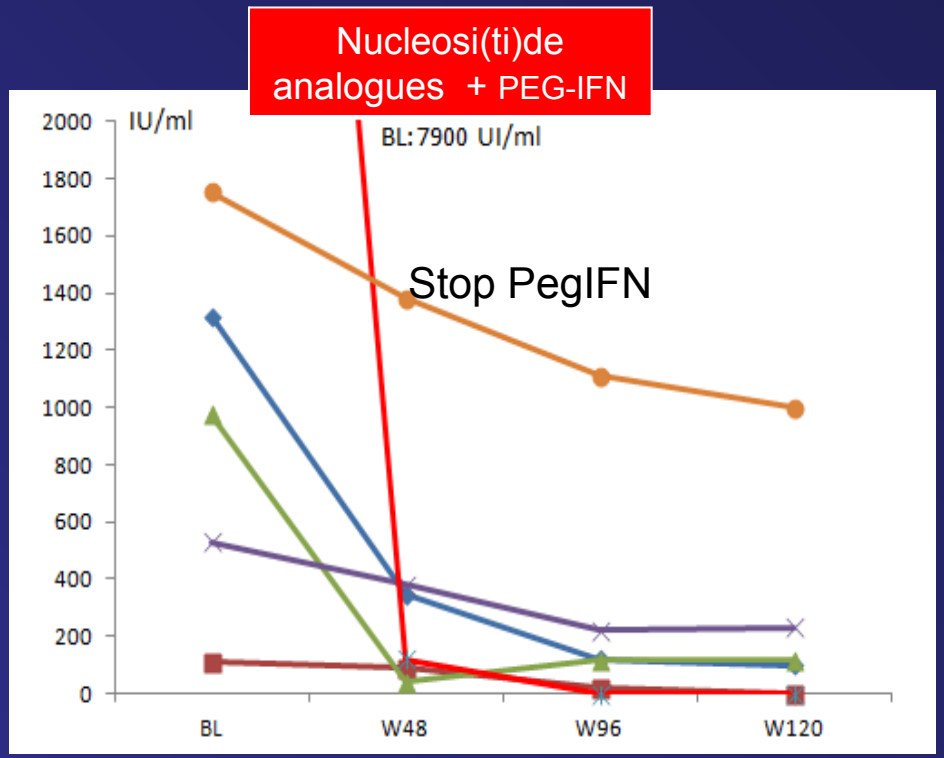
Add-on peg-interferon leads to loss of HBsAg in patients with HBeAg-negative chronic hepatitis and HBV DNA fully suppressed by long-term nucleotide analogs

Denis Ouzan [a,**], Guillaume Pénaranda [b], Hélène Joly [a], Hacène Khiri [b], Antonnella Pironti [a], Philippe Halfon [b,c,*]

HBs Ag levels of 10 HBe Ag negative patients who received additional Peg-interferon alpha2a during 48- 96 weeks to a stable NUCs therapy

All patients were treated with NUCs (3-7yrs) with HBVDNA neg since more than three years





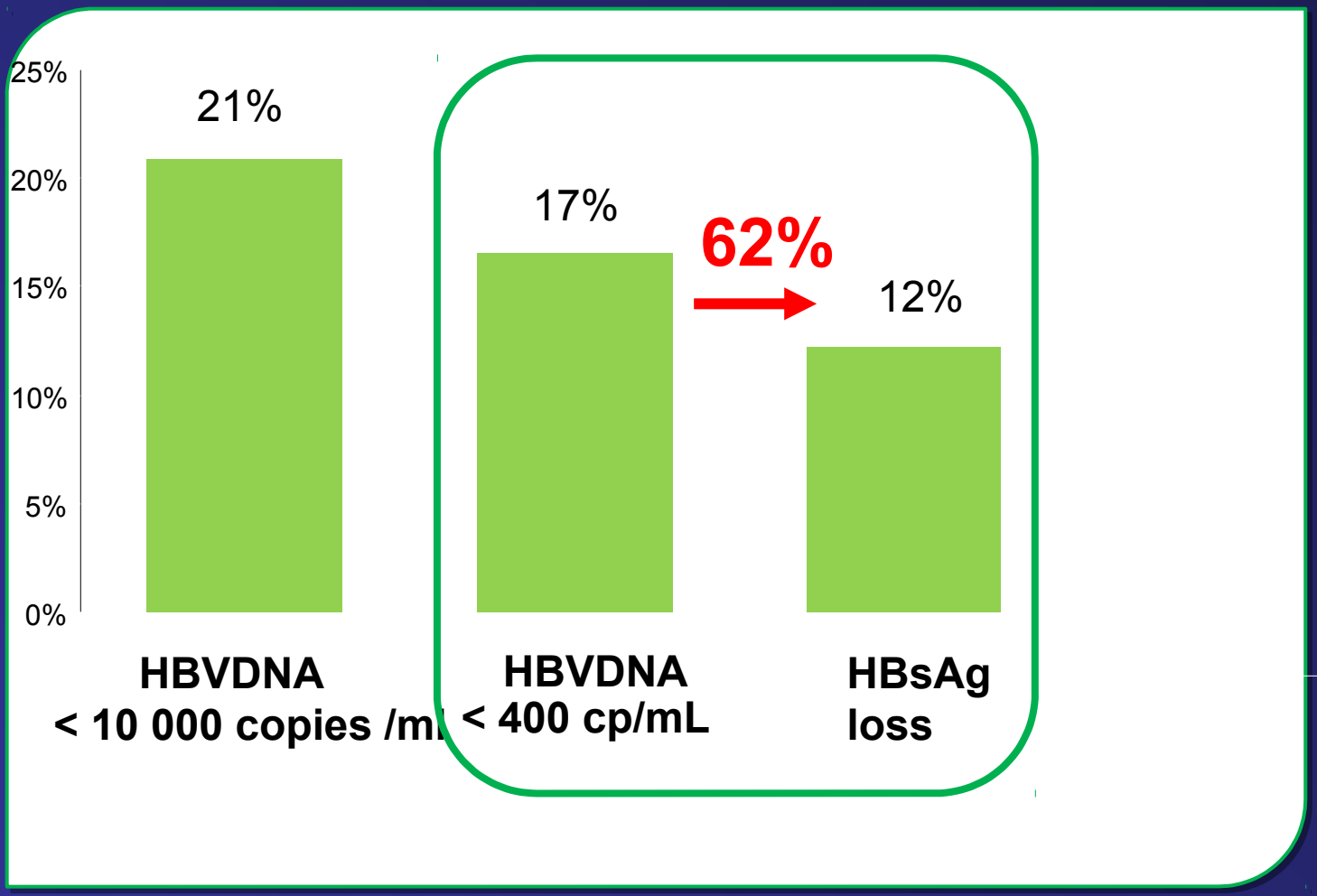
Ouzan D, Halfon J Clin Virol 2013

HBsAg titer decline constitutes a useful tool to predict the loss of HBsAg and the optimal duration of Peg-IFN therapy and add-on therapy

IFN is still needed for HBV !

Mr. IFN

PEGIFN 48 weeks : virological and HBs loss response at 5 years



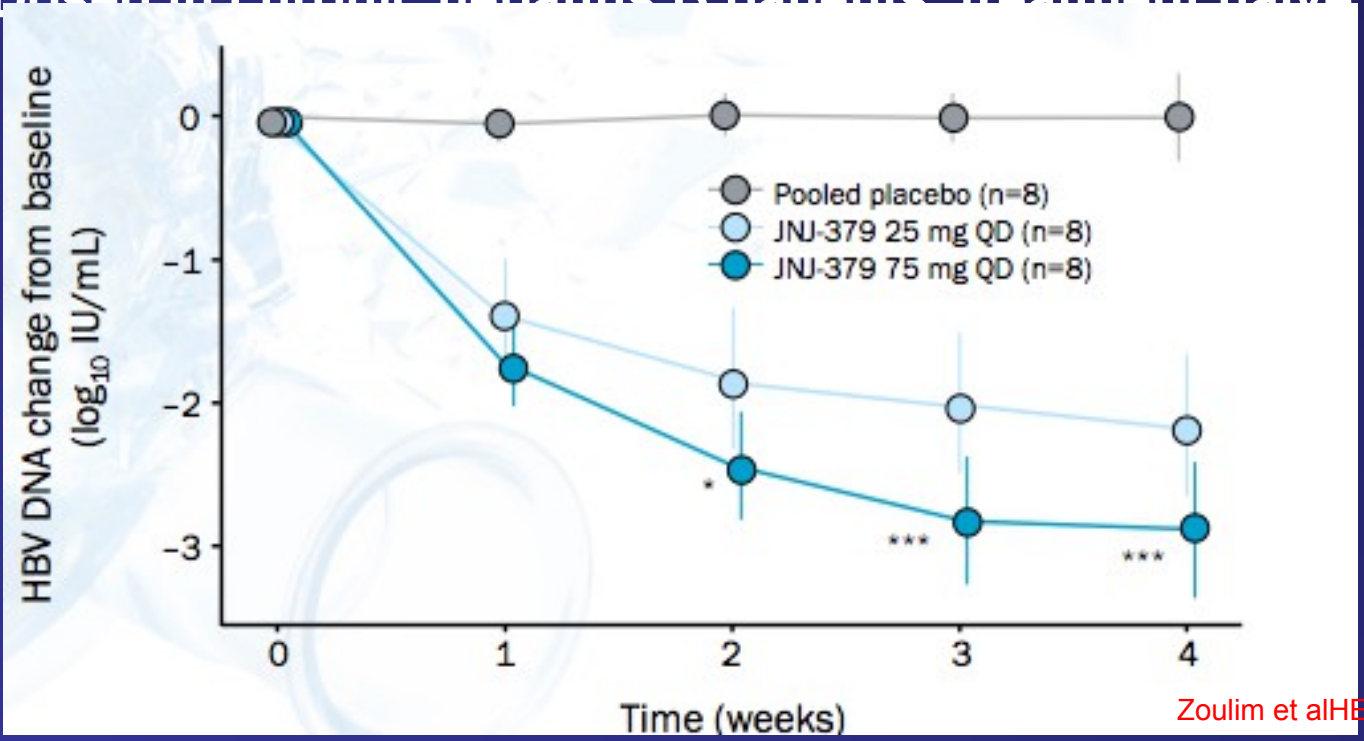
Reduction of HBV replication prolongs the early immunological response to IFN therapy

Marcellin P et al Hepatol Int .2013 ;7:88-97

Tan AT et al.J of Hepatol.2014; 60:54-61

Safety, Tolerability, Pharmacokinetics and Antiviral Activity of JNJ-56136379, a Novel HBV Capsid Assembly Modulator, in Non-cirrhotic, Treatment-naïve Subjects with Chronic HBV

- JNJ-56136379 (JNJ-379): potent capsid assembly modulator (CAM)
- JNJ-379 binds to the HBV core protein and interferes with the HBV capsid assembly, and prevents cccDNA formation during *de novo* infection, by interfering with capsid disassembly
- Dosed in chronic hepatitis B patients, treatment naive



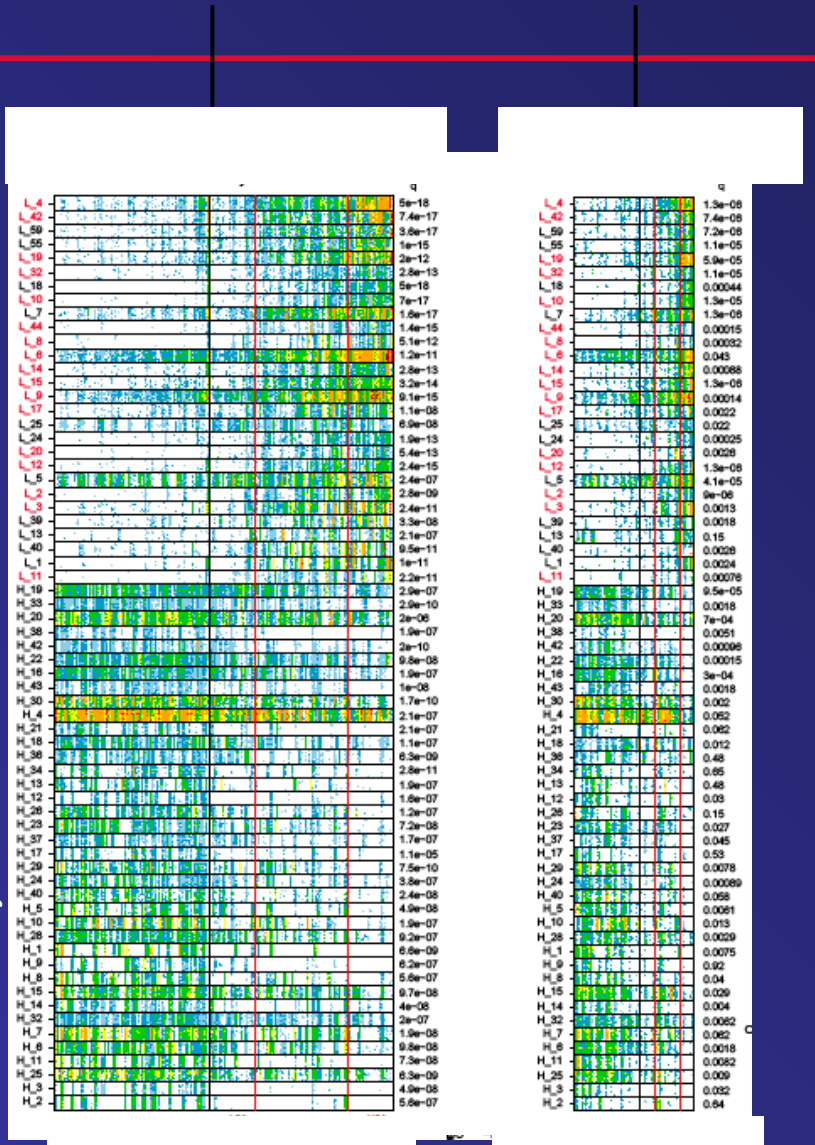
Three patients with HBV DNA <LLOQ of the HBV DNA assay.

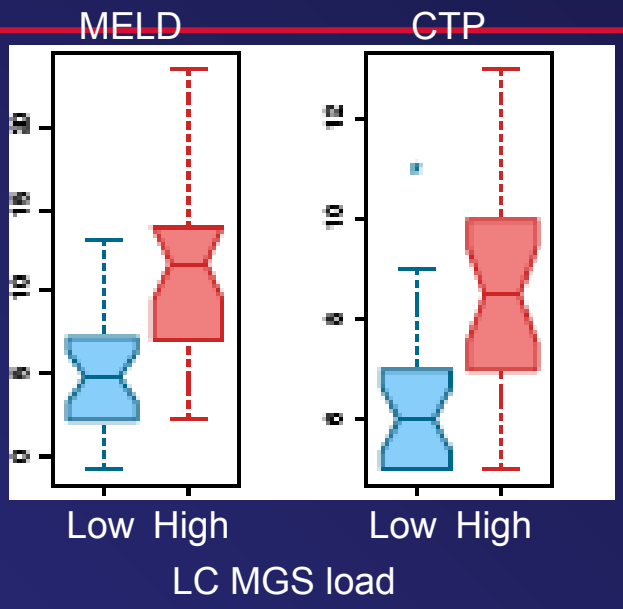
Zoulim et alHEPATOLOGY. 2017 66(1)39

Microbiome informs on the status of liver cirrhosis

MGS enriched in LC n=28

MGS enriched in Healthy n= 38





- Each column is an individual
- Each row is a gene, 50 are displayed for each species
- Colors indicate gene abundance

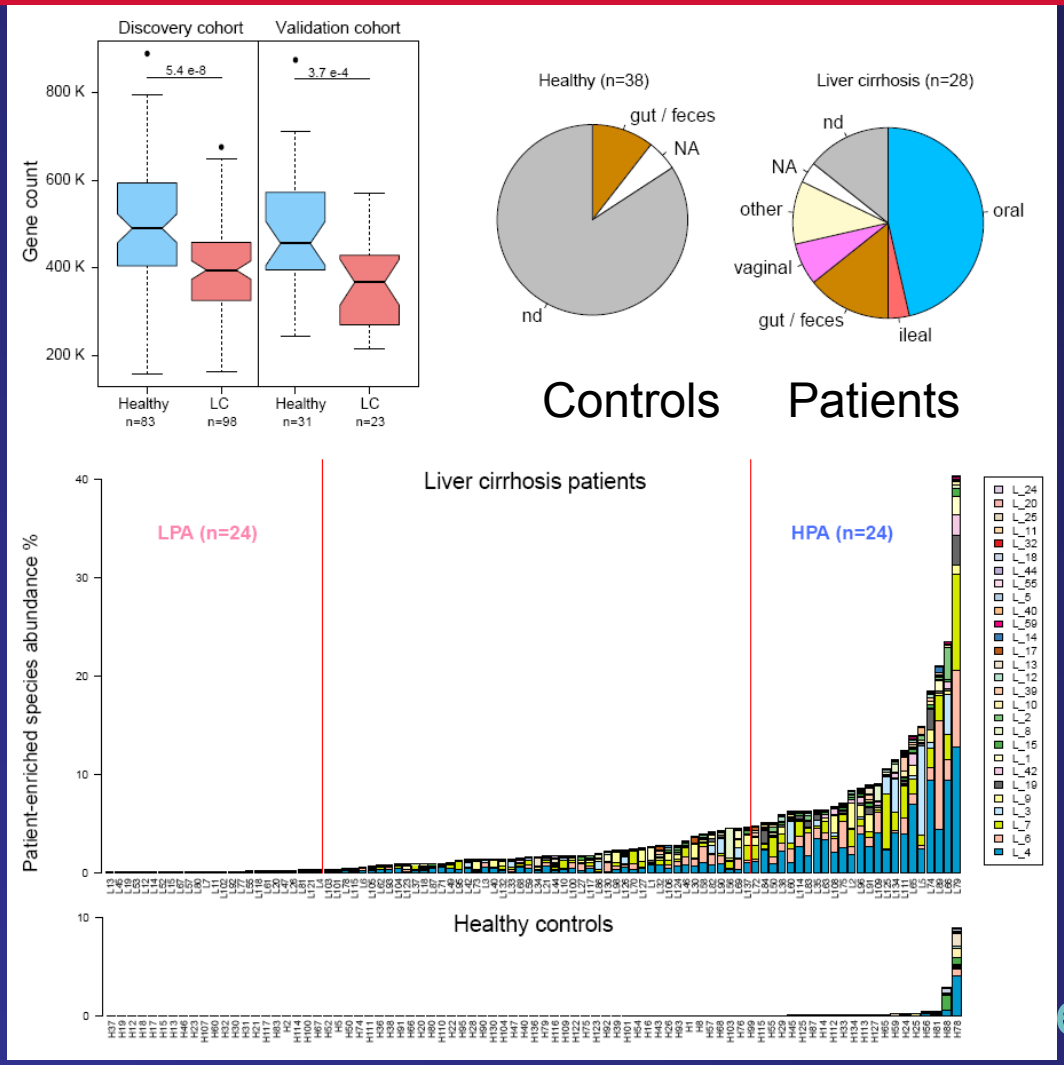
less more

Qin N. et al. Nature 2014,

Massive microbiome changes in cirrhosis

Low gene richness (p<10 e-10)

Invasion of the gut by 28 bacterial species rare in health: up to 40% abundance!



"Oral" species

Metabolic potential of the altered microbiome

NH3 ↑
Mn2+ ↑
GABA ↑

Hepatic encephalopathy

Qin N. et al. Nature 2014,

Summary

- We have the tools to suppress hepatitis B

  Tenofovir/ TAF/Entecavir highly effective therapies

  But not to cure HBV

  - While Peg-IFN and NA combination therapy should not be recommended currently, the addition of or the switch to Peg-IFN in NA-treated patients with chronic hepatitis B infection may be useful options
  - Novel therapies for hepatitis B seems promising
    - ARB-1467 LNP siRNA
    - JNJ-56136379HBV Capsid Assembly Modulator