How find a solution for alternative to indefinite nucleoside analogue therapy in patients chronic HBV infection?

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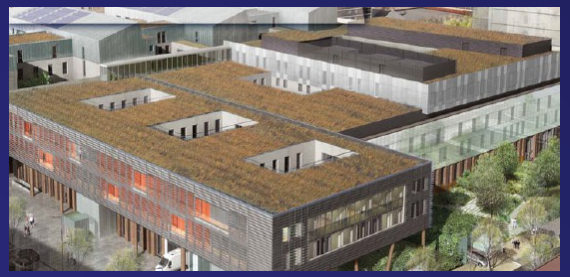
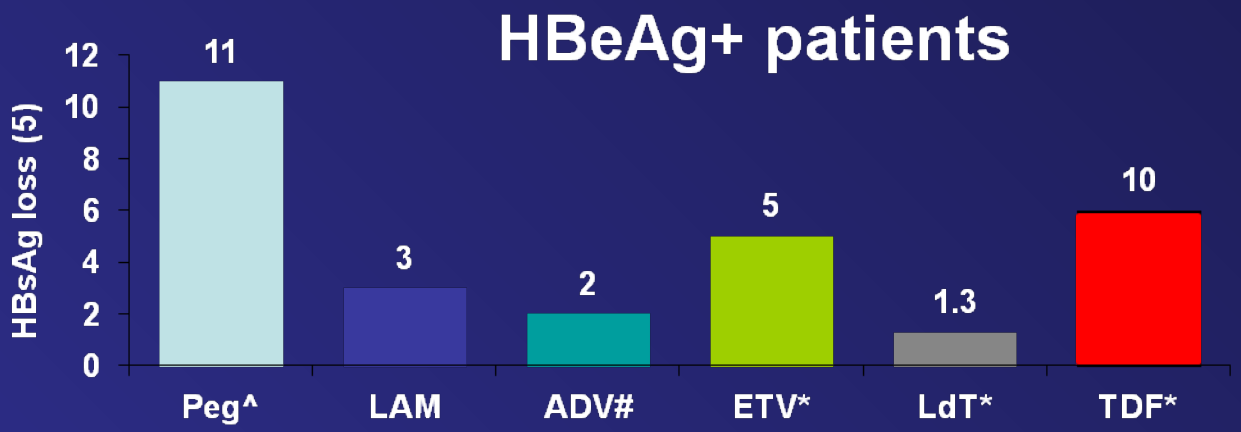
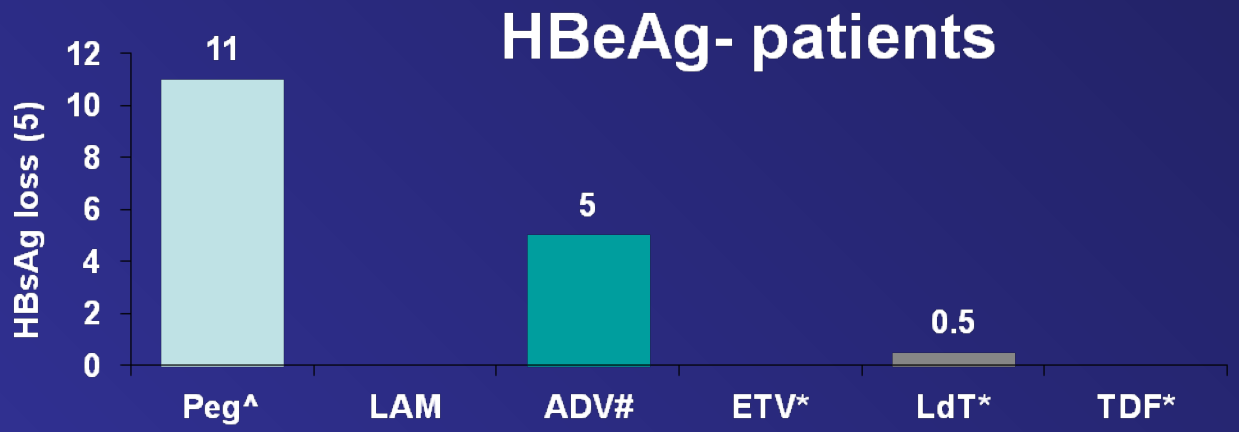


HBsAg loss after 2-5 years of treatment





Peg = peginterferon
LAM = lamivudine
ADV = adefovir
ETV = entecavir
LdT = telbivudine
TDF = tenofovir

^ 3-4 Years off Rx

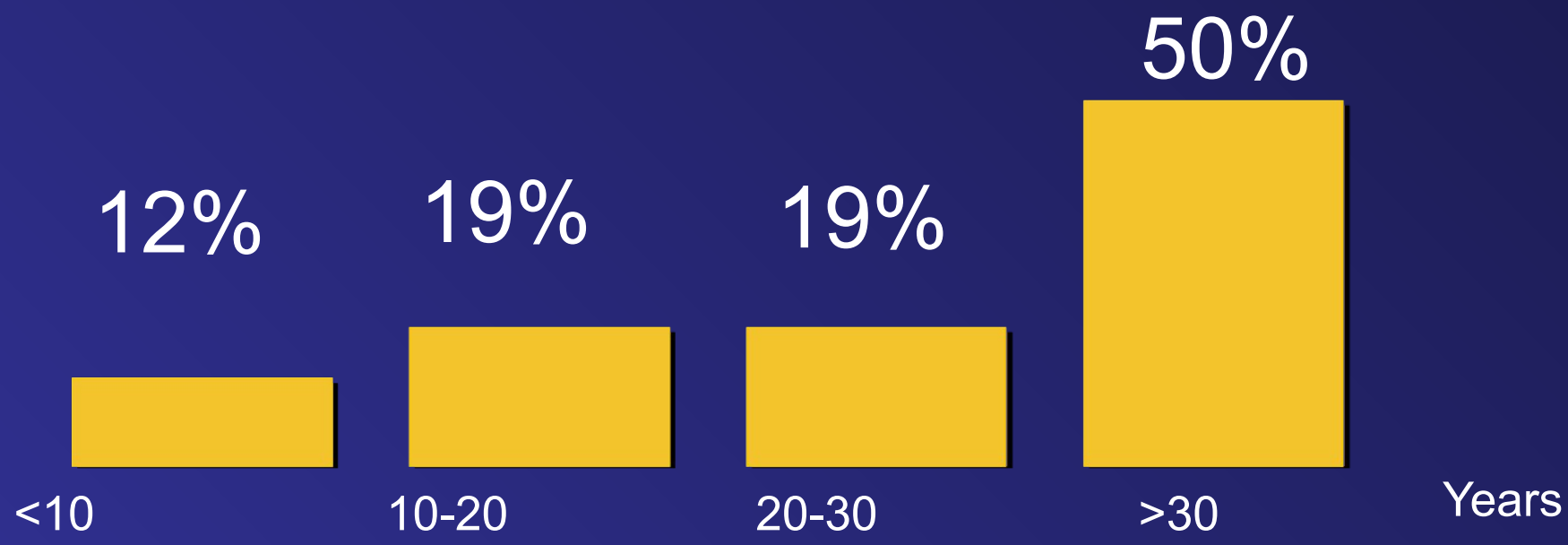
4-5 Years on Rx

* 2 Years on Rx

1. Dienstag J, NEJM, 2008;359:1486-1500. 2. Buster EH, Gastro, 2008;135:459-467 3. Marcellin P, J Hepatol, 2008;48 suppl 2:S46. 4. Heathcote J, Hepatology ,2008;48(4)suppl1:376A. 5. Liaw Y, Gastro, 2009;136:486. 6. Heathcote J, EASL 2009

Finite treatment duration unlikely

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



Average decline/year 0.11 $\log_{10}$ (0.02-0.42)

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

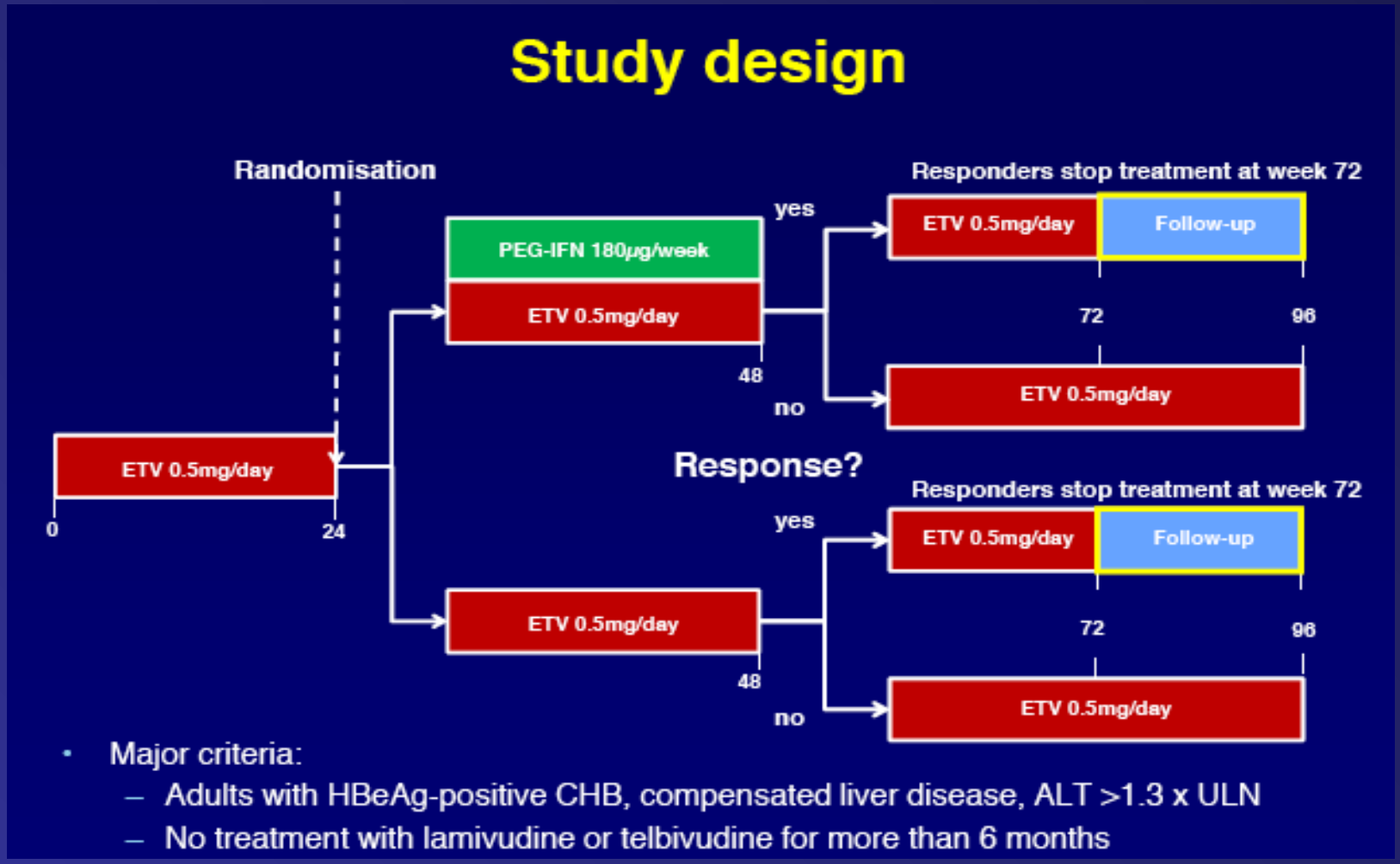
Doctor, for how long should I take the pills ?

Well, let's talk in 2064…

How find a solution for alternative to indefinite nucleos(t)ide analogue (NA) therapy in patients chronic hepatitis B, two concepts were developed

- Add-on Therapy
- Switching Therapy

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, P Hepatology 2014

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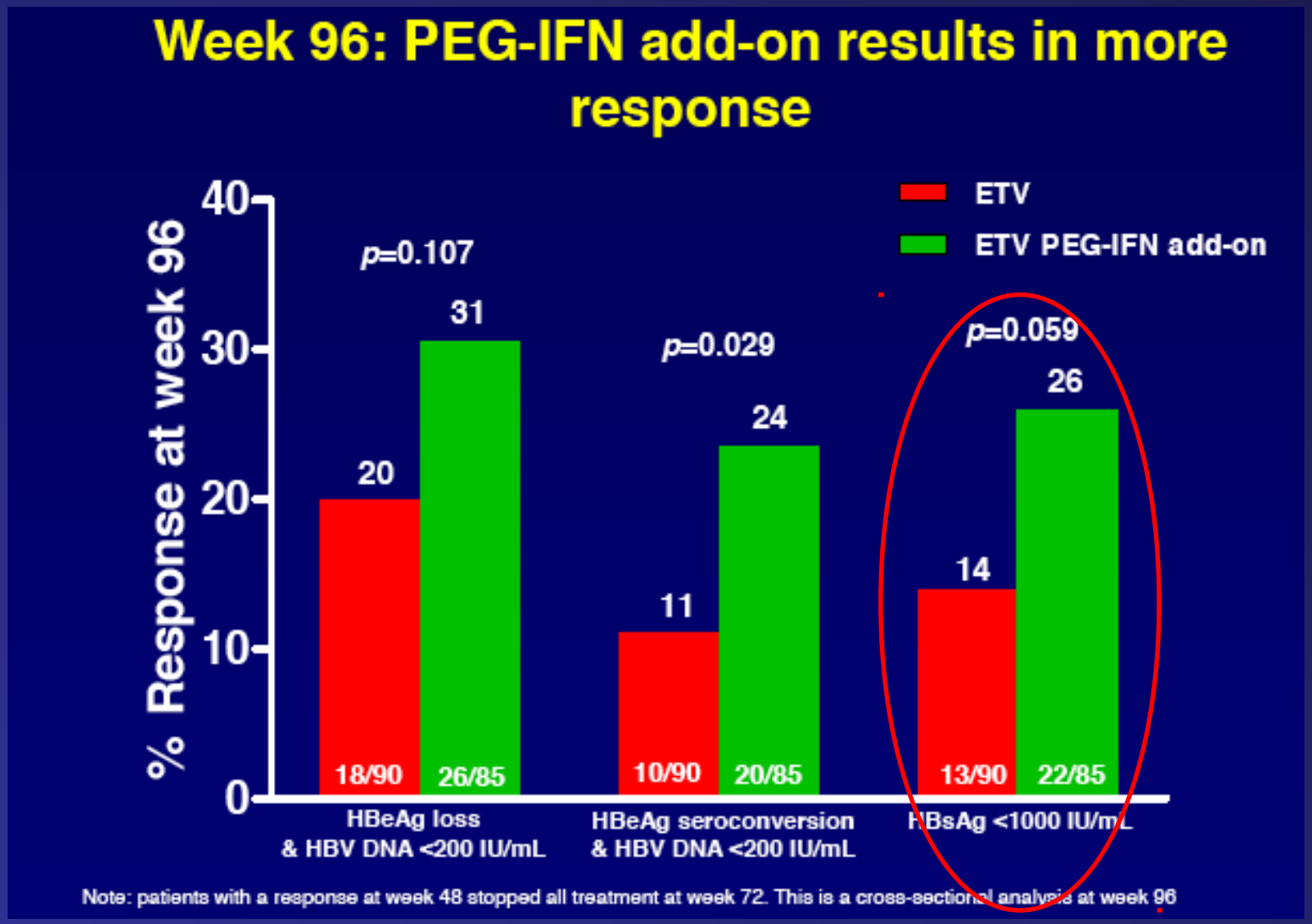
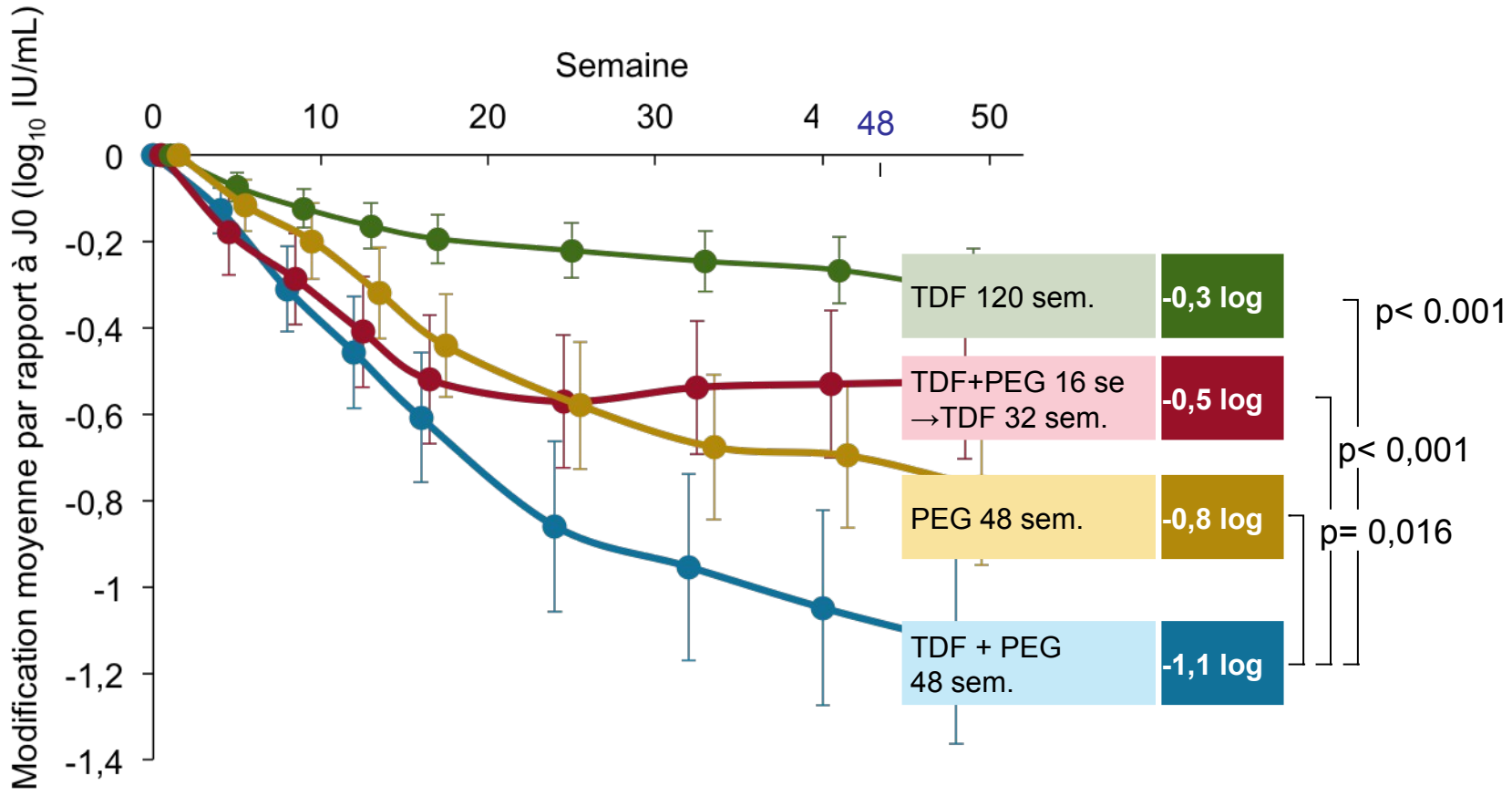


TDF + PEG-IFNα-2a in HBV patients

Modification du titre AgHBs à S48



Marcellin P, France, AASLD 2014, Abs. 193 actualise

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 an

*HBV DNA undetectable

Bourliere M AASLD 2014

Add-on of peg interferon to a stable nucleoside regimen

Loss HBsAg W48

	Analogs	PEG-IFN + analogs	p
Loss HBsAg ITT	1/93 (1 %)	7/90 (8 %)	0,0327
Loss HBsAg in patients with complete dosage	1/91 (1 %)	7/82 (9 %)	0,0276

At W 48 : Add-on Peg IFN increase the loss of Hbs Ag specifically in the subgroup of patient with abselie titer < 1000 UI/ml

Bourlière M , France, AASLD 2014, Abs. 1863 actualis

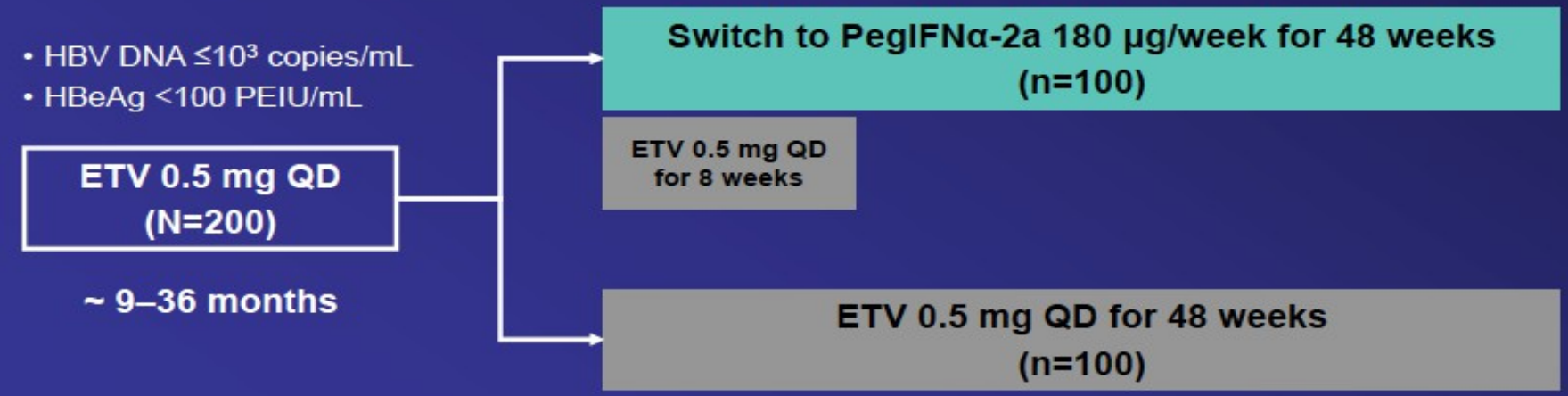
How find a solution for alternative to indefinite nucleos(t)ide analogue (NA) therapy in patients chronic hepatitis B, two concepts were developed

- Add-on Therapy
- Switching Therapy

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

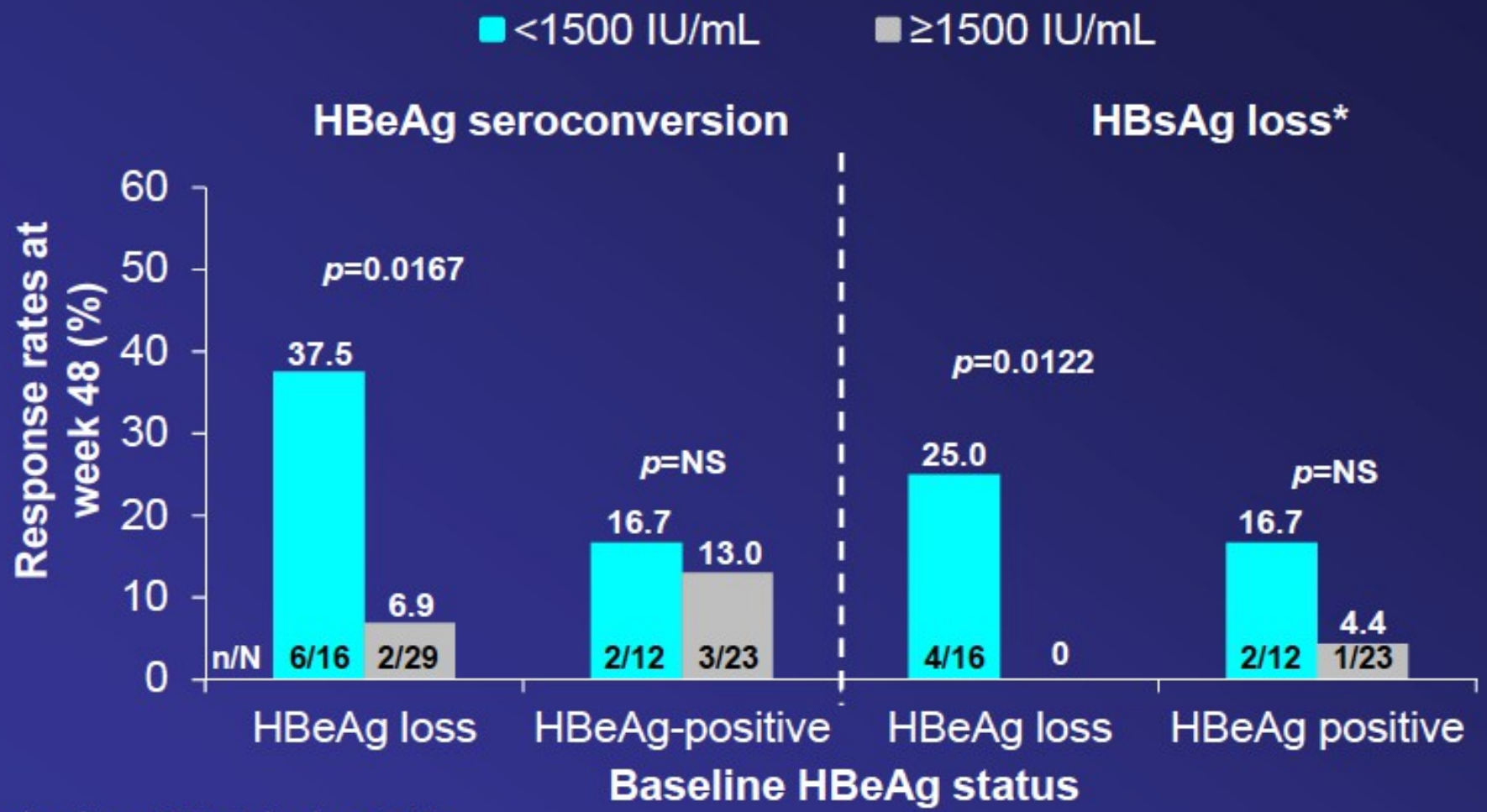
- Randomized, multicenter, open-label study
- Primary endpoint: HBeAg seroconversion at end of treatment (week 48)
- Secondary endpoint: HBsAg loss at week 48



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

Ning et al J Hepatol 2014

HBeAg loss + HBsAg <1500 IU/mL at baseline was associated with HBeAg seroconversion (37.5%) and HBsAg loss (25.0%) at week 48 (PegIFNα-2a arm)



Patients with available data at week 48

* Two patients with HBsAg loss had missing data at baseline and were excluded from this analysis

HBsAg <1500 IU/mL was determined by ROC analysis as the optimal cut-off in predicting HBsAg loss at week 48

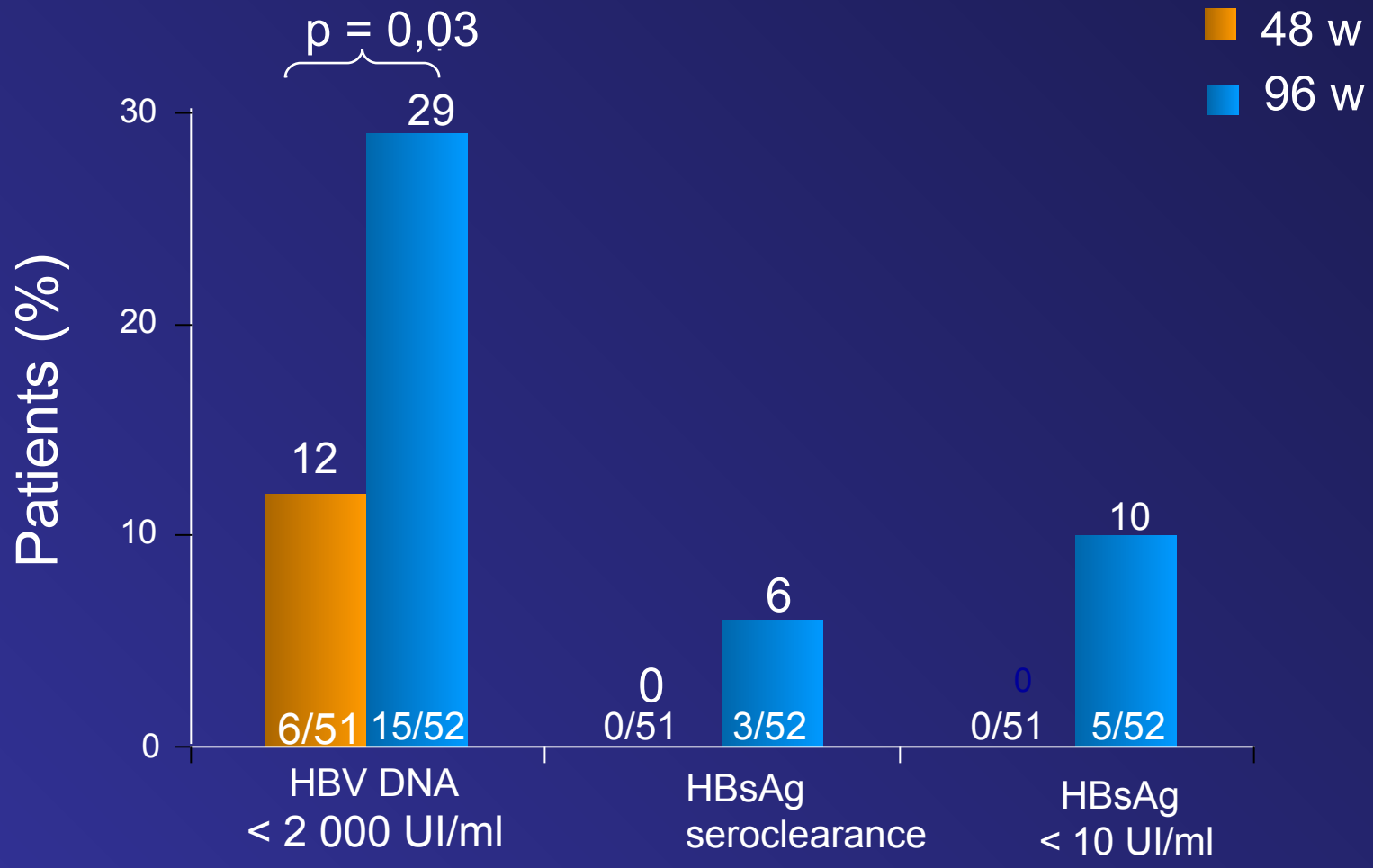
This cut-off is updated from time of abstract submission

How find a solution for alternative to indefinite nucleos(t)ide analogue (NA) therapy in patients chronic hepatitis B, two concepts were developed

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

HBeAg negative :PEG-IFNα-2a : 96 w > 48w

Results 12 month after stopping therapy PEG-IFNα-2a



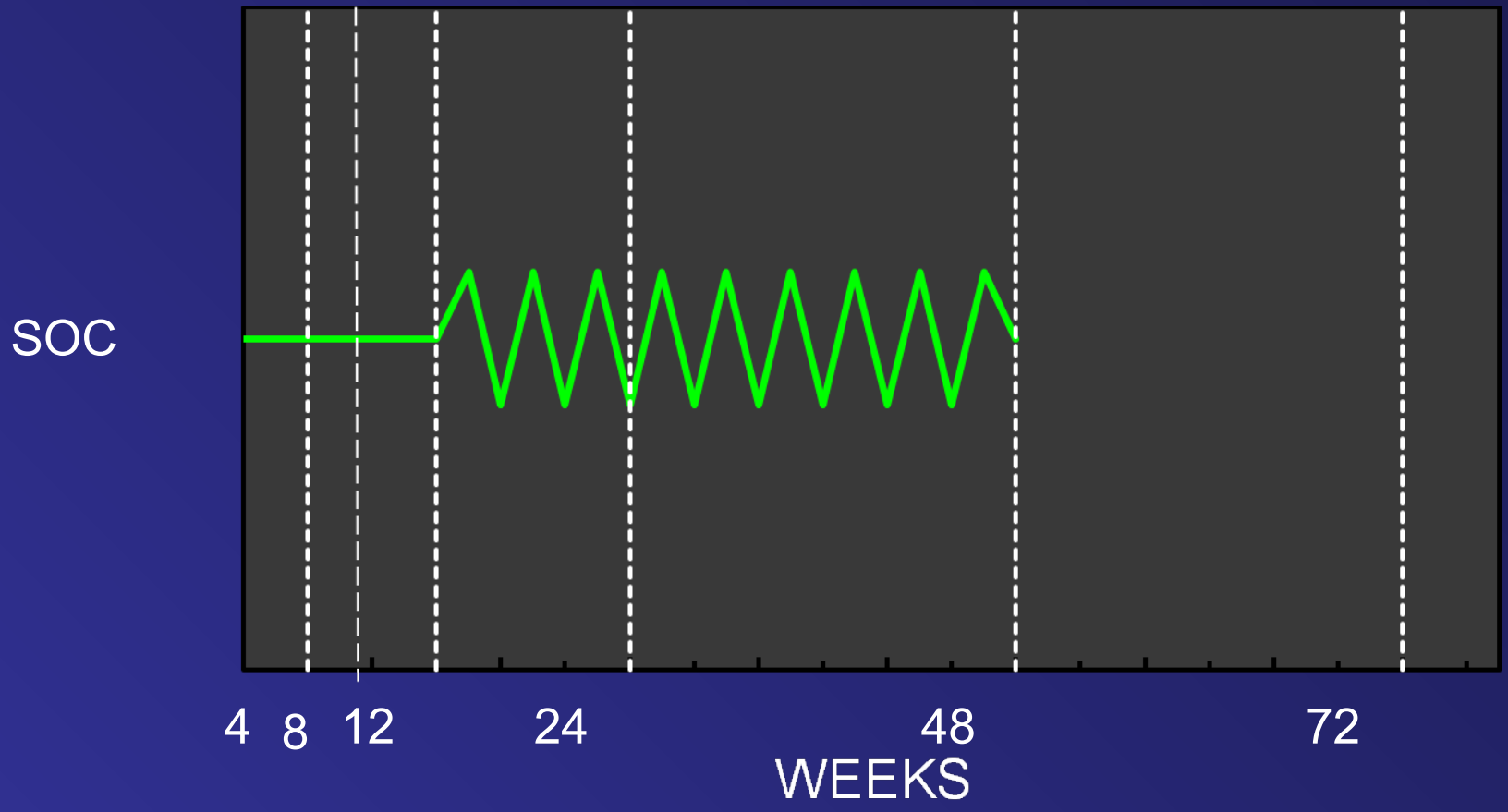
Lampertico P et al .GUT 2012

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

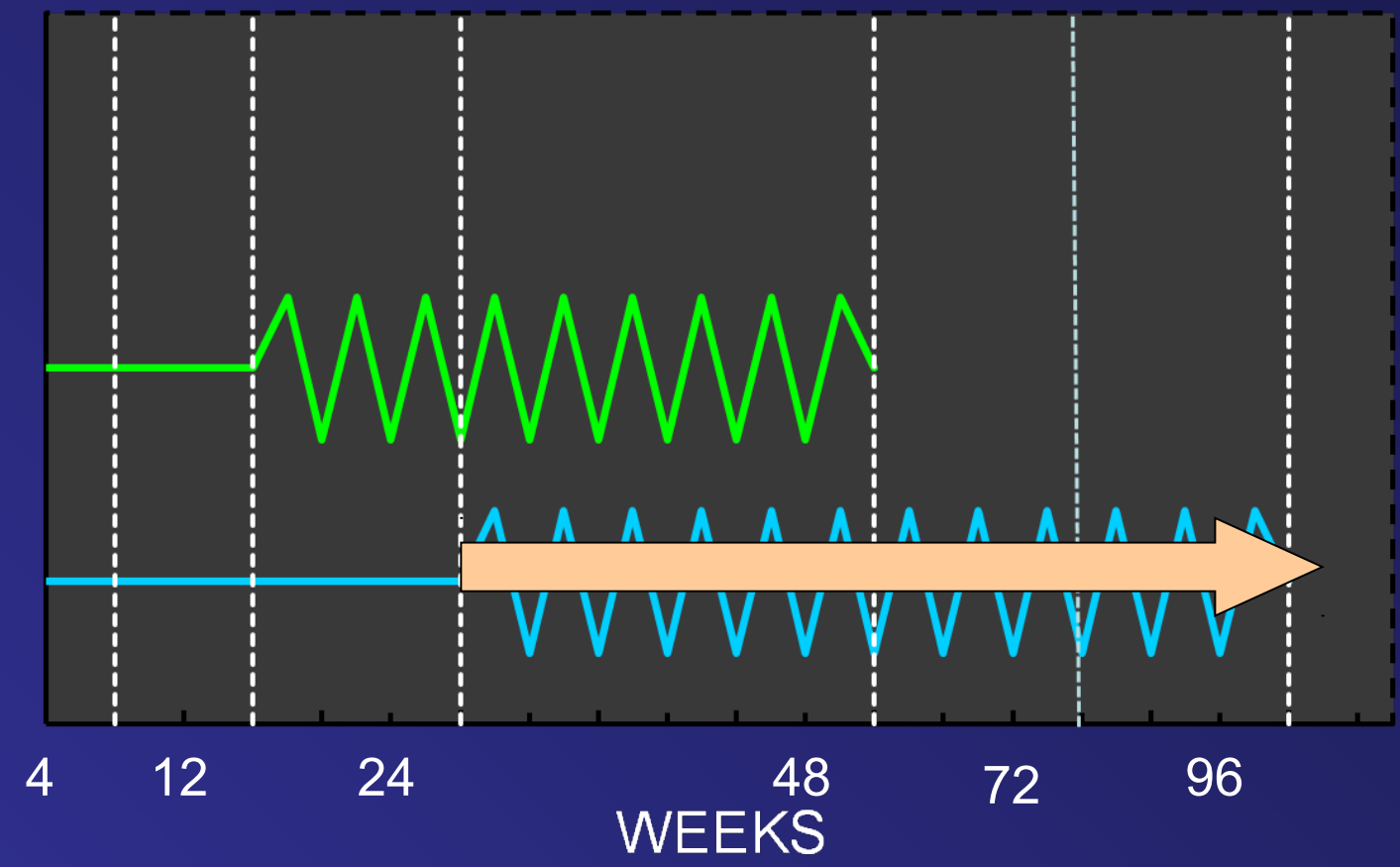
A response-guided approach based on HBsAg kinetics may identify patients with the greatest chance of success

Halfon P. J Hepatol 2014

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



TIME TO BECOME HBsAG NEGATIVE EXTEND DURATION OF TREATMENT:



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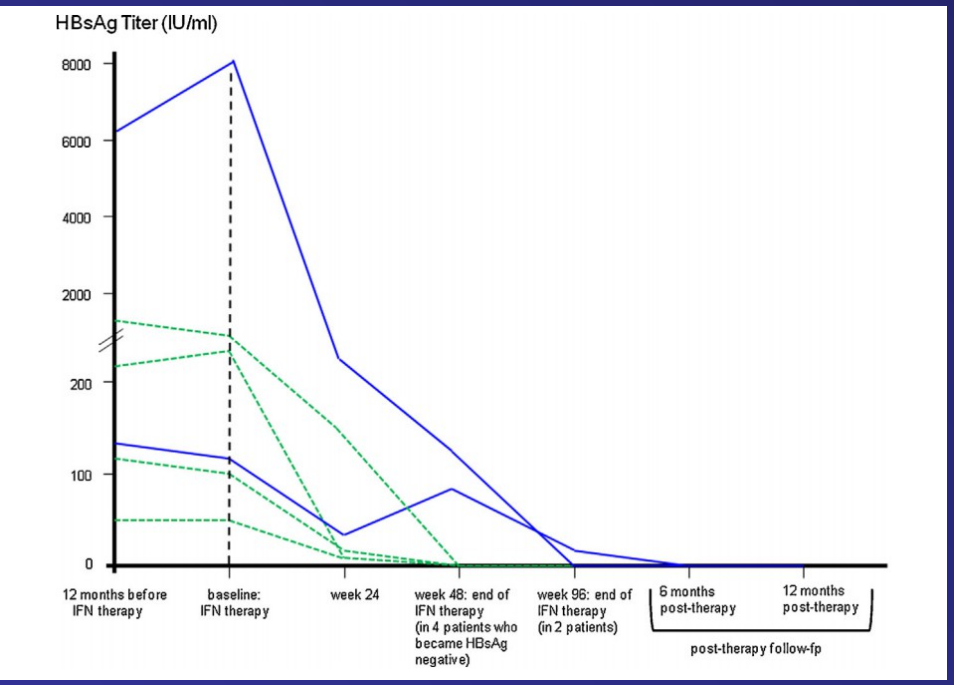
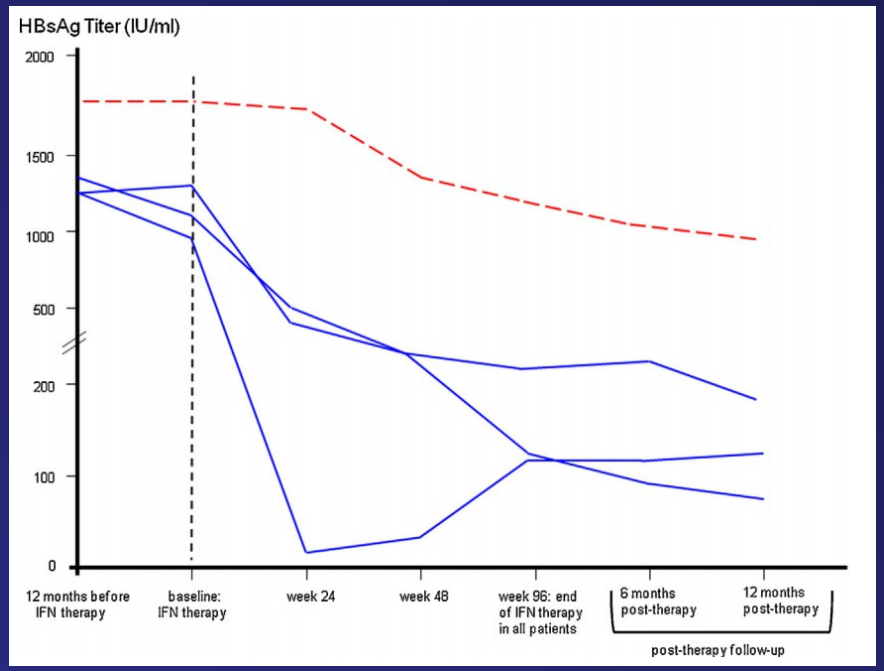
Add-on peg-interferon leads to loss of HBsAg in patients with HBeAg-negative chronic hepatitis and HBV DNA fully suppressed by long-term nucleotide analogs

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

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

An new add-on IFN treatment strategy based on tailored HBsAg monitoring allowed for the first time :

- a loss of HBsAg in 60% of patients
- persistence of loss > 18 mo after end of therapy
- seroconversion in 40%

HBsAg monitoring during interferon treatment for chronic hepatitis delta in four patients

Adapting interferon treatment duration through HBsAg titer monitoring provides a loss of HBs Ag and the cure of chronic HDV

Ouzan D, Halfon P et al J Hepatol 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

Nationwide large survey on HBs antigen quantification use in real life clinical practice in France

- 135 Practitionners (Hepatologists and Gastroenterologists)
- Survey conducted from march 2014 to may 2014
- Questions were related on :
  - Reason for prescription of HBsAg quantification,
  - Reasons for no-prescription
  - Knowledge of the asssay used for the HBsAg quantification
  - Site were the analyses were performed
  - Interest of the practitionner in HBsAg quantification

Halfon P et al *in press*

Reason for prescription of HBsAg quantification among the 102 (76%) practitionners that uses the test

- 88% of the practitionners prescript HBsAg quantification before treatment
- 76% prescript HBsAg quantification at week 12 or week 24 of treatment, or for stopping rules
- 73% prescript HBsAg quantification in combination with HBV viral load

Reason for no-prescription of HBsAg quantification among the 30 (24%) practitionners that do not use the test

- 50% of the practitionners did not prescript HBsAg quantification because of a difficult access to the test
- 27% did not prescript HBsAg quantification because the they thought the test is not refunded

Conclusions :

The usefulness of quantitative HBsAg

- Decisional algorithms based on HBsAg and HBV DNA kinetics leading to response guided therapy are needed

- “Time-individualized Peg-IFN treatment” according to the evolution of HBsAg titer should be validated in large clinical trial

- HBsAg monitoring have to be considered in EASL, APASL and AASLD recommandations