HBsAg quantification
"Clinical applications"

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Plan

Introduction

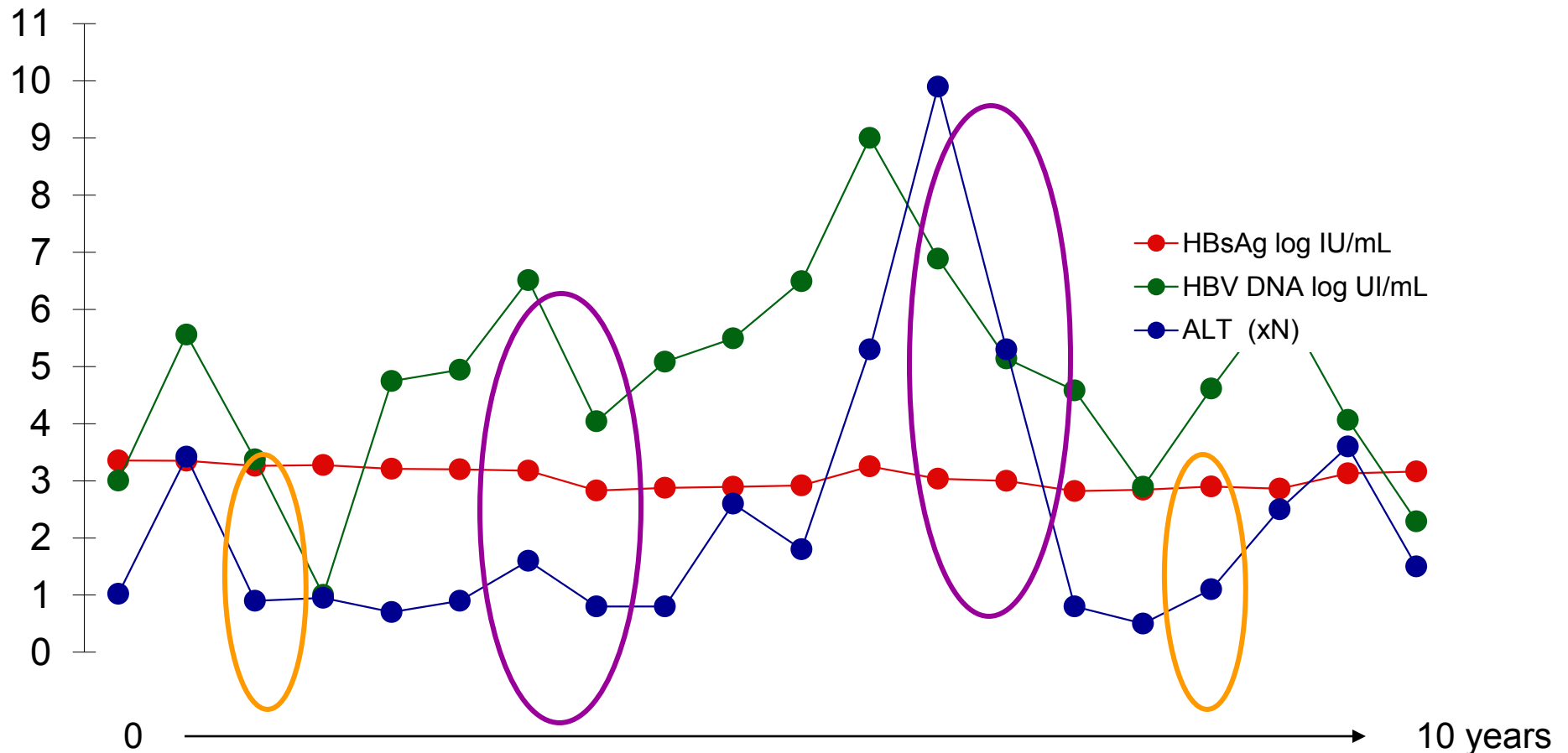## Clinical implications
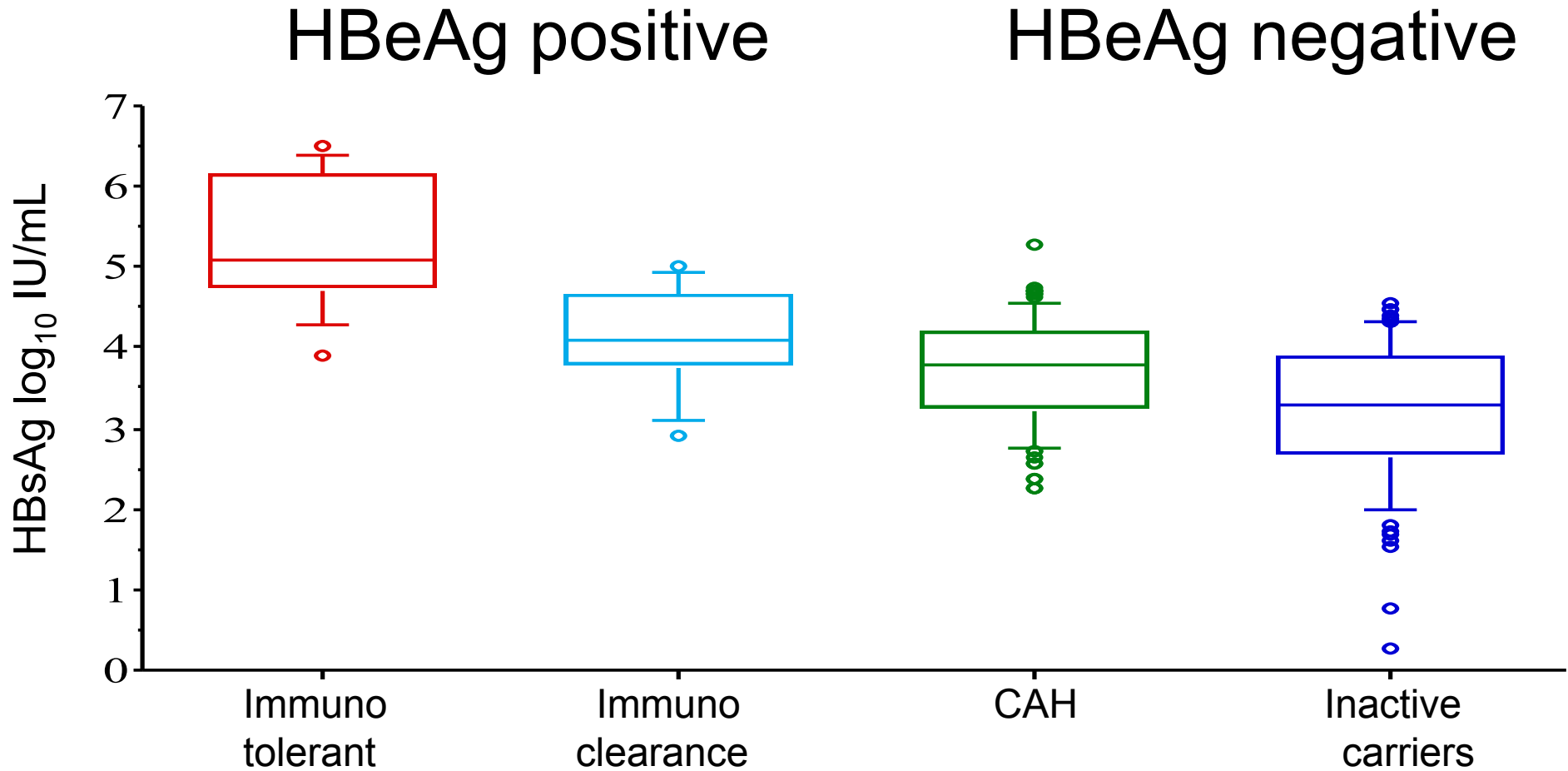
Natural History

PEG-IFN therapy

NUCs Therapy

Conclusions

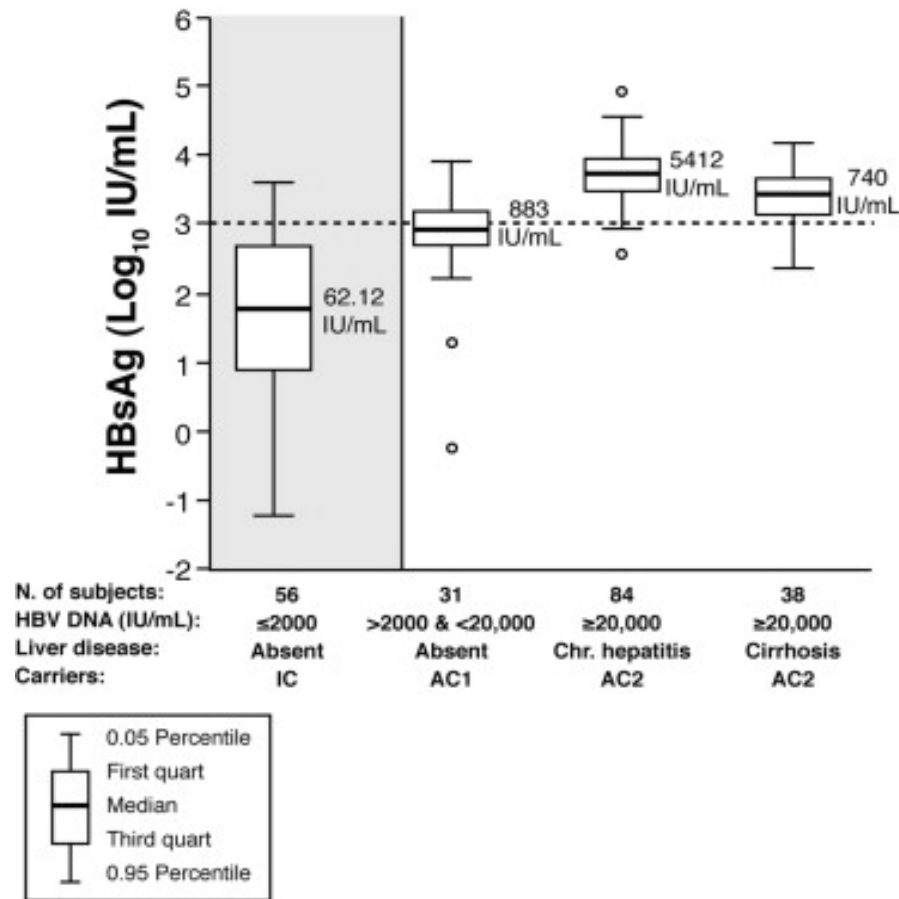# HBsAg reliable marker

Untreated patient: 10 years follow-up

Legend:
- HBsAg log IU/mL
- HBV DNA log UI/mL
- ALT (xN)

Martinot-Peignoux et al. Liver International On line

" HBsAg "
Natural History

HBsAg Natural History

HBeAg positive — HBeAg negative

HBsAg $\log_{10}$ IU/mL

Immuno tolerant · Immuno clearance · CAH · Inactive carriers

Nguyen T. et al. J Hepatol 2010;52;508
Chan et al Hepatology 2010;52:1232

Jaroszewicz. et al. J Hepatol 2010;52;514
Martinot-Peignoux et al. Hepatology 2010;52:992A

Prediction of inactive phase

HBeAg negative patients genotype D

HBsAg (Log$_{10}$ IU/mL)

6
5
4   5412 IU/mL   740 IU/mL
3   883 IU/mL
2   62.12 IU/mL
1
0
-1
-2

N. of subjects: 56   31   84   38
HBV DNA (IU/mL): ≤2000   >2000 & <20,000   ≥20,000   ≥20,000
Liver disease: Absent   Absent   Chr. hepatitis Cirrhosis
Carriers: IC   AC1   AC2   AC2

0.05 Percentile
First quart
Median
Third quart
0.95 Percentile

Combining
HBsAg <1000 IU/mL and HBV DNA <2000 IU/mL

Prediction   Inacive carriers

Sensitivity   91/1%
Specificity   95.4%
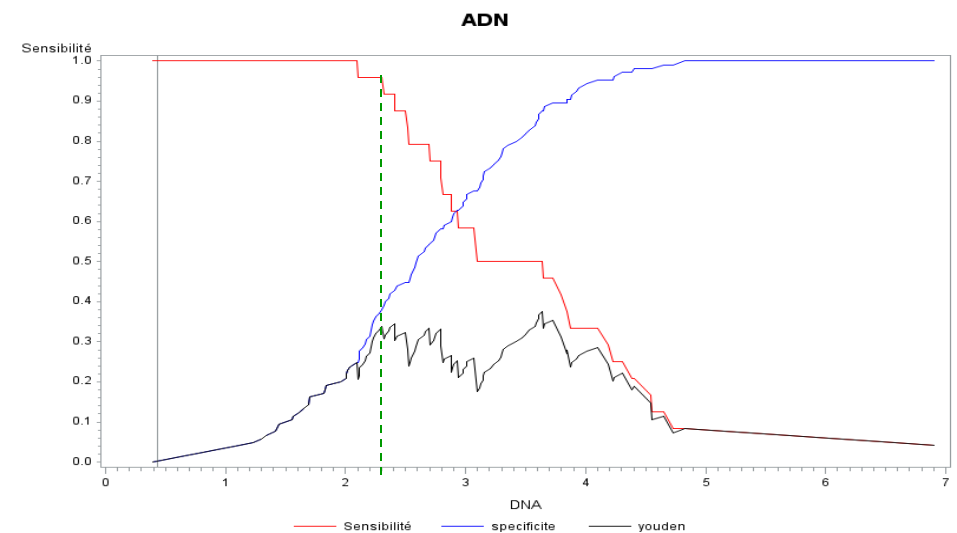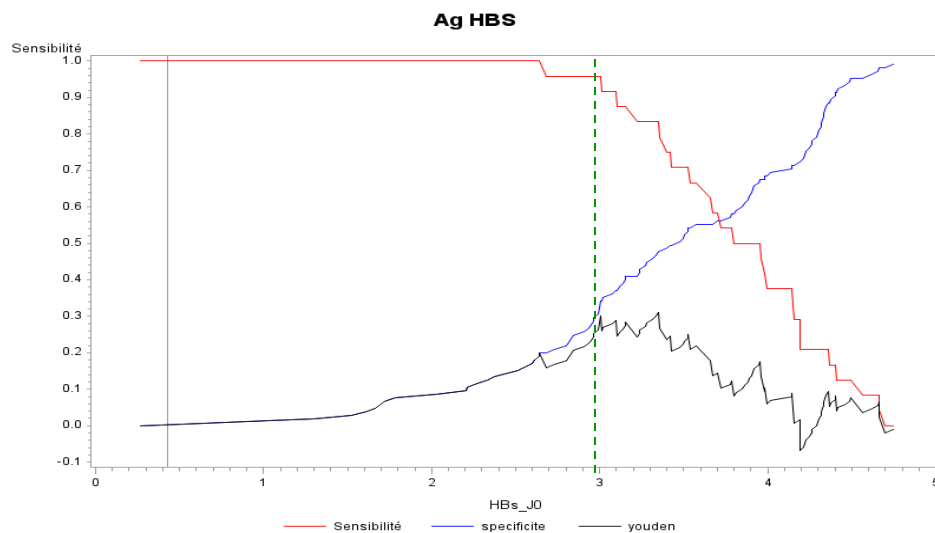PPV   87.9%
NPV   96.7%
Accuracy   94.5%C

Brunetto et al. Gastroenterology 2010;139:483

Prediction of Hepatitis Flare

HBeAg negative patients genotype A to E
Cutoff values of HBsAg and HBV DNA defined by the Youden's index of the ROC

HBsAg: 1000 IU/ml and ADN VHB: 200 IU/ml

VPN	96%	VPP	30%
Sensibilité	92%	Spécificité	51%

Martinot- Peignoux et al. J Hepatol 2002; 36: 543
Martinot-Peignoux et al. Hepatology 2012;56:434A

Prediction of Fibrosis stage

406 genotype A to E patients

HBeAg positive

HBsAg $\log_{10}$ IU/ml

4.95 ± 0.7
4.60 ± 0.56
4.19 ± 0.91
3.83 ± 0.75
3.34 ± 1.12

p < 0.01

F0 F1 F2 F3 F4

HBeAg negative

HBsAg $\log_{10}$ IUml

3.51 ± 1.08
3.55 ± 0.85
3.75 ± 0.92
3.71 ± 0.48
2.96 ± 135

ns

F0 F1 F2 F3 F4
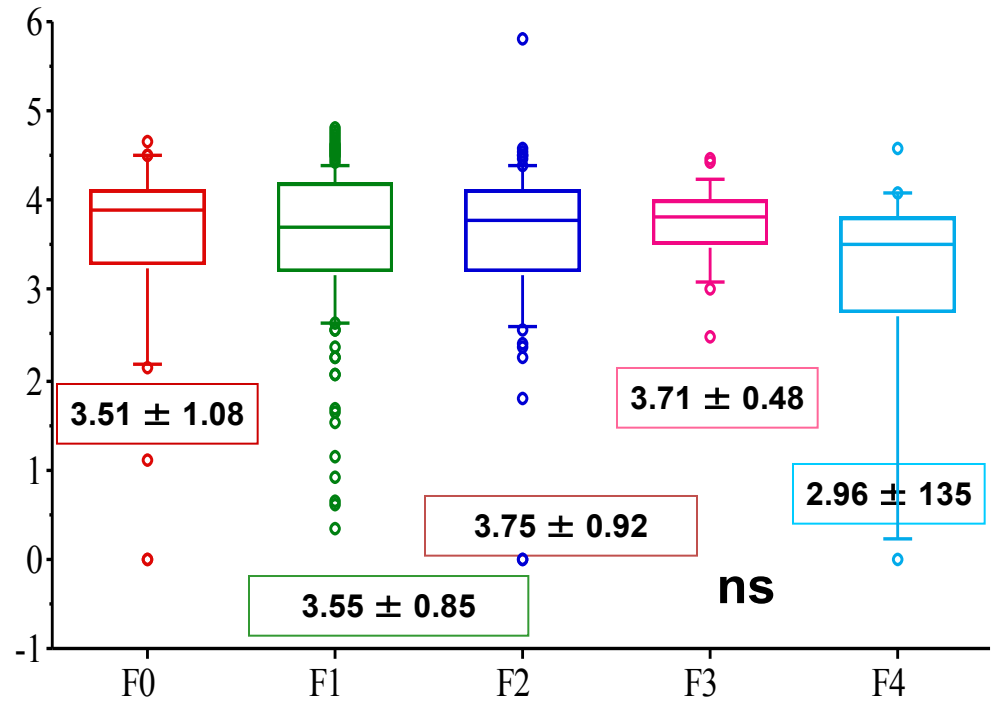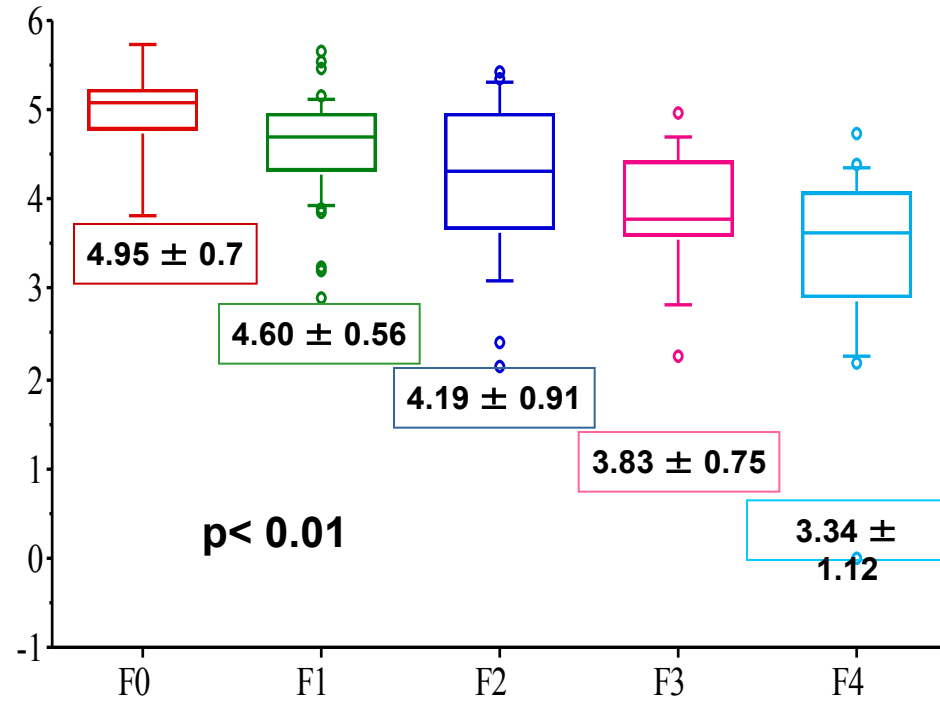
HBsAg threshold: 3.85 log IU/mL identifying F0-1 from 2-4

Martinot-Peignoux et al. J Hepatol 2013 in Press.

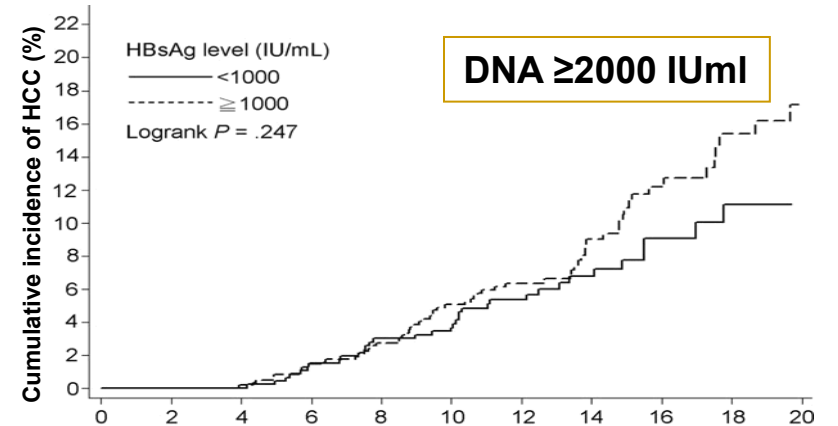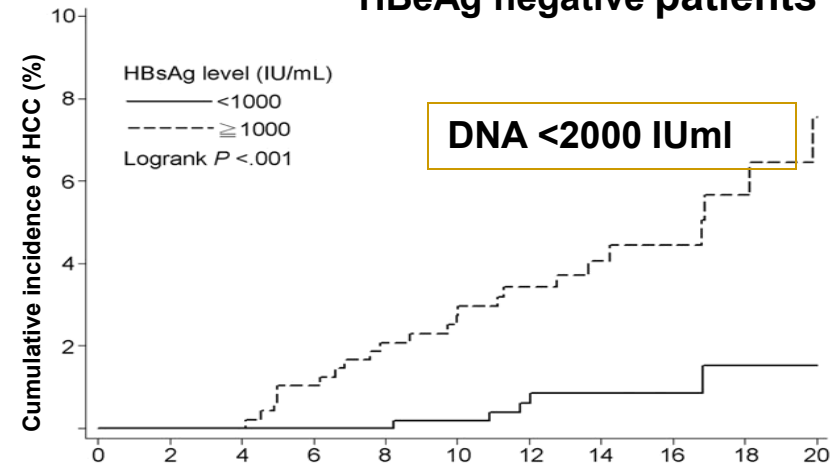# Prediction of HCC

Factors associated with HCC
2688 patients genotypes B+C ,15 years follow-up

- ✓ Age >60 years,
- ✓ Male,
- ✓ ALT >N
- ✓ Genotype C
- ✓ AgHBe positive
- ✓ HBV DNA >2000 UI/ml
- ✓ **Not HBsAg**

HBeAg negative patients (n=2165)
- ✓ Age,
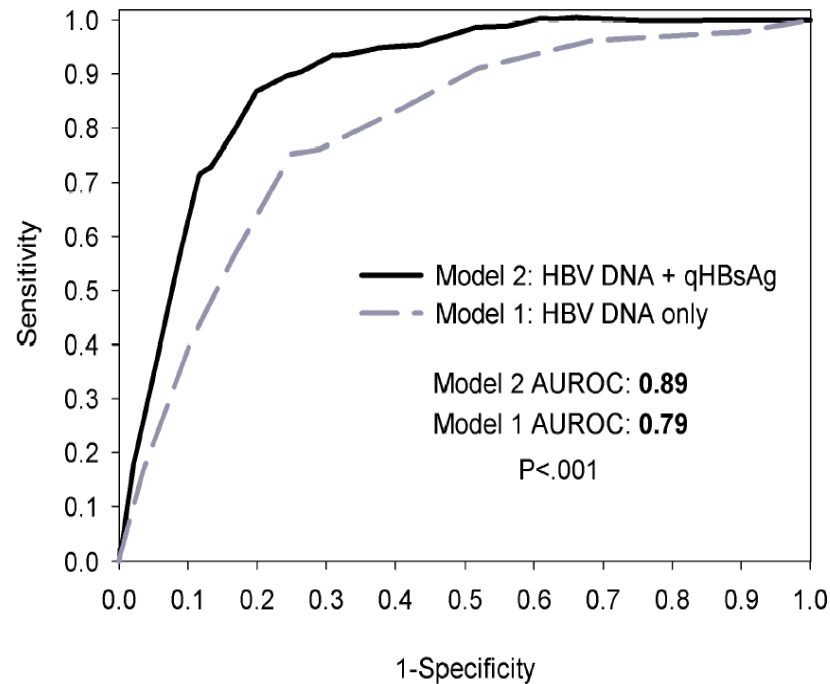- ✓ Male,
- ✓ ALT >N
- ✓ **AgHBs**
- ✓ **Not HBV DNA**

Tseng TC Gastroenterology 2012;142:1140
Tseng TC Hepatology 2013 in Press

HBeAg negative patients

HBsAg level (IU/mL)
— <1000
---- ≧1000
Logrank *P* <.001

DNA <2000 IUml

HBsAg level (IU/mL)
— <1000
---- ≧1000
Logrank *P* = .247

DNA ≥2000 IUml

Minimal risk for HCC
HBsAg <1000 IU/ml et DNA <2000 IU/ml
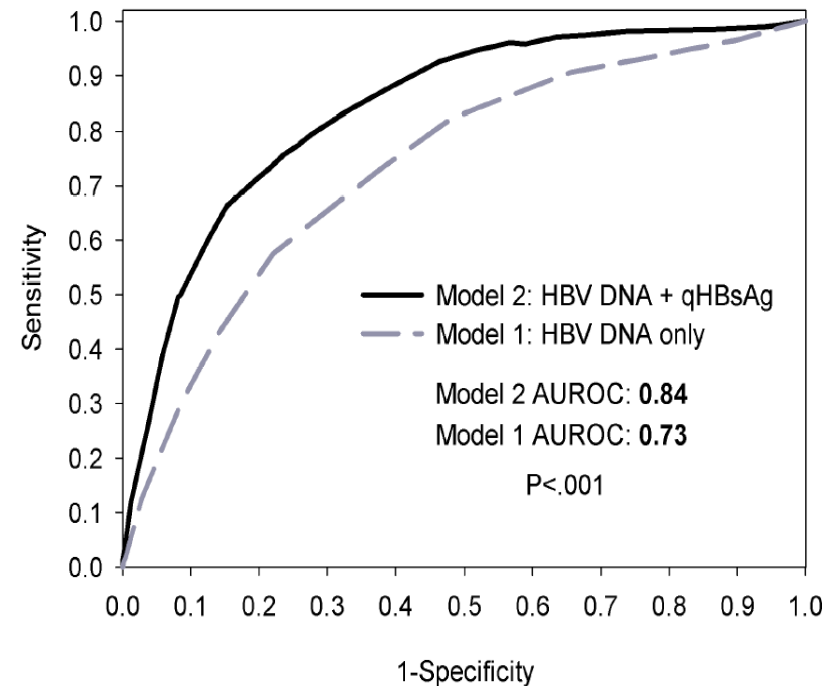
Prediction of HBsAg seroclearance

2491 untreated genotype B and C participants (R.E.V.E.A.L-HBV study)

Model 1: Age, BMI, Baseline HBV DNA.

Model 2: Age, BMI, Baseline HBV DNA +HBsAg

Model 2: HBV DNA + qHBsAg
Model 1: HBV DNA only

Model 2 AUROC: **0.89**
Model 1 AUROC: **0.79**

P<.001

5 years

Model 2: HBV DNA + qHBsAg
Model 1: HBV DNA only

Model 2 AUROC: **0.84**
Model 1 AUROC: **0.73**

P<.001

10 years

Tseng TC Hepatology 2012;55: 68
Liu J. et al Gastroenterology 2010;139:474 and J Hepatol.2013 in Press

Summary (Natural history)

In HBe positive patients

✓ HBsAg levels allow differentiating F 0-1 from F 2-4 patients

HBsAg threshold 1000 IU/mL allows accurate

✓ Identification

    Inactive carriers

    Patients with high risk of reactivation
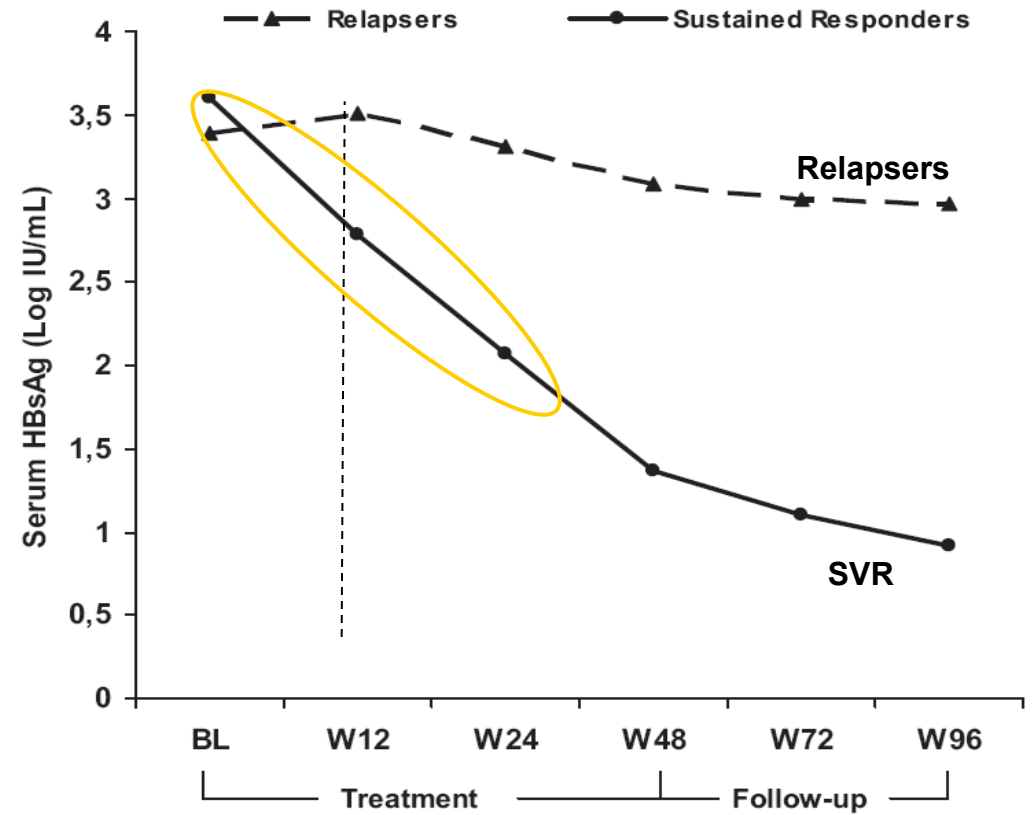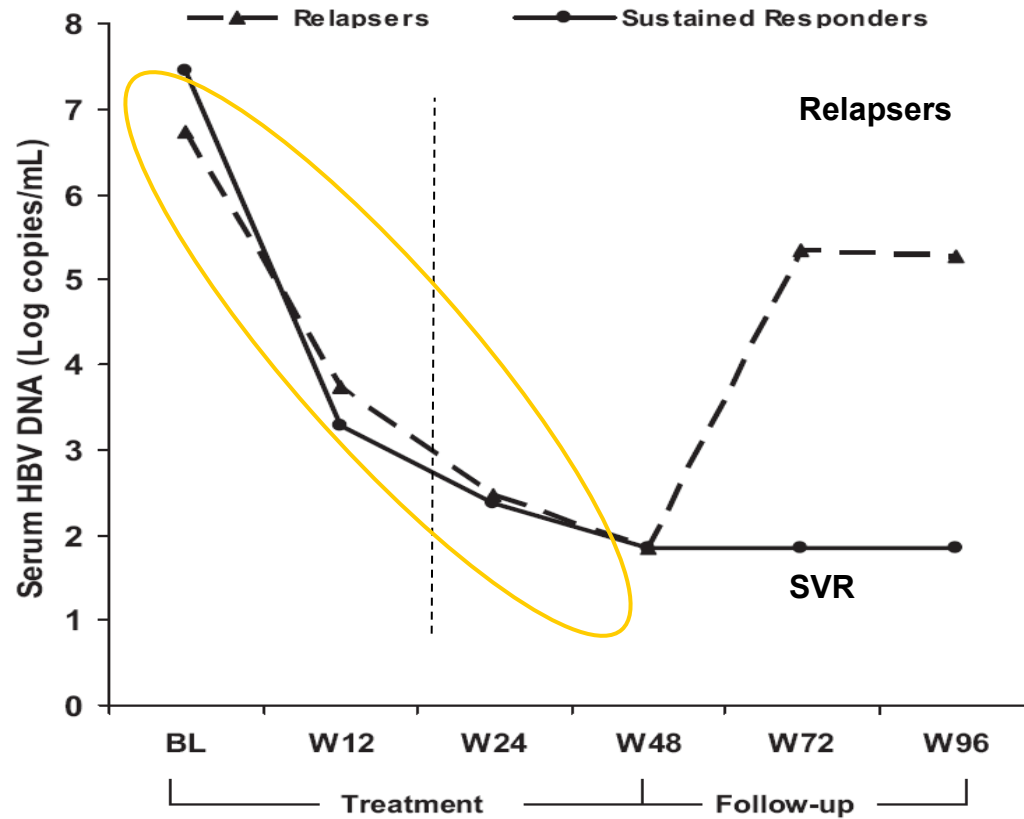
    Patients with minimal risk for HCC

✓ Prediction of HBsAg sero-clearance

    Most of the studies performed in genotype Band C patients

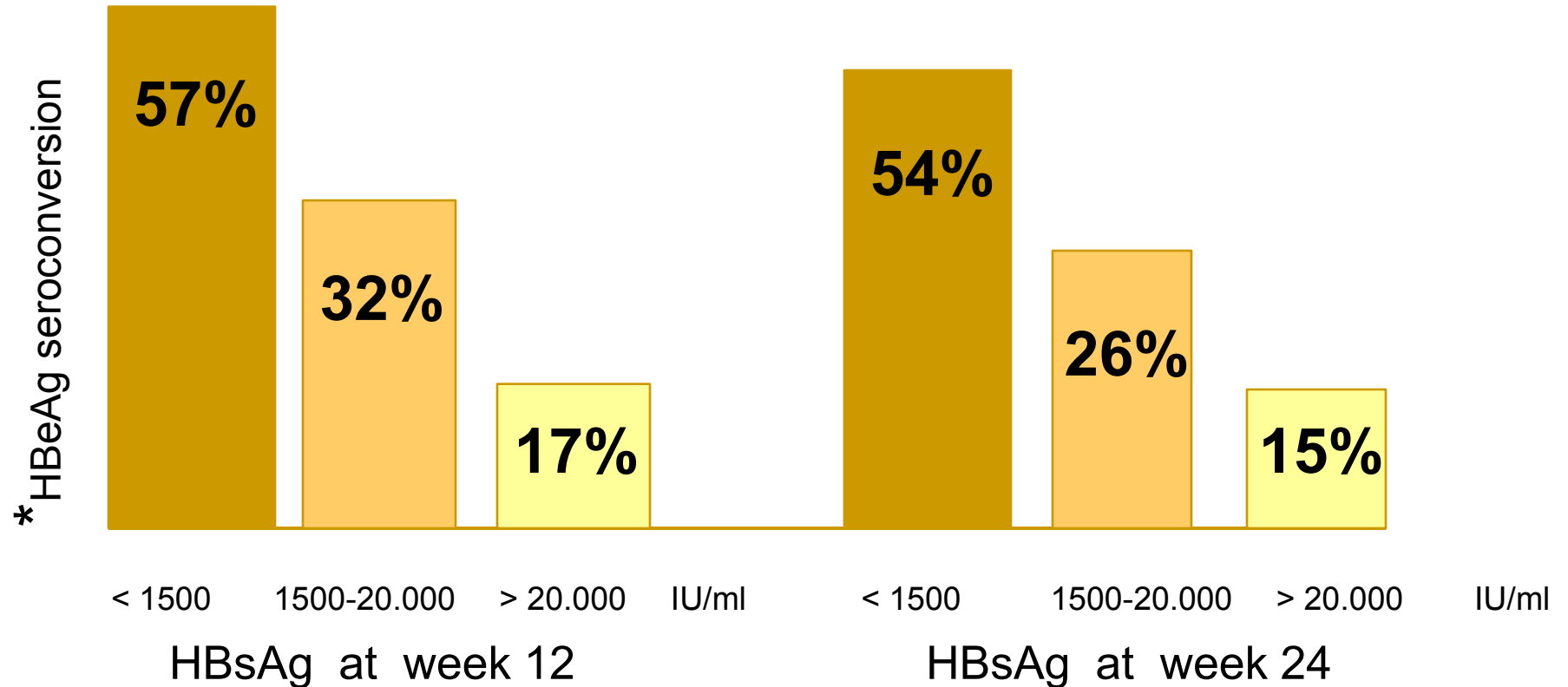# Pegylated Interferon (PEG-IFN) therapy

Prediction of response to PEG-IFN

HBV DNA and HBsAg Kinetics

Moucari et al. Hepatology 2009;49:1151
Brunetto et al. Hepatology 2009;49:114

Prediction during therapy

HBeAg positive 48 weeks PEG-IFN alfa-2a :NEPTUNE study

*HBeAg seroconversion

HBsAg at week 12

< 1500	1500-20.000	> 20.000	IU/ml
57%	32%	17%	

HBsAg at week 24

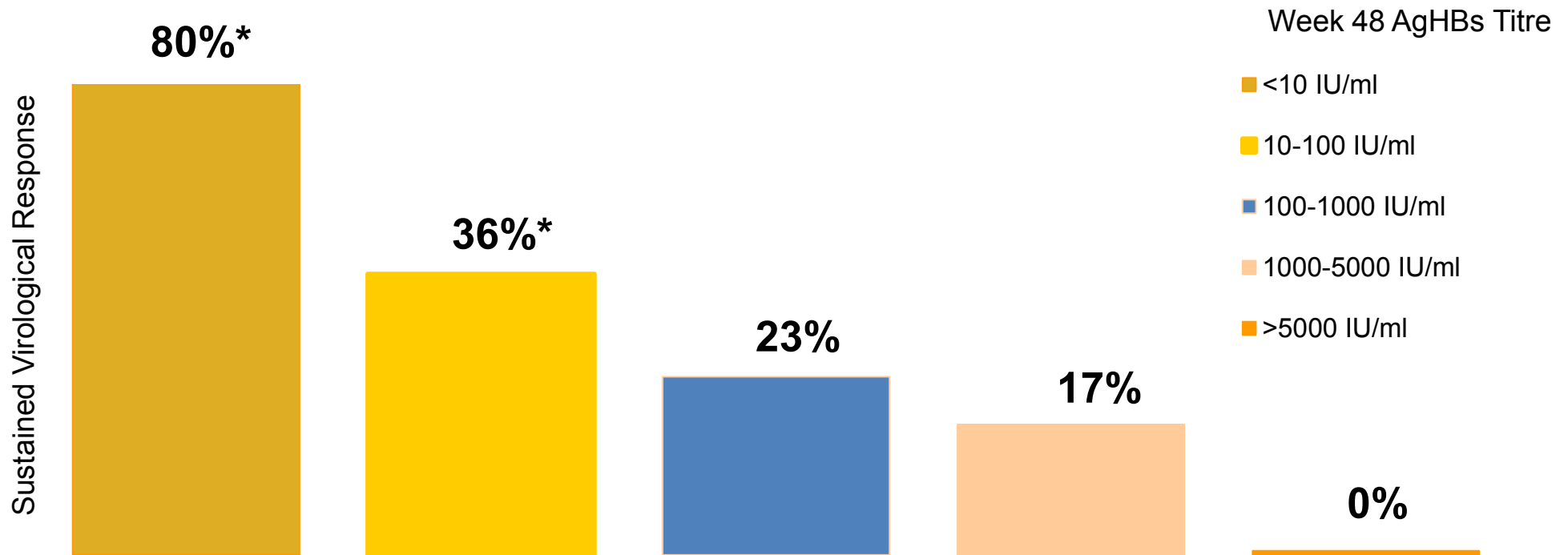| < 1500	1500-20.000	> 20.000	IU/ml
54%	26%	15%	

*HBeAg seroconversion 24 weeks post-treatment

Piratvisuth et al. Neptune APASL 2010
Lau G. et al. EASL 2009; S333
Gane et al. EASL 2011 A69

Prediction at end of treatment

Italian genotype D patients: SVR and HBsAg loss according to end of treatment HBsAg levels

Week 48 AgHBs Titre
- <10 IU/ml
- 10-100 IU/ml
- 100-1000 IU/ml
- 1000-5000 IU/ml
- >5000 IU/ml

80%* 36%* 23% 17% 0%

Sustained Virological Response

* At 3 years :HBsAg <10 IU/ml 52% HBsAg loss and 2 HBsAg > 10 UI/m: 2% HBsAg loss

Brunetto et al. Hepatology 2009;49:1141

Summary (PEG-IFN)

Authors	HBeAg	HBsAg	Week12 NPV	Week 24 NPV
Chan (2010)	Positive	< 1 log decline	na	85%
Lau (2009)	Positive	< 1500 IU/ml log decline	72%	76%
Gane (2011)	Positive	> 20 000	84%	na
Sonneveld (2010)	Positive	No decline	97%	na
Piratvisuth (2010)	Positive	No decline	82%	na
Liaw (2011)	Positive	< 1500 IU/ml log decline > 20 000 IU/ml	84% 100%	85% 100%
Ma (201)	Positive	< 1500 IU/ml log decline	91%	na
Rijckborst (2012)	Negative	No decline	100%	na
Moucari (2009)	Negative	<0.5 log decline	90%	97%

Summary (PEG-IFN)

"Week 12 stopping rule"

✓ Absence of any decline (decrease <2 log) of HBsAg at week 12 and 24 of a 48- week course of PEG-IFN is associated with a NPV of 84-100% for SVR

✓ HBsAg can be used as a surrogate marker to predict PEG-IFN treatment outcome:

- absence of HBsAg decline at **week 12**

    prediction of non-response **"stop therapy"**

- any HBsAg decline at **week 24**

    prediction of response **"continue therapy"**

HBsAg should be used for monitoring PEG-IFN therapy

# Nucleosi(ti)des Analogues (NUCs) therapy

Why quantify HBsAg?

NUCs therapy

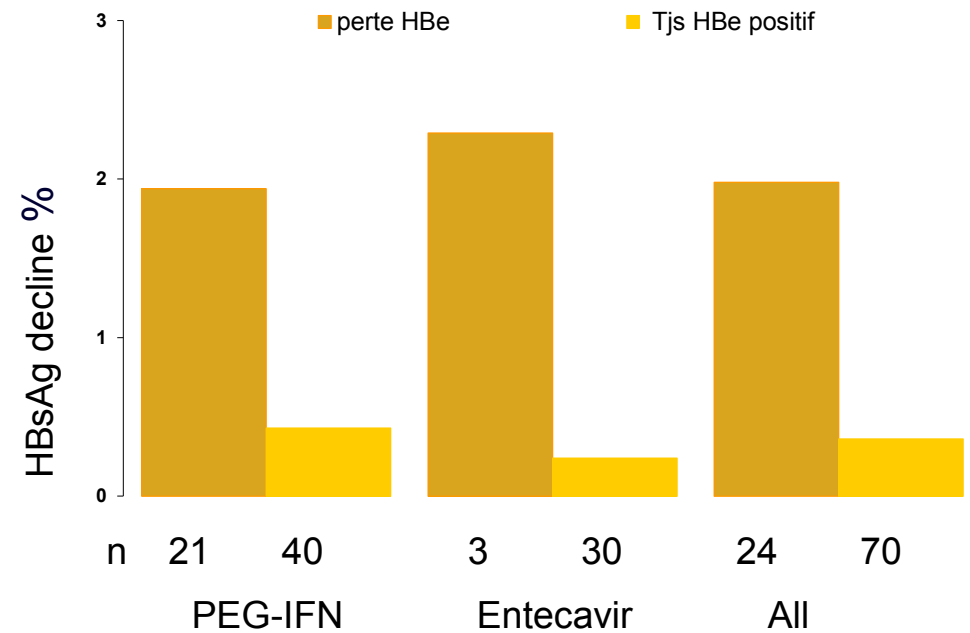|	HBeAg positive	HBeAg negative
HBsAg (Baseline)	4.1 log UI/ml	3.4 log UI/ml
Decline (log IU/year)	0.11 (0.004-0.34)	0.007 (0.001-0.18)
Duration* (1log decrease)	**6.6 (1.7-17.5)**	**8.0 (0.5-14.9)**
Duration* (HBsAg loss)	36.4 (9.6-93.)	38.9 (1.3-89.5)

*Years

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

Prediction during therapy

HBeAg + /- patients 48 weeks PEG-IFN or Entecavir
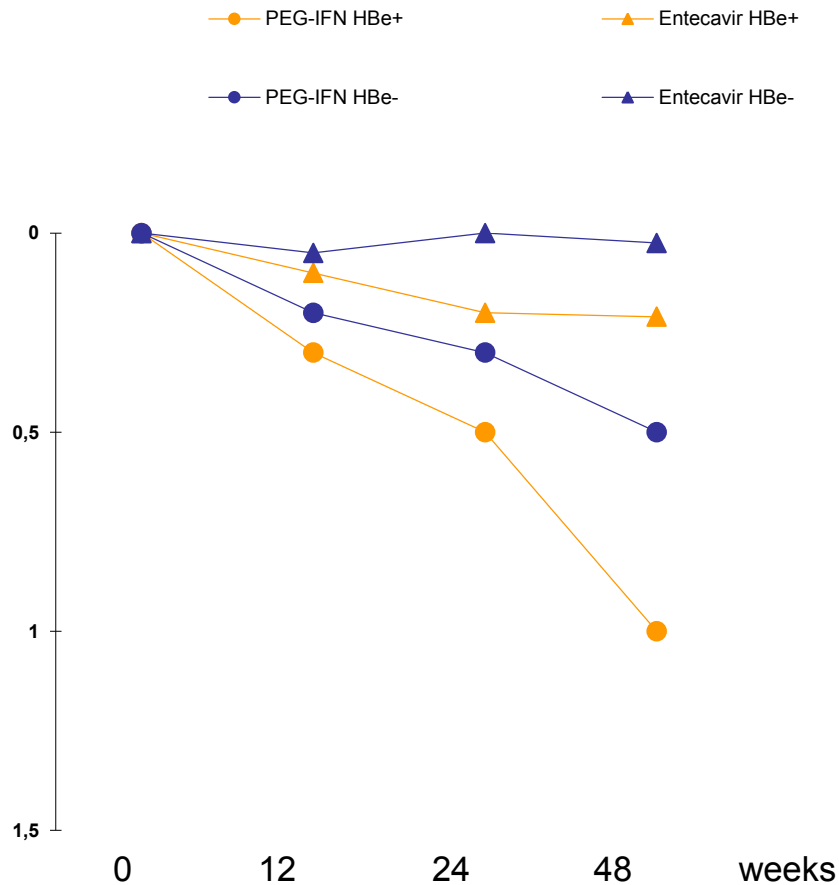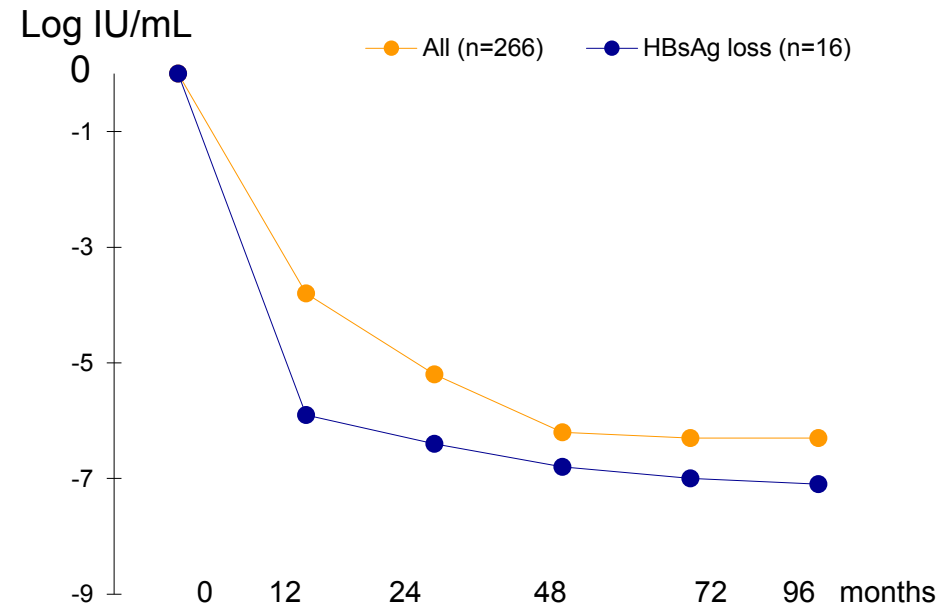
Prediction during therapy

48 weeks ADV+ 96 weeks TDV and 144 weeks TDV

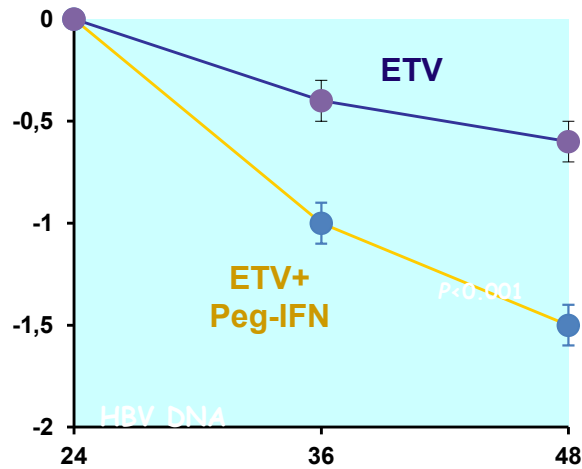HBsAg Kinetics during therapy
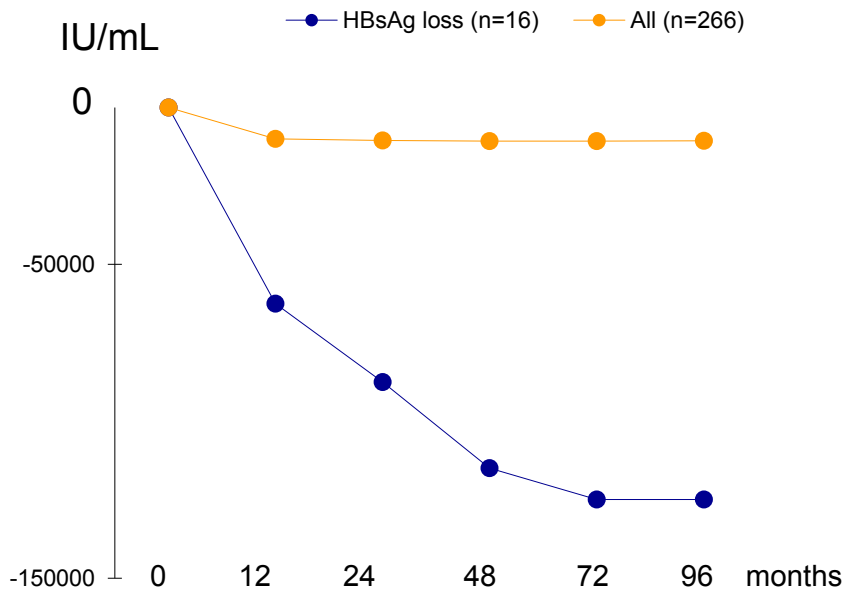
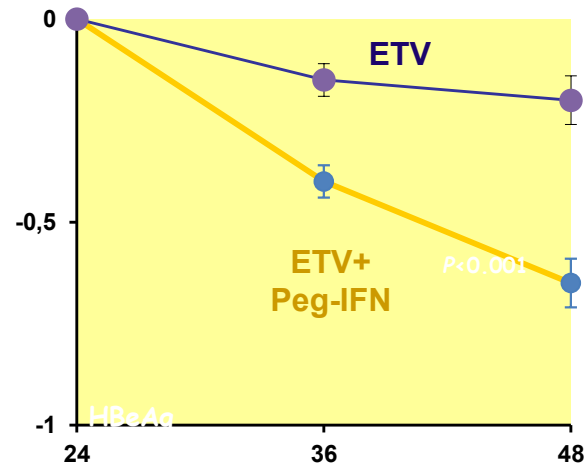HBV DNA Kinetics during therapy

An HBsAg decrease <2.41 log IU/mL at 24 weeks of therapy was associated with an HBs loss in 3%, 6% 8% at 1, 2 3 years, only in HBeAg positive patients

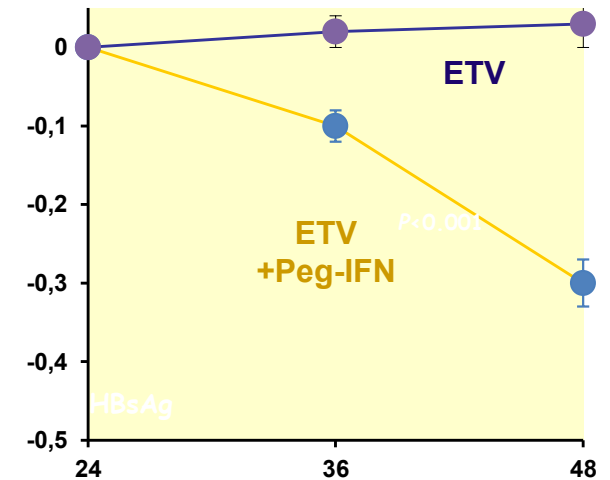Heathcote et al. J Hepatol 2009:50:S331
Heathcote et al. Gastroenterology 2011;140:132

Marcellin et al.N Engl J Med 2008;359:2442
Marcellin et al. Lancet 2012 on line

Add on therapy

HBeAg positive patients treated with 48 weeks ETV or +ETV + PEG-IFN


HBV DNA decline

HBeAg decline

HBsAg decline

Adding PEG-IFN Alfa-2a to ETV Increases HBsAg Decline and HBeAg Clearance
PEG-IFN add-on was independently associated with SVR 3.78 (95%CI: 1.2-10.7)

Marcellin et al. J Hepatol 2012; 54:449
Sonnevelg et al. Hepatology 2012;56(Suppl);199A

Prediction of outcome

Prediction of outcome after NUCs therapy discontinuation
2 measurements with HBeAg or ADN negative

Cumulative probability of virological relapse

HBsAg >3 log IU/ml at end of therapy

HBsAg 2-3 log IU/ml at end of therapy

p=0,01

HBsAg ≤ 2log IU/ml at end of therapy
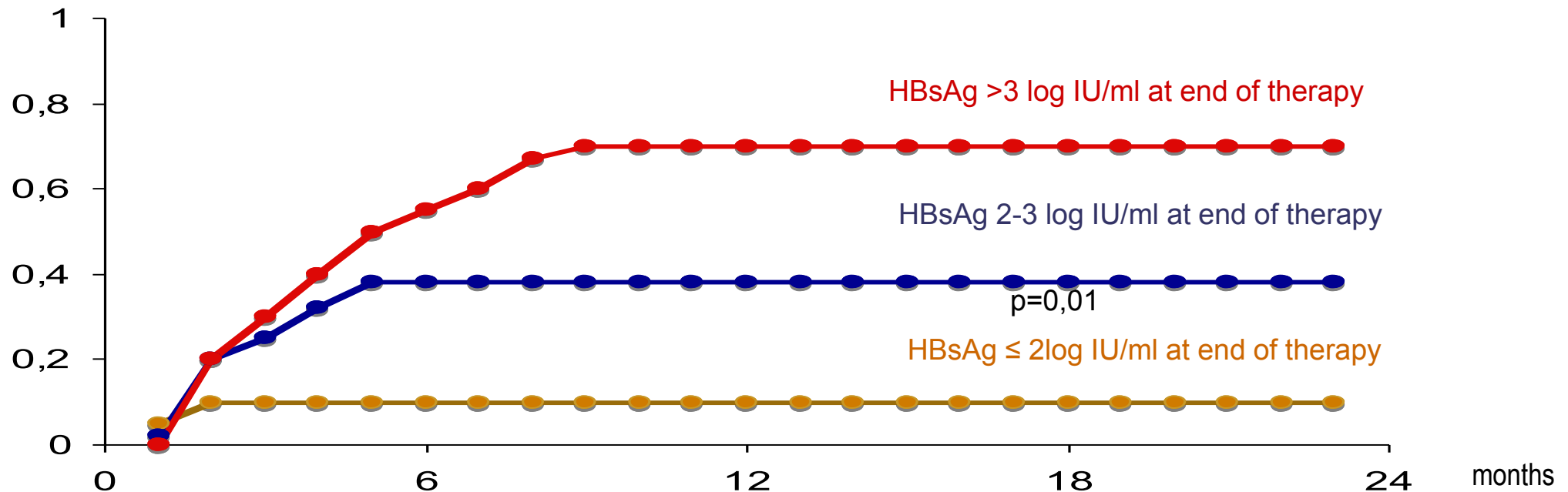
HBsAg ≤ 2log IU/ml at treatment discontinuation is predictive of sustained response

Liaw et al. Hepatol Int 2008;2:263 APASL
Liang Y. AP&T 2011: 34:344

Summary NUCs

HBeAg positive patients

Early identification of patients who experience rapid decline:

✓ high probability of SVR and HBsAg loss

HBeAg negative patients

Low decrease

✓ can be useful: HBVDNA rapidly undetectable

Can we stop therapy? When?

NEEDS FURTHER INVESTIGATION

Conclusions

Why quantify HBsAg in 2013?

Baseline identification of:
- ✓ Inactive carriage,
- ✓ Severity of liver disease,
- ✓ Probability of HCC and
- ✓ Probability of HBsAg loss

Kinetics:

- ✓ Spontanous outcome of liver disease

- ✓ Outcome of therapy

PEG-IFN: Stopping rule

NUCs: HBeAg postive

Perspectives

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

PEG-IFN
- Week 12 or 24 stopping rule?
- Tailor duration of therapy (96 weeks)?

NUCs
- Define optimal HBsAg thresholds associated with effective immune control that enable treatment discontinuation (stopping rule) with low risk of relapse

- AASLD, APASL, EASL guidelines need to be actualized

Working lucheon: The clinical application of HBsAg quantication Room 251 level 2