european hiv hepatitis co-infection

Overview of biomarkers for viral evolution and liver disease progression in hepatitis B and Hepatitis C

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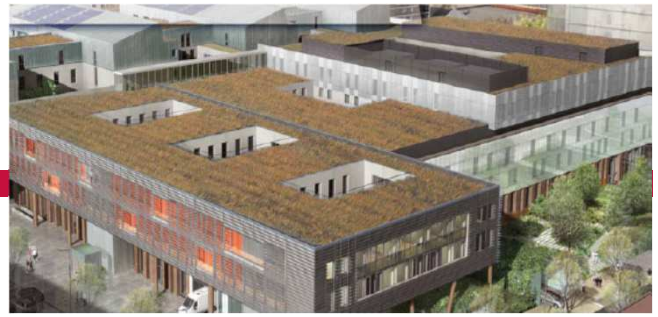

10-11 December 2015

EUROPEAN HIV HEPATITIS CO-INFECTION (EHHC)

CONFERENCE

ehhc
european hiv hepatitis co-infection

Dr Philippe Halfon

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COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Philippe Halfon	Nothing to declare
Date	December 2015

Disclosures Philippe Halfon

- **Speaker** : Merck, Janssen, Gilead, BMS
- **Scientific advisory Board** : Provepharm
- **Shareholders and Founder**: GenosciencePharma
- **Scientific Grant** : Gilead

Overview

1. **Introduction**

2 Biomarkers for viral evolution and liver disease progression in Hepatitis C

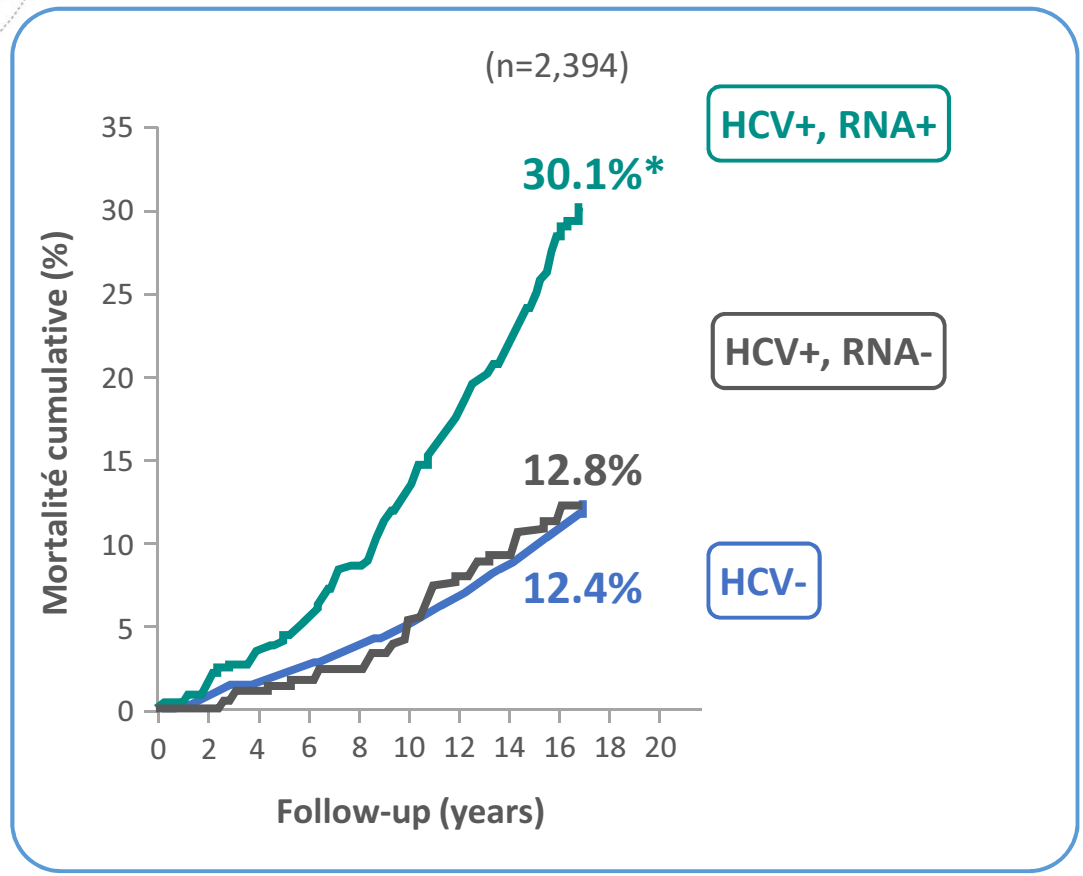
3 Biomarkers for viral evolution and liver disease progression in Hepatitis B

- Fibrosis Markers
- Clinical utility of HBsAg Quantification

4 Conclusion

Overview of biomarkers for viral evolution and liver disease progression in Hepatitis C

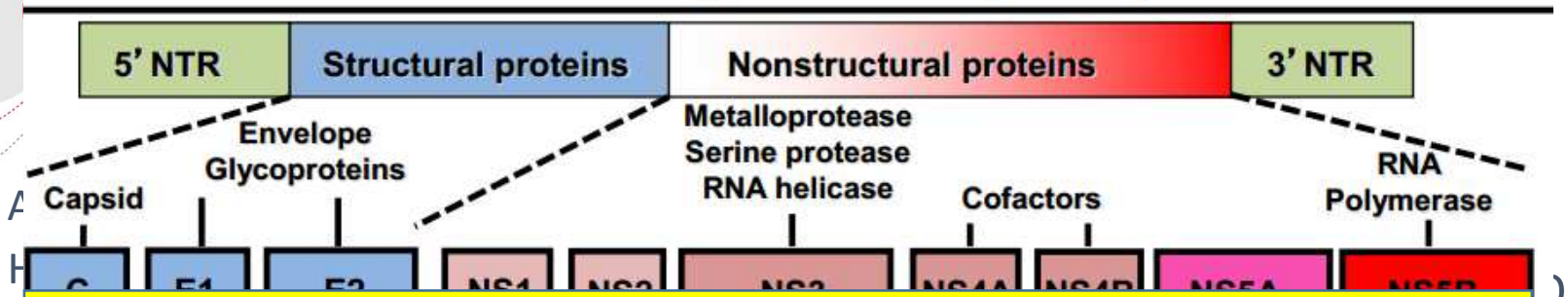
Chronic HCV infection and all-causes of mortality



- 23 820 adults, Taiwan
- 1095 anti-HCV positive
- 760 (69%) detectable Viral RNA

Lee MH, et al. J Infect Dis 2012;206:469-77

Direct-acting antivirals (DAAs)



Do we need any biomarkers for viral evolution and liver disease progression with a SVR > 90% using the DAA?

Protease Inhibitors

Telaprevir
Boceprevir
Simeprevir
Faldaprevir
Asunaprevir
ABT-450
MK-5172
Sovaprevir
ACH-2684

NS5A Inhibitors

Daclatasvir
Ledipasvir
ABT-267
GS-5816
ACH-3102
PPI-668
GSK-2336805
Samatasvir
MK-8742

Polymerase Inhibitors

Nucs	Non-Nucs
Sofosbuvir	ABT-333
VX-135	Deleobuvir
IDX-20963	BMS-791325
ACH-3422	PPI-383
	GS-9669
	TMC-647055

Schinazi R, Halfon P, Marcellin P, Asselah T. Liver International 2014

EASL. J Hepatol 2011;55:245.

The HCV Toolbox : Change of paradigm with the DAA

IFN

RBV

Nuc

High barrier to resistance

PI

Modest barrier to resistance (esp to GT1a)

NS5A

NNI

Low barrier to resistance (esp to GT1a)

Challenges

Treatment Duration

Genotype

Subtype

Cirrhosis

Prior Tx/ IL28B

Race

BMI

HCV RNA

The HCV Toolbox

IFN

RBV

Nuc

High barrier to resistance

PI

Modest barrier to resistance (esp to GT1a)

NS5A

NNI

Low barrier to resistance (esp to GT1a)

Challenges

Treatment Duration

Genotype

Subtype

Cirrhosis

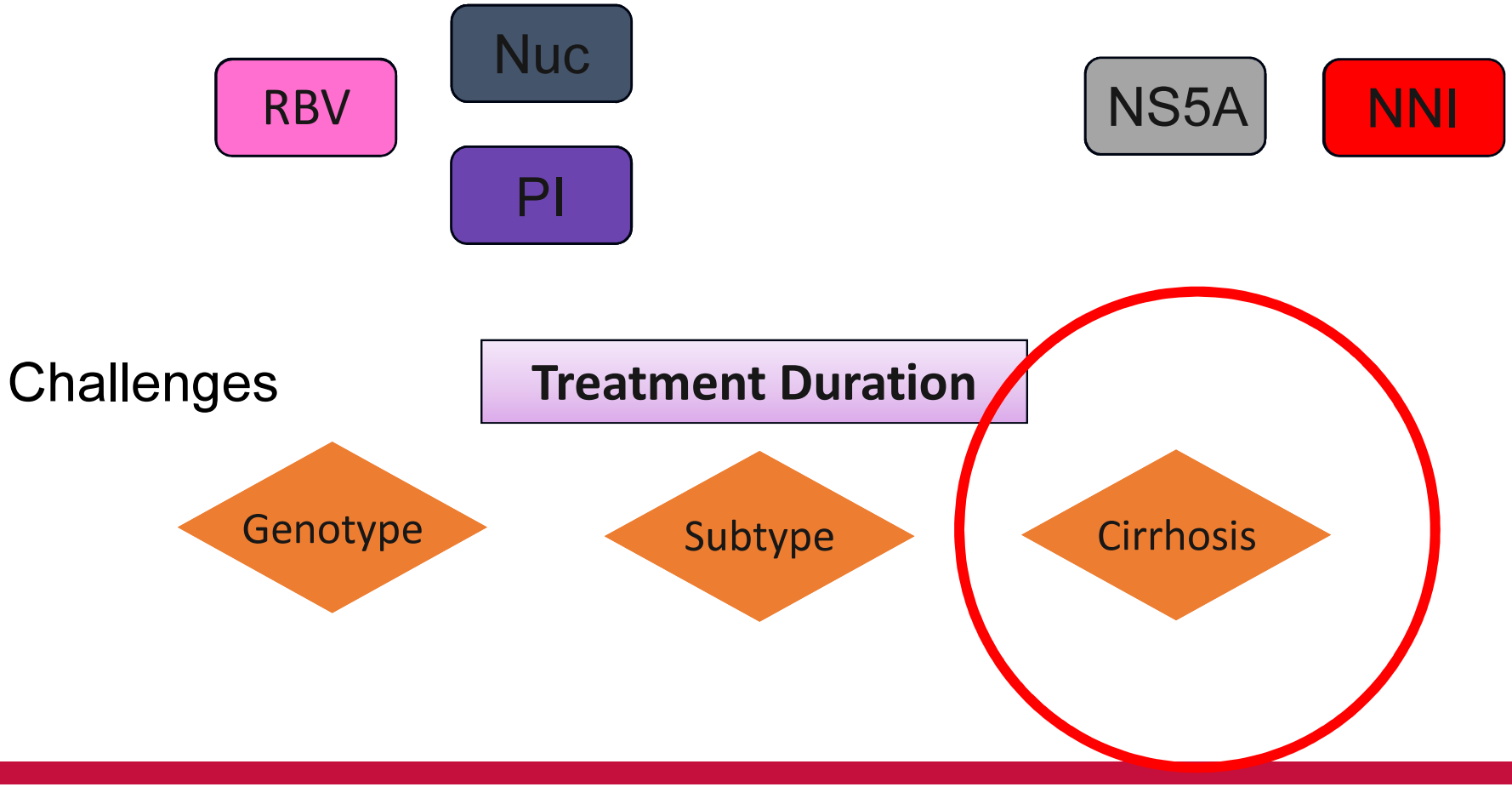
Prior Tx/ IL28B

Race

BMI

HCV RNA

The HCV Toolbox: Mix and Match



Liver fibrosis is the common stage of liver dammage from several different causes

Viral : HCV, HBV..

Alcohol

Fibrotic Liver Disease

F0

F1

F2

F3

F4

Metabolic

Genetic : HFE, Wilson…

Autoimmune Diseases

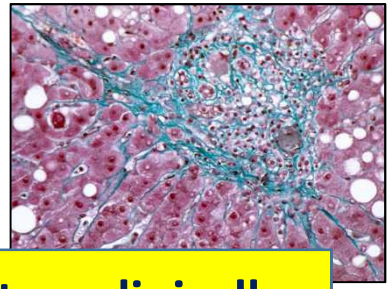
Hemorrhage | **Liver Failure** | **Cancer**

A progressif mechanism defined by 5 histological stages (METAVIR)

F0 : Normal Liver

Mild Hepatitis
F0, F1 : 20 – 30 %

F1 : Periportal Fibrosis



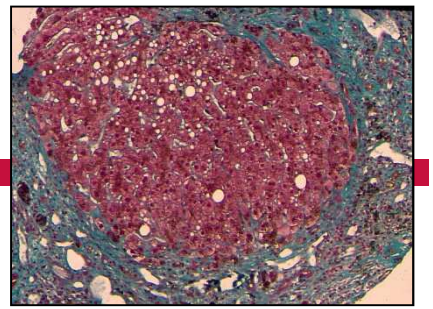
In patients with viral hepatitis (including HIV/HCV), there are two clinically relevant endpoints:

- **detection of significant fibrosis**
- **detection of cirrhosis. ++++++**

F3 : fibrosis septal with cirrhosis

F3 – F4 : 20 – 35%

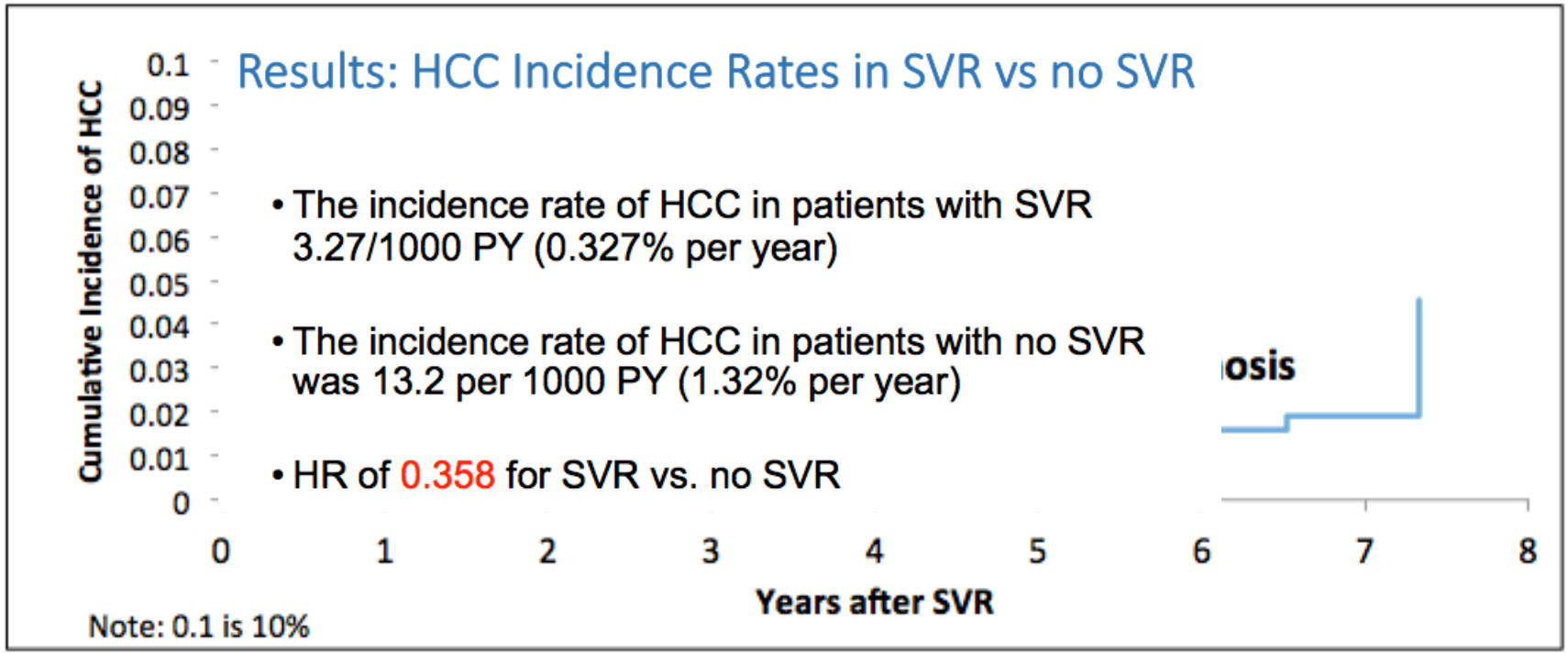
F4 : Cirrhosis



F0 – F4 : 20 to 35 years if progression

Risk for Liver Cancer even After SVR is Achieved

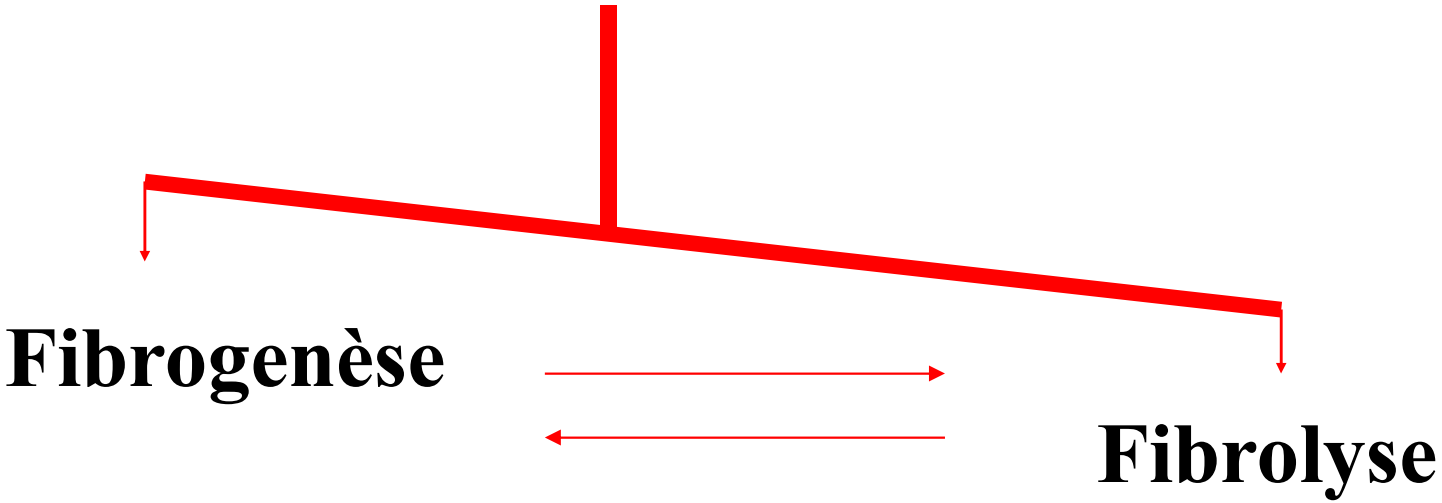
HCC Incidence Following SVR: by Cirrhosis



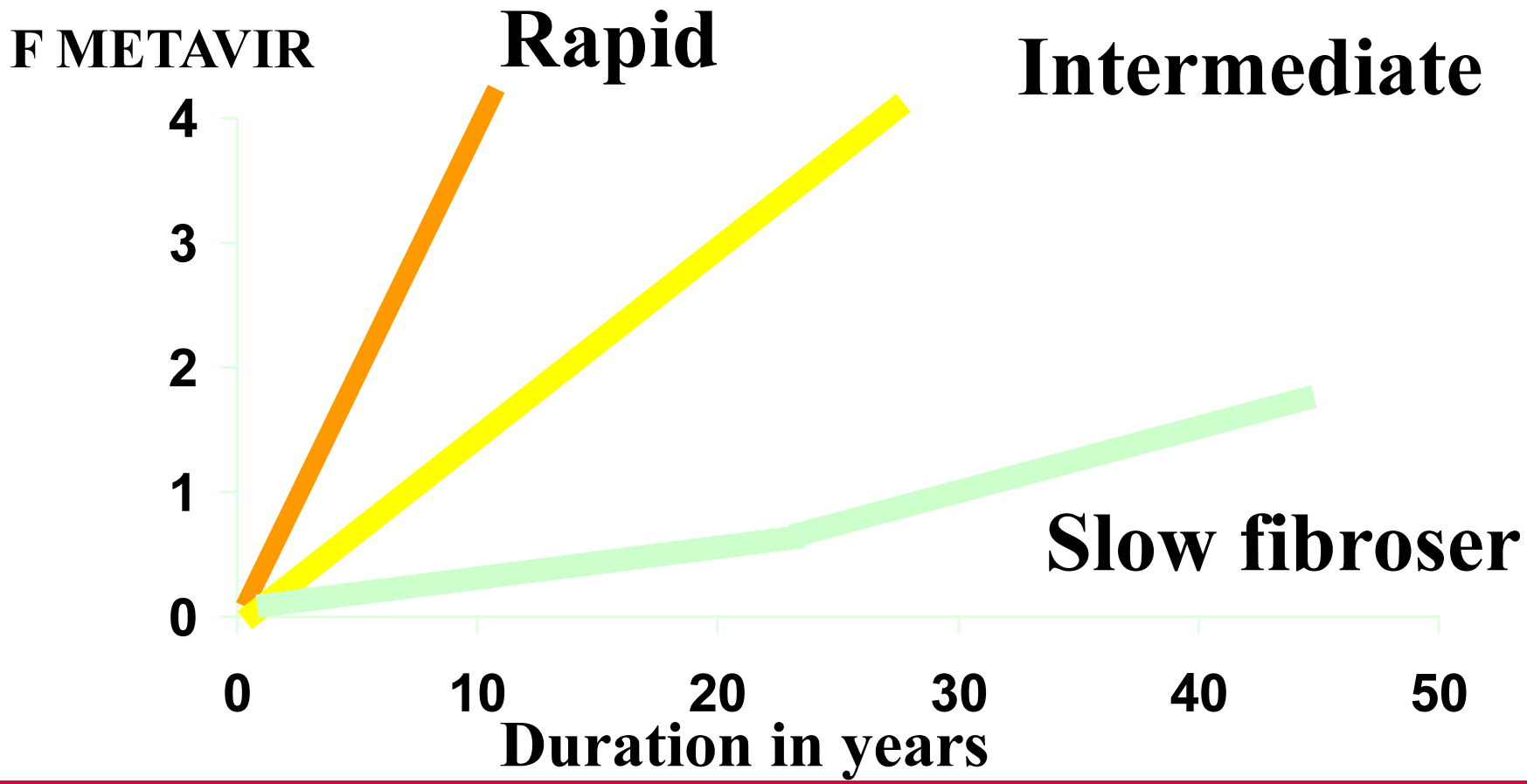
El-Serag et al. AASLD 2015

Fibrosis is a dynamic process

Reversible Process

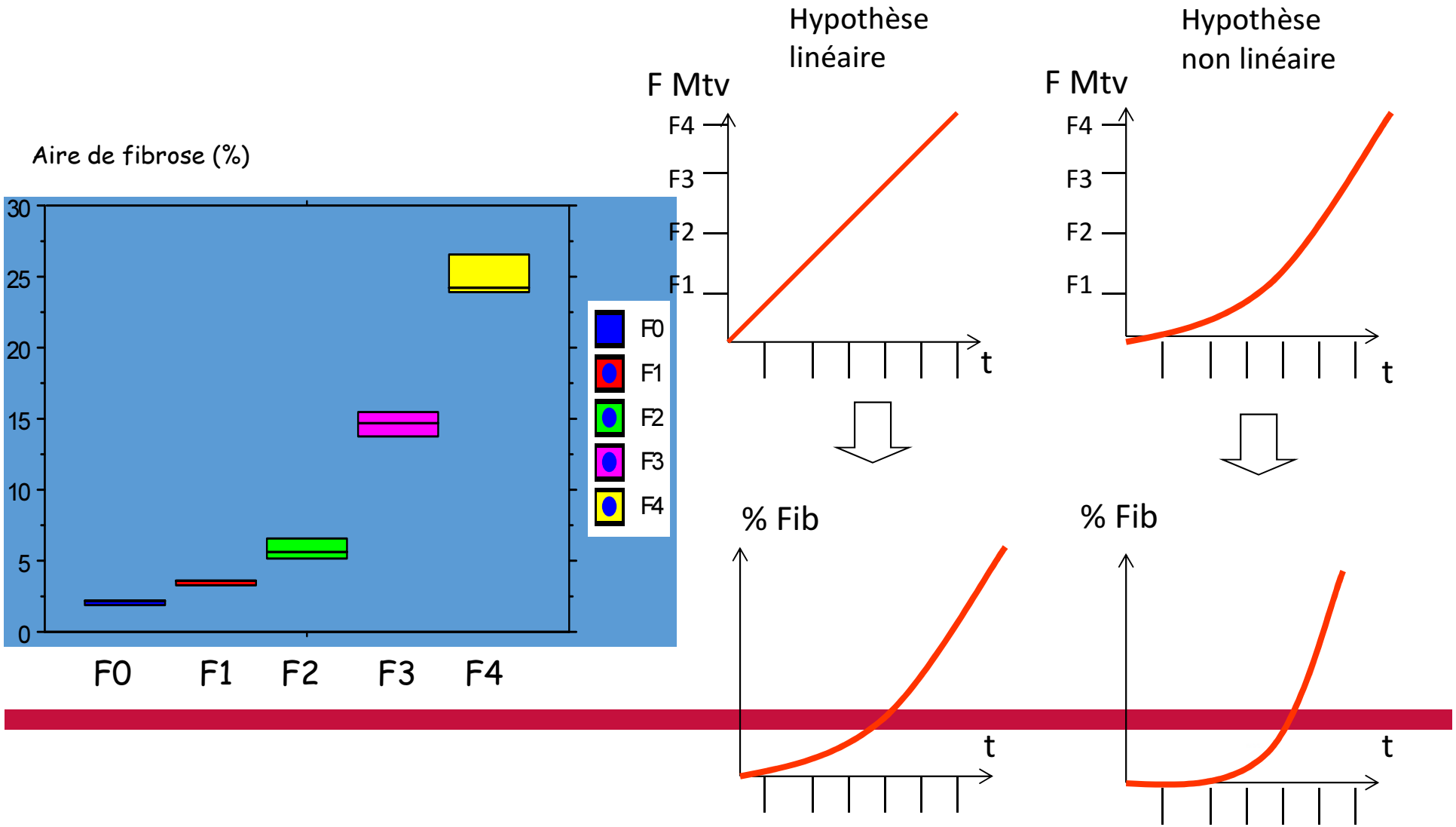


Progression of liver fibrosis

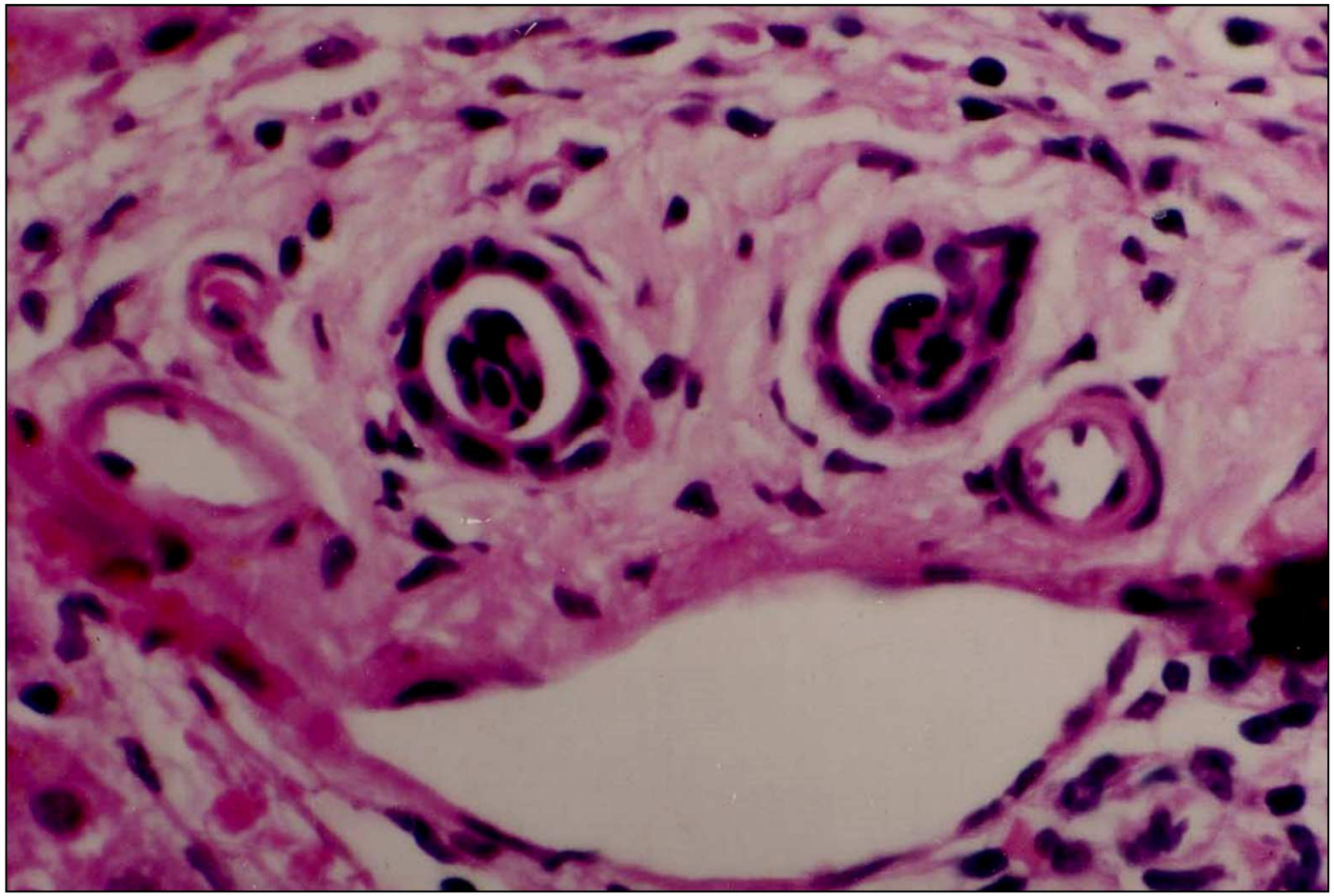


Poynard T et al, *Lancet 1997; 349: 825* *n=1157*

Dynamique de la Fibrose hépatique
Progression exponentielle

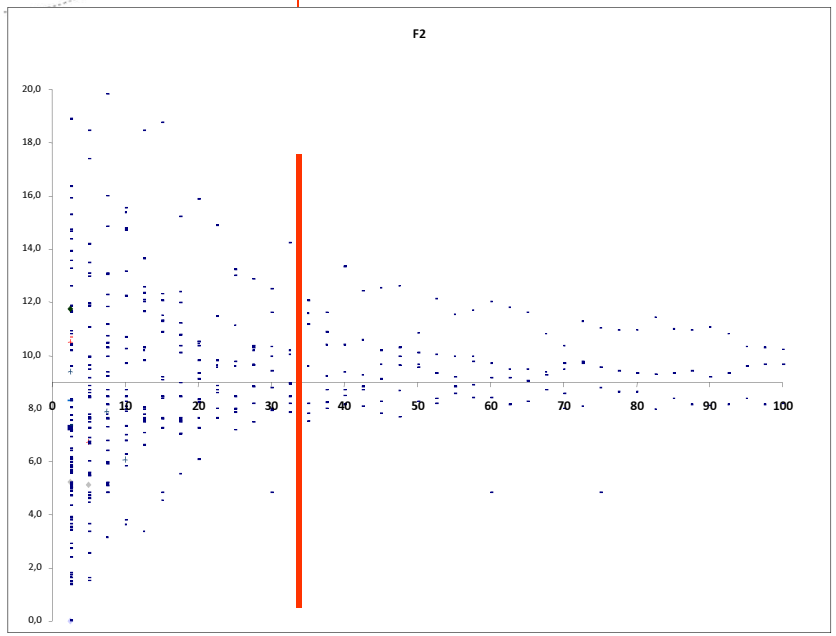


The relevance of Liver Biopsy in predicting fibrosis progression

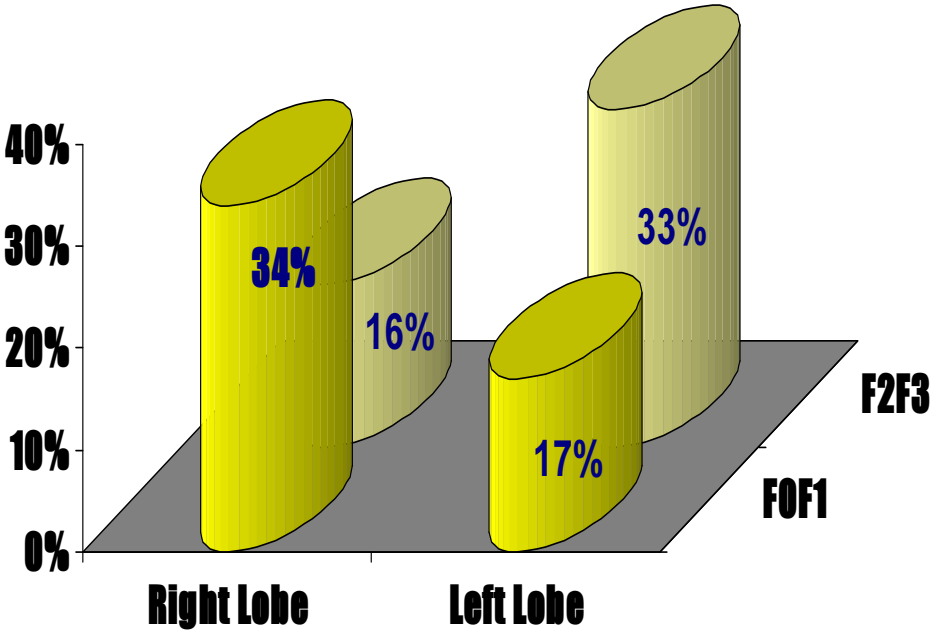


The limits of liver biopsy

Fibrosis area %)



Size of liver biopsy at least 25 mm



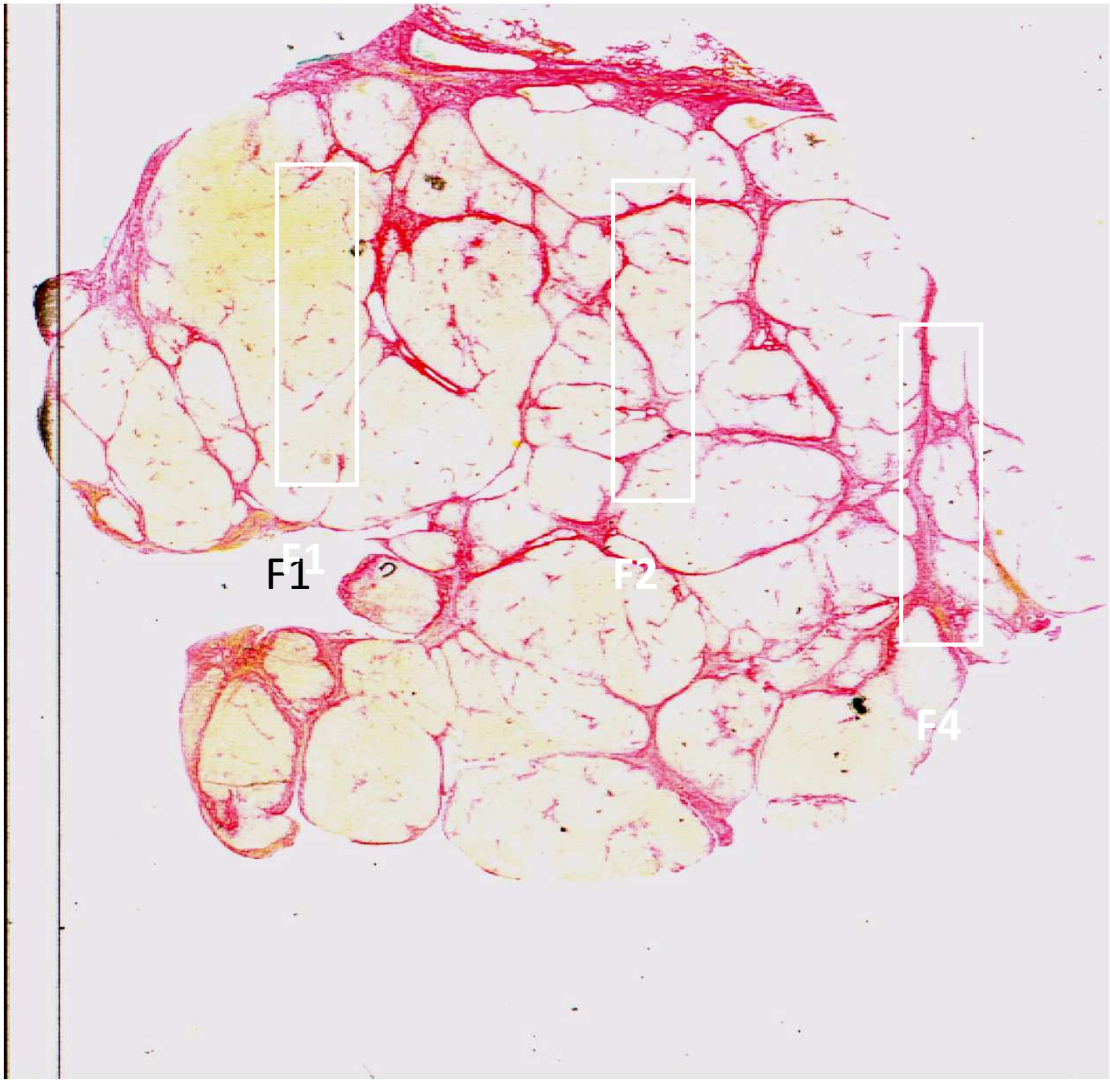
Fibrosis left lobe vs right lobe vs 124 patients : Discordance 33 %

Bedossa.P et al Hepatology 2003; 38 : 1449-1457
Poniachik J et al. Gastrointest Endosc 1996;43: 568-571
Regev A, el al. Am J Gastroenterol 2002; 97: 2614-2618
Poynard T et al. Clin Chem 2004; 50: 1344-1355

F1

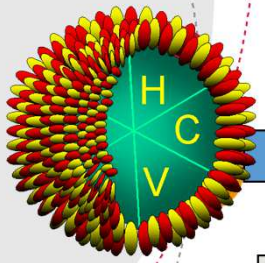
F1

F4

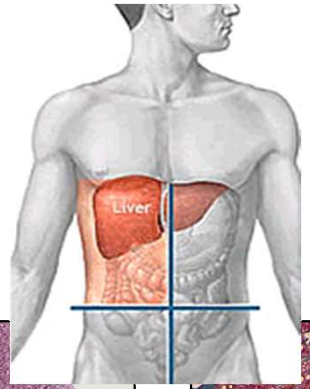

F1
F1
F2
F4

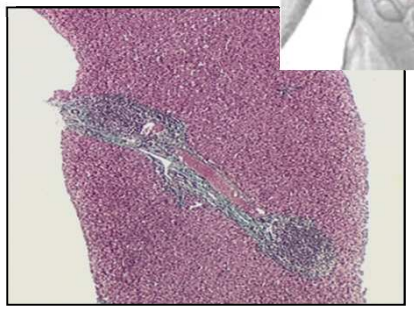
Liver Histology evaluation
Switch : From Invasive vs non invasive process

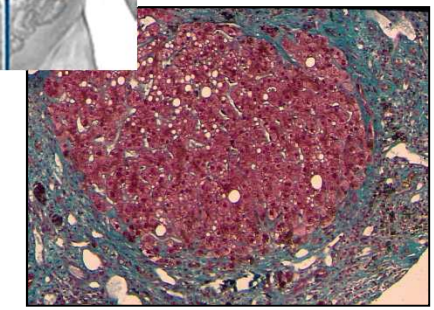
Virus



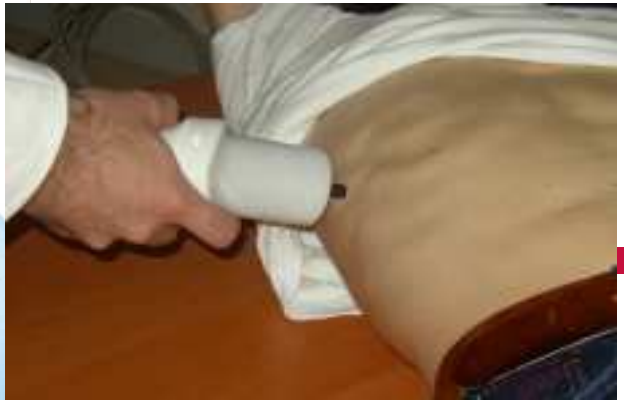
Patient







Physician



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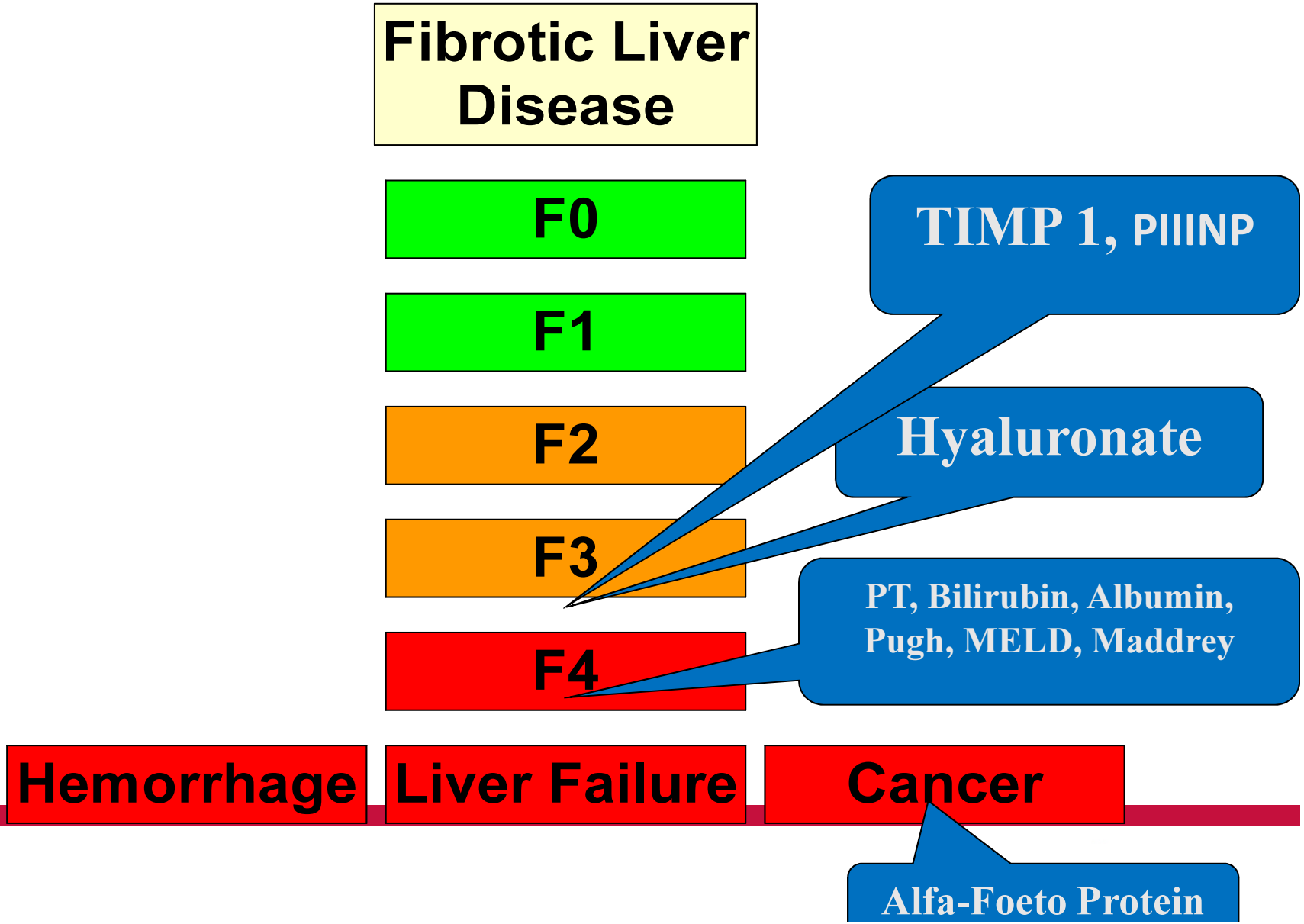
Non-invasive tests for evaluation of liver disease severity and prognosis

Blood markers

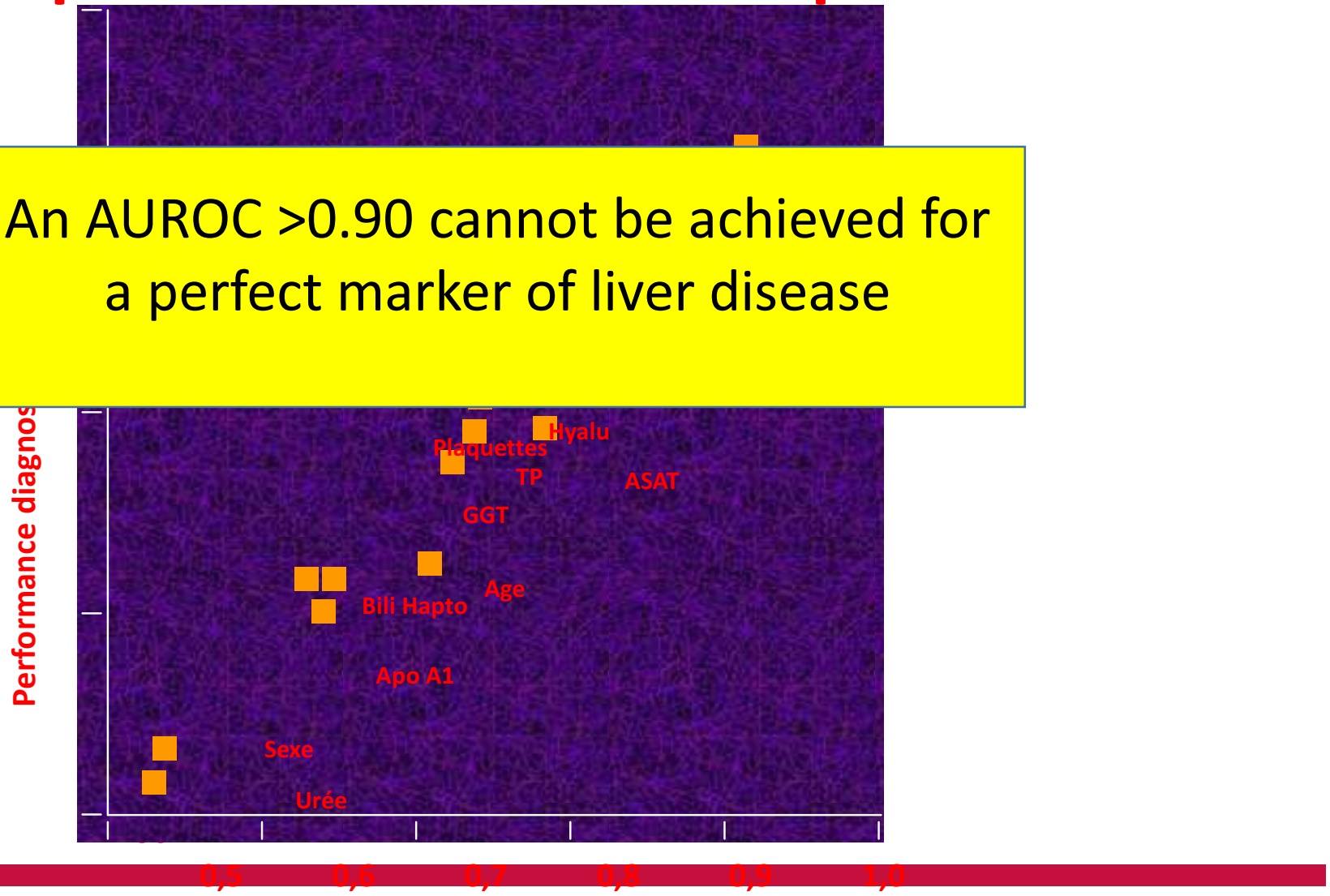
Liver Stiffness Measurement

Serum BioMarkers of liver injury



Performance comparison of tests depends on variables composites

An AUROC >0.90 cannot be achieved for a perfect marker of liver disease



Non invasive Serum markers of liver injury :

Non HCV specific

- APRI
- Forns
- Fibrotest®
- Fibrospect II ®
- Fibrometre ®
- Hepascore
- ELF ®
- Fib-4

HBV specific

- Hui Score
- Zeng Score

Diagnostic performance of serum biomarkers of fibrosis for significant fibrosis and cirrhosis in patients with chronic liver disease.

Biomarkers	Etiologies	Year	Patients (n)	F≥2 (%)	F4 (%)	Cut-offs	AUROC	Se (%)	Sp (%)	CC (%)
FibroTest® [21]	HCV	2001	339	80		>0.48	0.87	75	85	46
Forns Index [22]	HCV	2002	476	26		<4.2 >6.9	0.81	30-94	51-95	45
APRI [23]	HCV	2003	270	50		≤0.5 >1.5	0.80	41-91	47-95	44
					17	<1.0 ≥2.0	0.89	57-89	75-93	72
FibroSpectII® [24]	HCV	2004	696	52		>0.36	0.83	77	73	75
MP3 [25]	HCV	2004	194	45		<0.3 >0.4	0.82	35-65	85-96	n.a.
FPI [26]	HCV	2005	302	48		≤0.2 ≥0.8	0.77	42-85	48-98	40-49
Hepascore® [27]	HCV	2005	211	57		≥0.5	0.82	63	89	92
					16	>0.84	0.89	71	89	n.a.
Lok index [28]	HCV	2005	1141		38	<0.2 ≥0.5	0.81	40-98	53-99	52
GUCI [29]	HCV	2005	179		12	>0.1	0.85	80	70	n.a.
ViraHep-C [30]	HCV	2006	398	37		≤0.22 >0.55	0.83	51-90	54-90	52
Fibroindex [31]	HCV	2007	360	50		≤1.25 ≥2.25	0.83	30-40	97-97	35
FIB-4 [32]	HCV	2007	830		17*	<1.45 >3.25	0.85	38-74	81-98	68
HALT-C model [33]	HCV	2008	512		38	<0.2 >0.5	0.81	47-88	45-92	48
Hui Score [36]	HBV	2005	235	25		≤0.15 >0.5	0.79	37-88	50-88	49
Zeng score [37]	HBV	2005	372	58		<3.0 >8.7	0.77	40-98	28-90	35
SHASTA [38]	HIV-HCV	2005	95	27		<0.3 >0.8	0.87	15-88	72-100	42
FIB-4 [39]	HIV-HCV	2006	832		22*	<1.45 >3.25	0.76	70	97	62
ELF® [34]	Mixed	2004	1021/496**	40		0.102	0.78	87	51	n.a.
		2005			12	n.a.	0.89	n.a.	n.a.	n.a.
Fibrometer® [35]	Mixed	2007	598/503**	56		n.a.	0.89	80	84	82
NFS [40]	NAFLD	2008	733		27*	<-1.455 >0.676	0.82	43-77	97-97	68
BARD score [41]	NAFLD		669		30*	≥2	0.81	n.a.	n.a.	n.a.

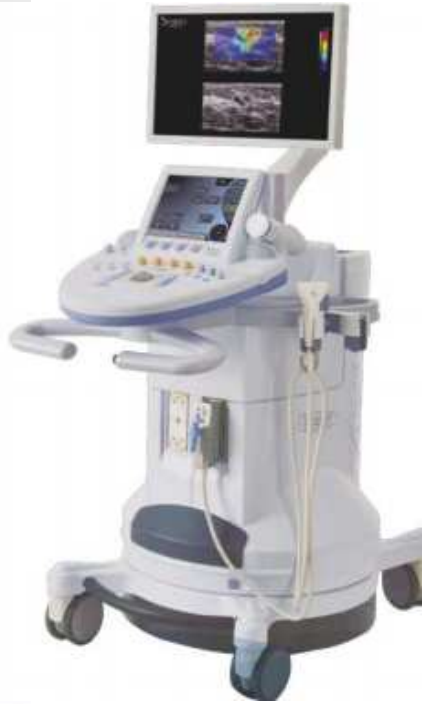
EASL Clinical guidelines practices

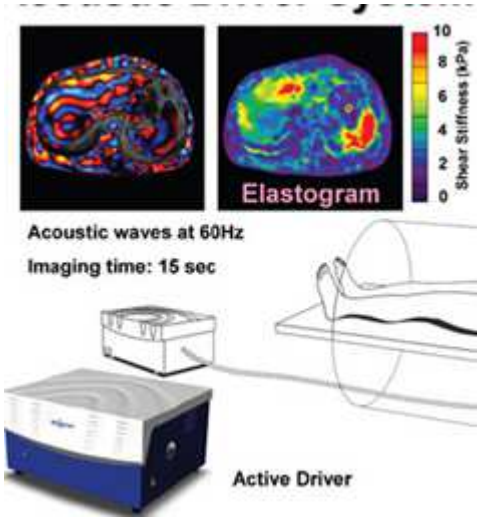
HIV-HCV patients : Non-invasive tests Diagnostic performances

Test	Fibrosis (Metavir)	Cut-off	AUC [95% CI]	PPV	NPV	Référence
FibroTest®	≥ F2	0,49	0.64 [0.58 ;0.70]	83%	35%	{Cacoub, 2008 #12}
	F4	0,75	0.81 [0.76 ;0.85]	32%	97%	{Cacoub, 2008 #12}
FibroMetre®	≥ F2	0,50	0.70 [0.64 ;0.76]	80%	41%	{Cacoub, 2008 #12}
	F4	-	0.84 [0.78 ;0.88]	-	-	{Cacoub, 2008 #12}
Hepascore	≥ F2	0,50	0.69 [0.63 ;0.74]	82%	39%	{Cacoub, 2008 #12}
	F4	0,84	0.83 [0.78 ;0.88]	18%	98%	{Cacoub, 2008 #12}
	≥ F2	4.5 kPa	0.72 [0.60 ;0.84]	64%	63%	{de Ledinghen, 2006 #15}
		5,9 kPa	0.85 [0.75 ;0.95]	91%	74%	{Miailhes, 2011 #13}
		7,0 kPa	0.93 [0.85-1.00]	70%	81%	{Sanchez-Conde, 2010 #14}
FibroScan®		9,4 kPa	0.96 [0.92 ;1.00]	79%	98%	{Miailhes, 2011 #13}
	F4	11,8 kPa	0.97 [0.94 ;1.00]	81%	100%	{de Ledinghen, 2006 #15}.
		14,0 kPa	0.99 [0.97 ;1.00]	57%	100%	{Sanchez-Conde, 2010 #14}
		14,5 kPa	0.97 [0.94 ;1.00]	88%	96%	{de Ledinghen, 2006 #15}

Morlat Report

Measurement of Liver Stiffness





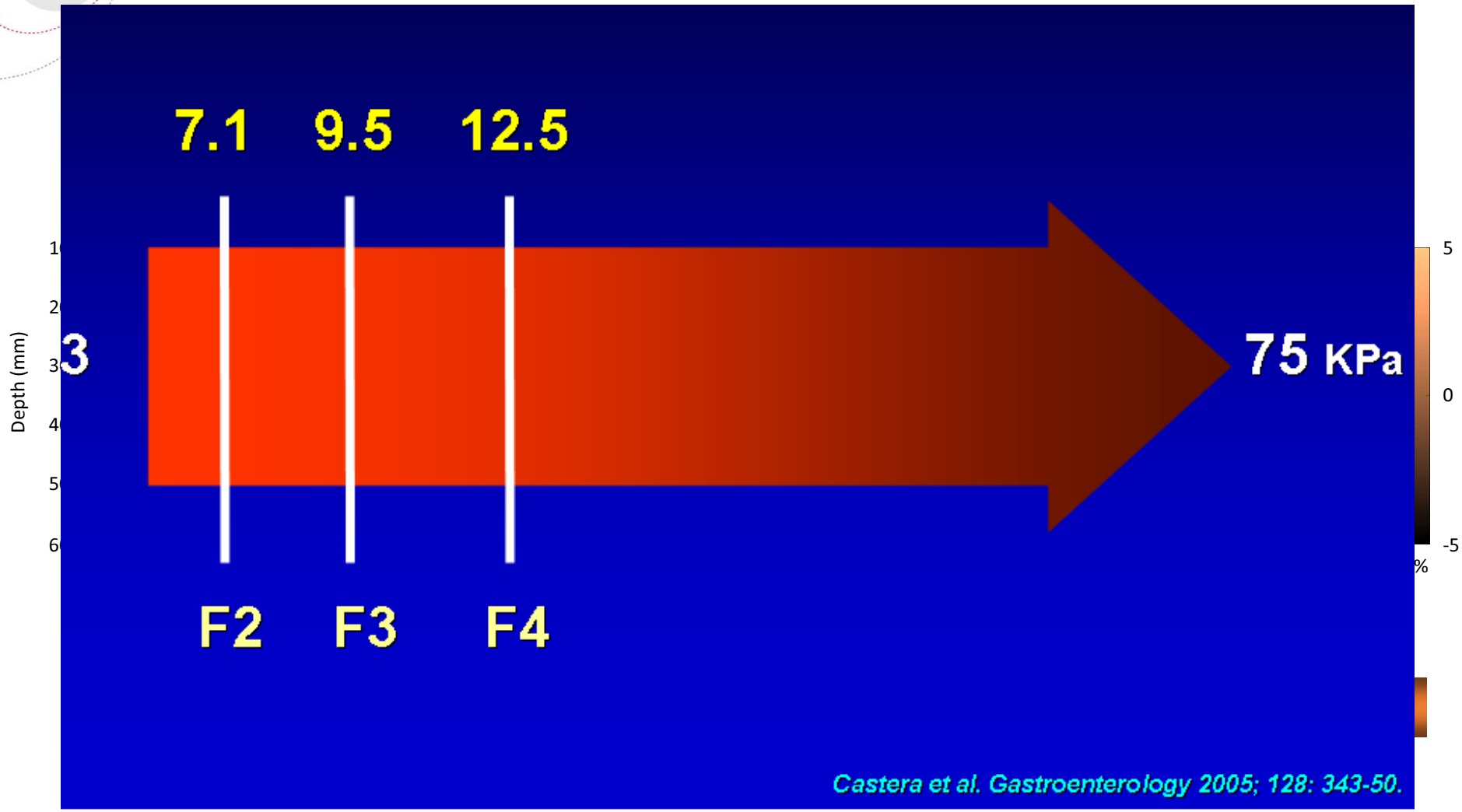
Fibroscan : Transient Elastography

ARFI :Acoustic Radiation Force Impulse Elastography

SWE : Supersonic shear wave imaging

MR elastography

Fibroscan : Transient Elastography



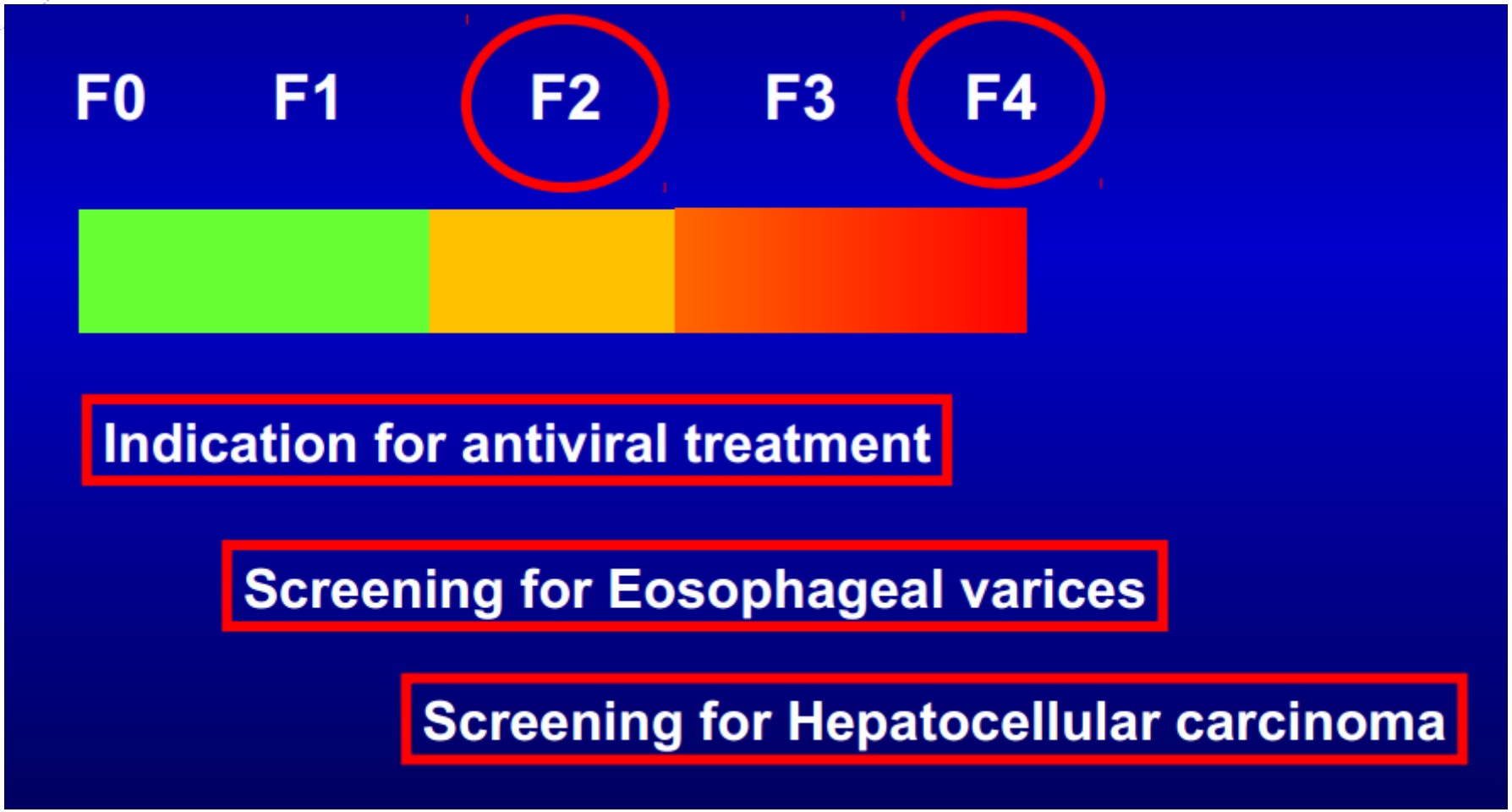
F0 F2 F4

7.1 kPa for F ≥ 2 9.5 kPa for F ≥3 12.5 kPa for F4

Correct interpretation of TE results in clinical practice must consider the following parameters

- IQR/ median value (<30%),
- Serum aminotransferases levels (<5 x ULN),
- BMI (use XL probe above 30 kg/m2 or if skin-to- capsule distance is >25 mm),
- Absence of extra-hepatic cholestasis,
- Absence of right heart failure, or other causes of congestive liver
- Absence of ongoing excessive alcohol intake

Ends point in Hepatitis B and C



Cirrhosis Complication

12 16 27 49 54 63 75 kPa

VO = 0

VO grade 2 ou 3

DOA

CHC

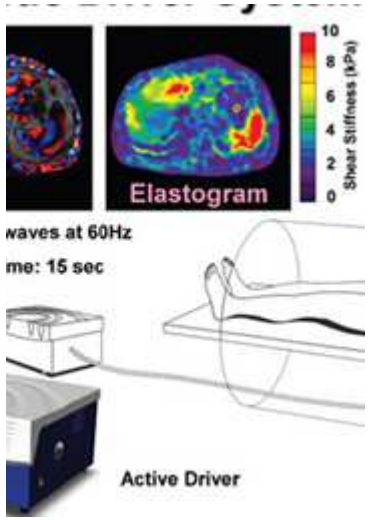
RVO

N=711 patients (cirrhose n=95)

Chanteloup et al. AASLD Boston 2004

Measurement of Liver Stiffness

- pSWE/ARFI performs better for detecting cirrhosis than significant fibrosis and is better validated in chronic hepatitis C than for hepatitis B, HIV-HCV coinfection, NAFLD and other liver diseases (**A1**)
- pSWE/ARFI shows equivalent performance to TE for detecting significant fibrosis and cirrhosis (**A1**)
- 2D-SWE is a promising technique that is currently under investigation. It seems to be at least equivalent to TE and pSWE/ARFI for non-invasive staging of liver fibrosis in viral hepatitis (**B1**)
- Comparison between MR elastography and TE has provided conflicting results. Further data are needed (**A1**)



Fibroscan : T
Elastography

Force Impulse Elastography

shear wave imaging

MR elastography

Respective advantages and disadvantages of currently available non-invasive methods in patients with chronic liver diseases

Serum biomarkers	Measurement of liver stiffness			
	Transient elastography	ARFI (pSWE)	2D-SWE	MR elastography
Advantages				
• Good reproducibility • High applicability (95%) • No cost and wide availability (non-patented) • Well validated • Can be performed in the outpatient clinic	• Most widely used and validated technique: standard to be beaten • User-friendly (performed at bedside; rapid, easy to learn) • High range of values (2-75 kPa) • Quality criteria well defined • Good reproducibility • High performance for cirrhosis (AUROC >0.9) • Prognostic value in cirrhosis	• Can be implemented on a regular US machine • ROI smaller than TE but location chosen by the operator • Higher applicability than TE (ascites and obesity) • Performance equivalent to that of TE for significant fibrosis and cirrhosis	• Can be implemented on a regular US machine • ROI can be adjusted in size and location and chosen by the operator • Measures liver stiffness in real-time • High range of values (2-150 kPa) • Good applicability • High performance for cirrhosis	• Can be implemented on a regular MRI machine • Examination of the whole liver • Higher applicability than TE (ascites and obesity) • High performance for cirrhosis
Disadvantages				
• Non-specific of the liver • Unable to discriminate between intermediate stages of fibrosis • Performance not as good as TE for cirrhosis • Cost and limited availability (proprietary) • Limitations (hemolysis, Gilbert syndrome, inflammation…)	• Requires a dedicated device • ROI cannot be chosen • Unable to discriminate between intermediate stages of fibrosis • Applicability (80%) lower than serum biomarker: (obesity, ascites, operator experience) • False positive in case of acute hepatitis, extra-hepatic cholestasis, liver congestion, food intake and excessive alcohol intake	• Unable to discriminate between intermediate stages of fibrosis • Units (m/sec) different from that of TE (kPa) • Narrow range of values • (0.5-4.4 m/sec) • Quality criteria not well defined • Prognostic value in cirrhosis?	• Further validation warranted • Unable to discriminate between intermediate stages of fibrosis • Quality criteria not well defined • Learning curve? • Influence of inflammation?	• Further validation warranted especially in comparison with TE • Not applicable in case of iron overload • Requires a MRI facility • Time-consuming • Costly

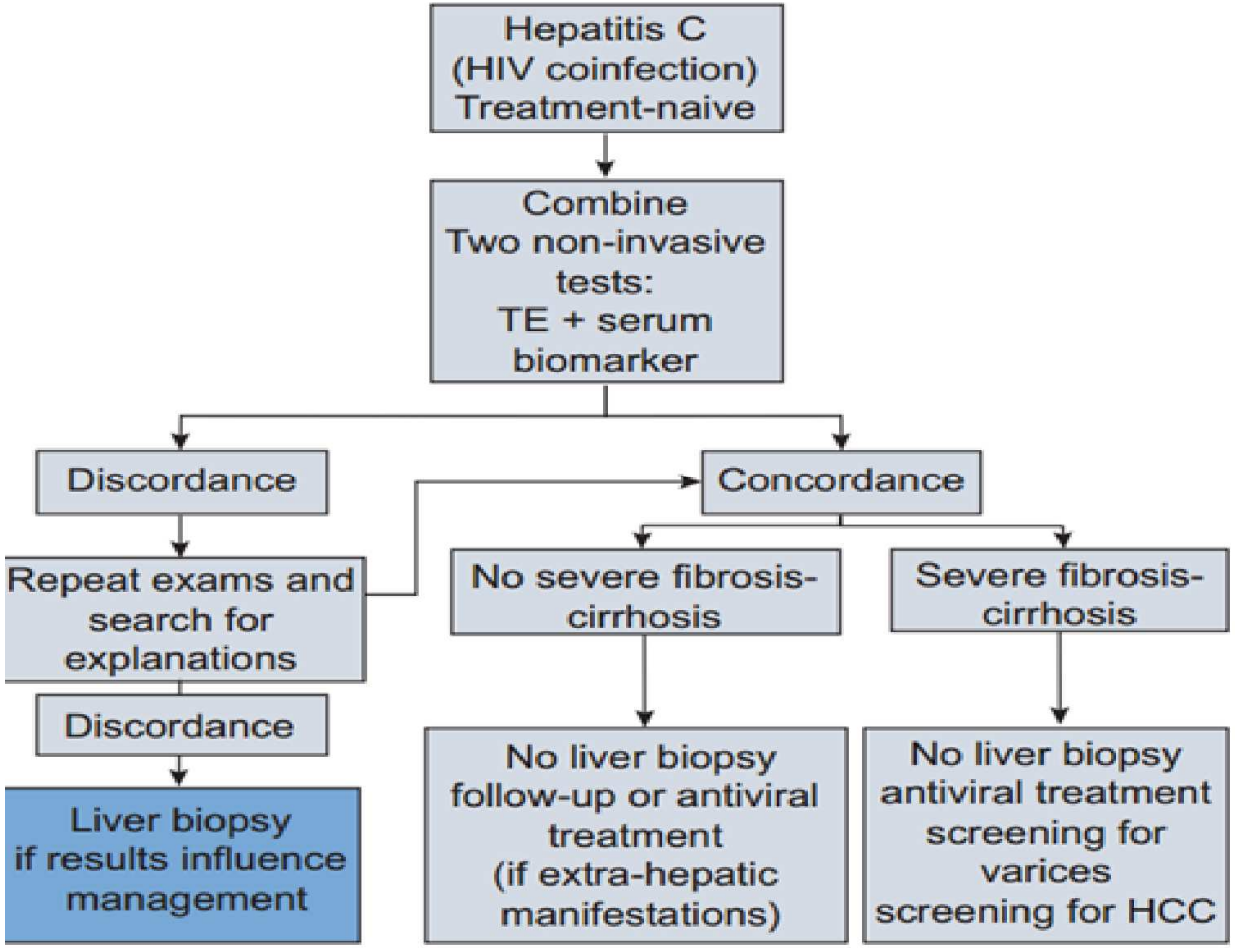
The lessons from Hepatitis C

- Fibrosis stage can be assessed by non-invasive methods initially, with liver biopsy reserved for cases where there is uncertainty or potential additional etiologies (**recommendation B1**)

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER

EASL clinical Practices Guidelines 2014

Proposed algorithm for the use of non-invasive tests in treatment naive patients with Hepatitis C with or without HIV coinfection



AFEF
ASSOCIATION FRANÇAISE POUR L'ETUDE DU FOIE

Recommandations

La maladie hépatique est sévère

PBH antérieure F3 ou F4	**Traitement à court terme**
Ou Fibroscan ≥ 9,5 kPa	
Ou FibroTest ≥ 0,59	
Ou FibroMètre ≥ 0,63	

Le bénéfice clinique à traiter rapidement le malade est important : diminution du risque de décompensation de la maladie hépatique, diminution du risque de carcinome hépatocellulaire, amélioration de la survie.

La maladie hépatique est peu sévère

Fibroscan < 5,6 kPa	**Surveillance annuelle. Le traitement à court terme n'est pas nécessaire.**
ou FibroTest < 0,27	
ou FibroMètre < 0,33	

Le bénéfice clinique à traiter le malade dans l'année qui vient n'est pas montré. Cependant, une surveillance annuelle par l'une de ces méthodes est recommandée.

La maladie hépatique est difficile à évaluer

Fibroscan 5,6 – 9,4 kPa	**Faire un deuxième test**
ou FibroTest 0,27 – 0,58	
ou FibroMètre 0,33 – 0,62	

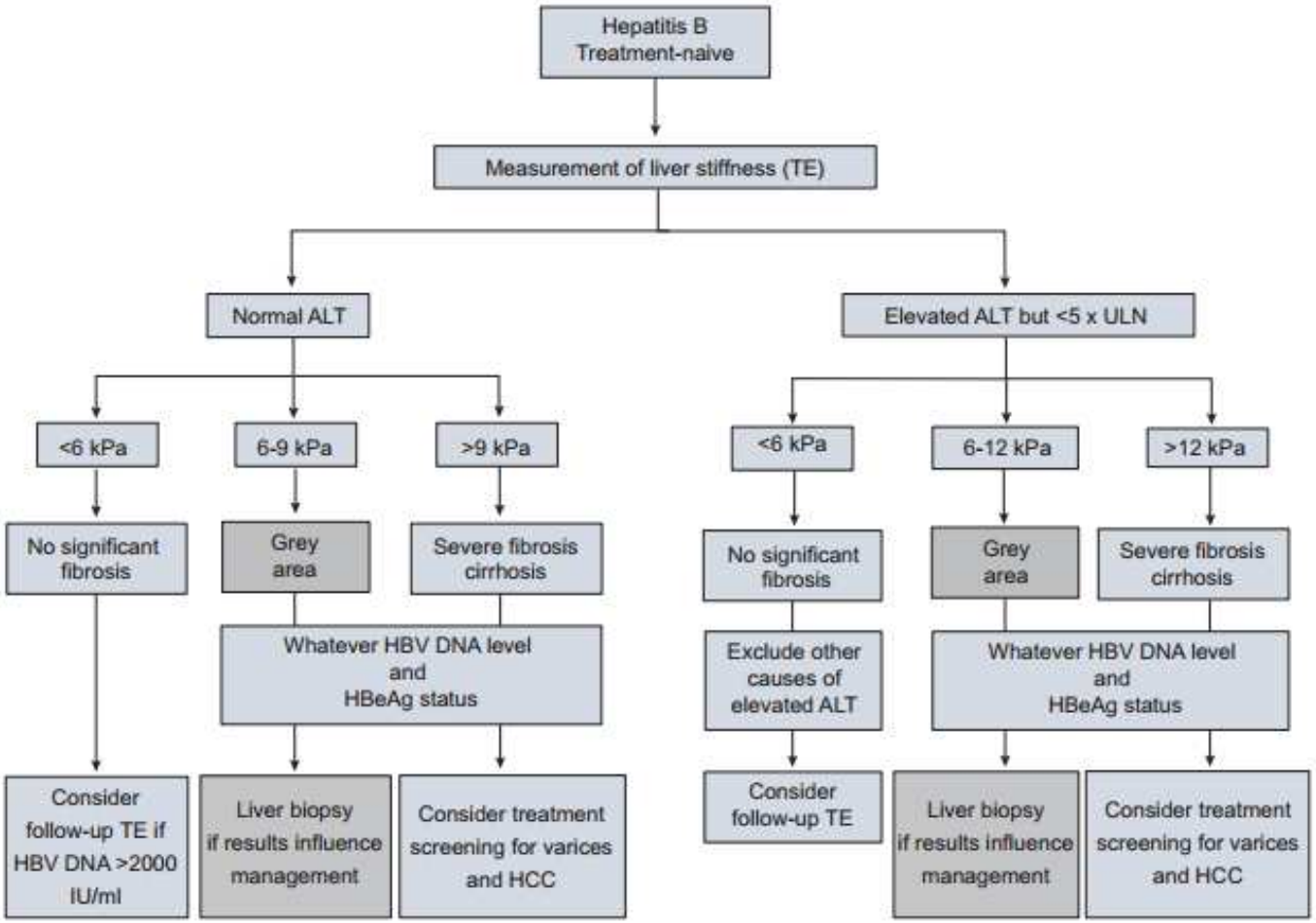
Lorsque deux méthodes sont utilisées successivement, il convient d'associer une mesure de l'élasticité hépatique à un test sanguin (et non deux tests sanguins).

Fibroscan 5,6 – 9,4 kPa et Fibrotest ≥ 0,59 ou Fibroscan 5,6 – 9,4 kPa et Fibromètre ≥ 0,63	**La maladie hépatique est sévère** **Traitement à court terme**
FibroTest 0,27 – 0,58 et Fibroscan ≥ 9,5 kPa ou Fibromètre 0,33 – 0,62 et Fibroscan ≥ 9,5 kPa	
Fibroscan < 7,1 kPa et Fibrotest < 0,48 ou Fibroscan < 7,1 kPa et Fibromètre < 0,41	**La maladie hépatique est peu sévère. Surveillance annuelle. Le traitement à court terme n'est pas nécessaire.**
Dans les autres cas	**Surveillance à un an et envisager un traitement à moyen terme (2 à 3 ans)**

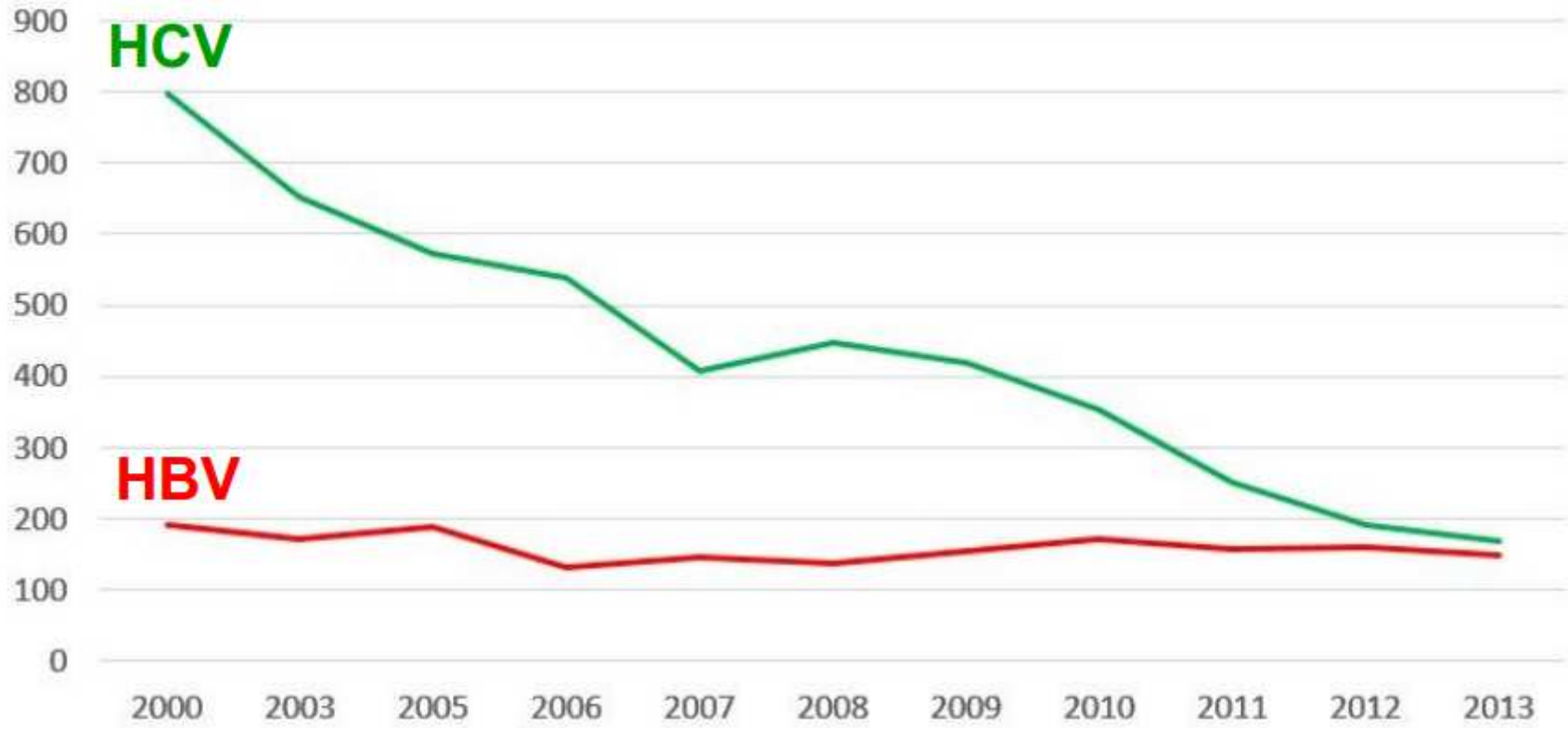
Overview of biomarkers for viral evolution and liver disease progression in Hepatitis B

Proposed algorithm for the use of transient elastography in treatment-naive patients with Hepatitis B

JOURNAL OF HEPATOLOGY

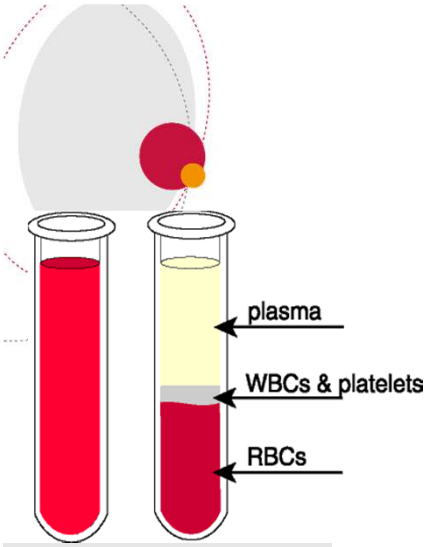


Trends in Liver Biopsy practice in HCV vs HBV from 2000 -2013



Courtsey Pierre Bedossa

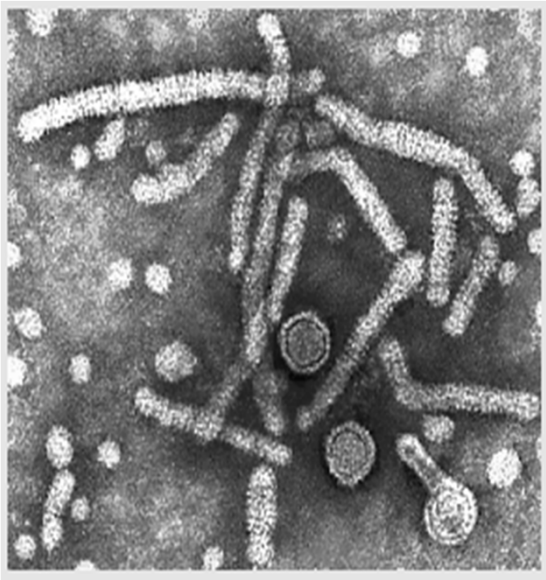
“Back to the future with Australia Antigen”

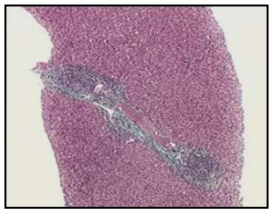


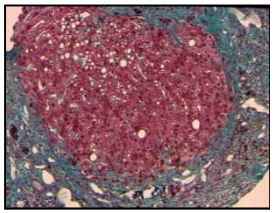
HBV Viral Load

Plasma HBsAg: Measurement

Virions	42 nm
Filaments	22 nm
Spherical particles	22nm







Liver Histological assessement

cccDNA Correlation

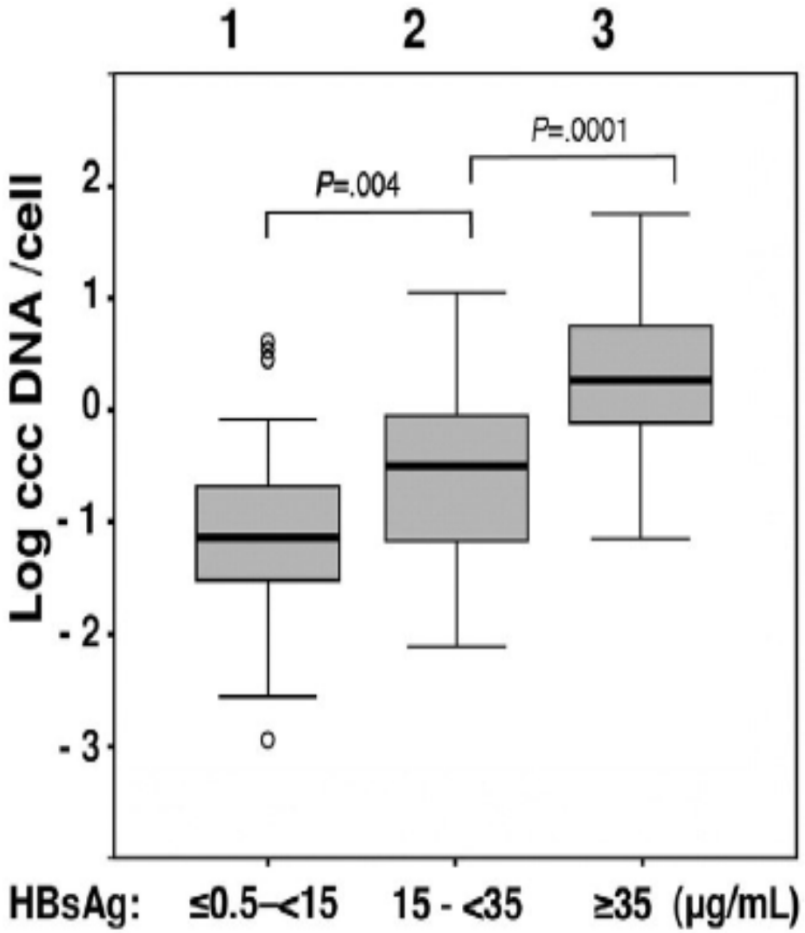
Treatment Indication

Definition of Response

Monitoring antiviral Therapy

Prediction of Response

Impaired Intrahepatic Hepatitis B Virus Productivity Contributes to Low Viremia in Most HBeAg-Negative Patients

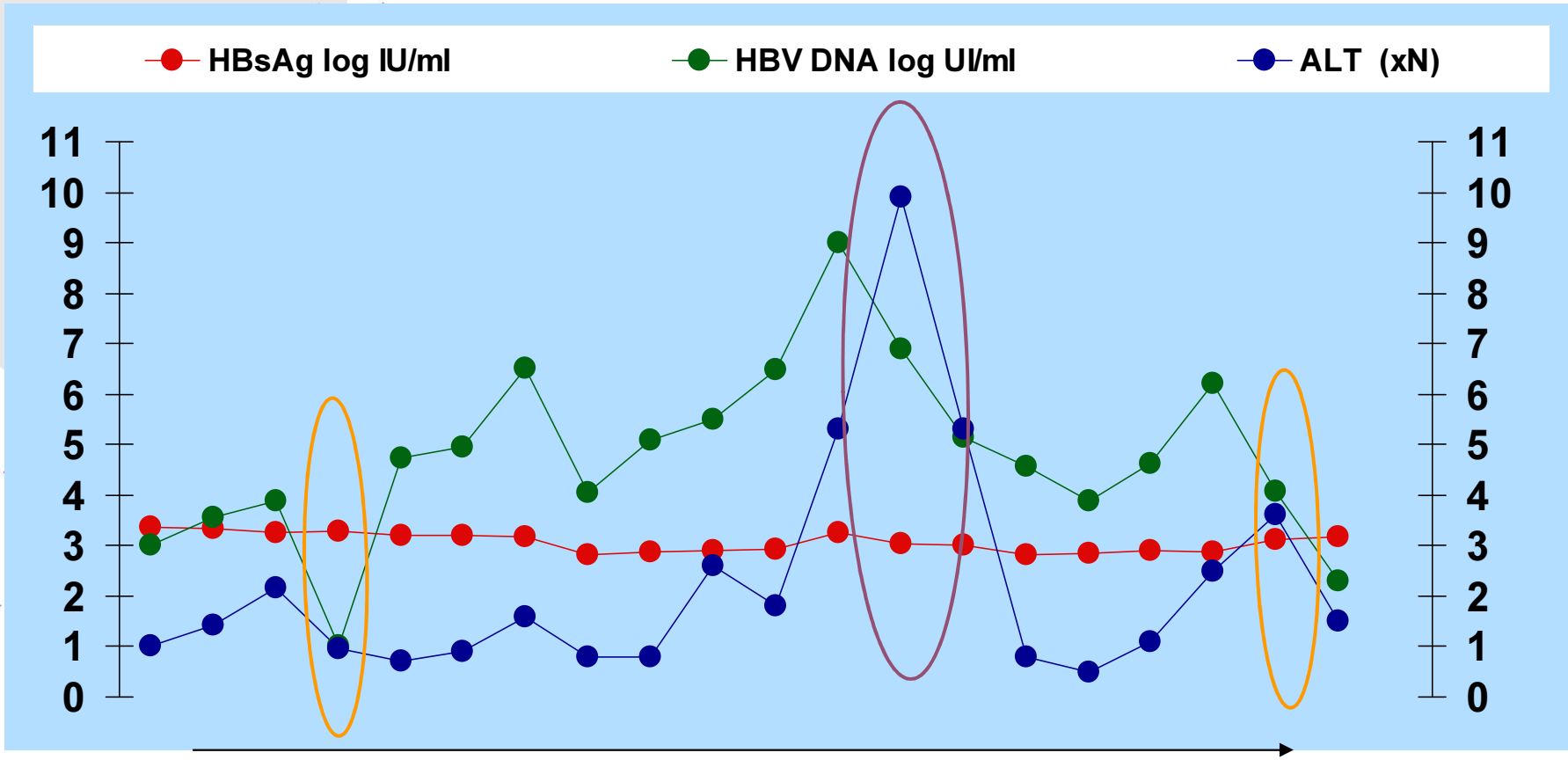


Relationship between HBsAg serum levels (by the Laurell test) and intrahepatic cccDNA amounts (median values 0.07, 0.3 and 1.8 cccDNA copies/cell)

GASTROENTEROLOGY 2007;133:843–852

Low levels of serum HbsAg titers are correlated with low quantity of liver cccDNA

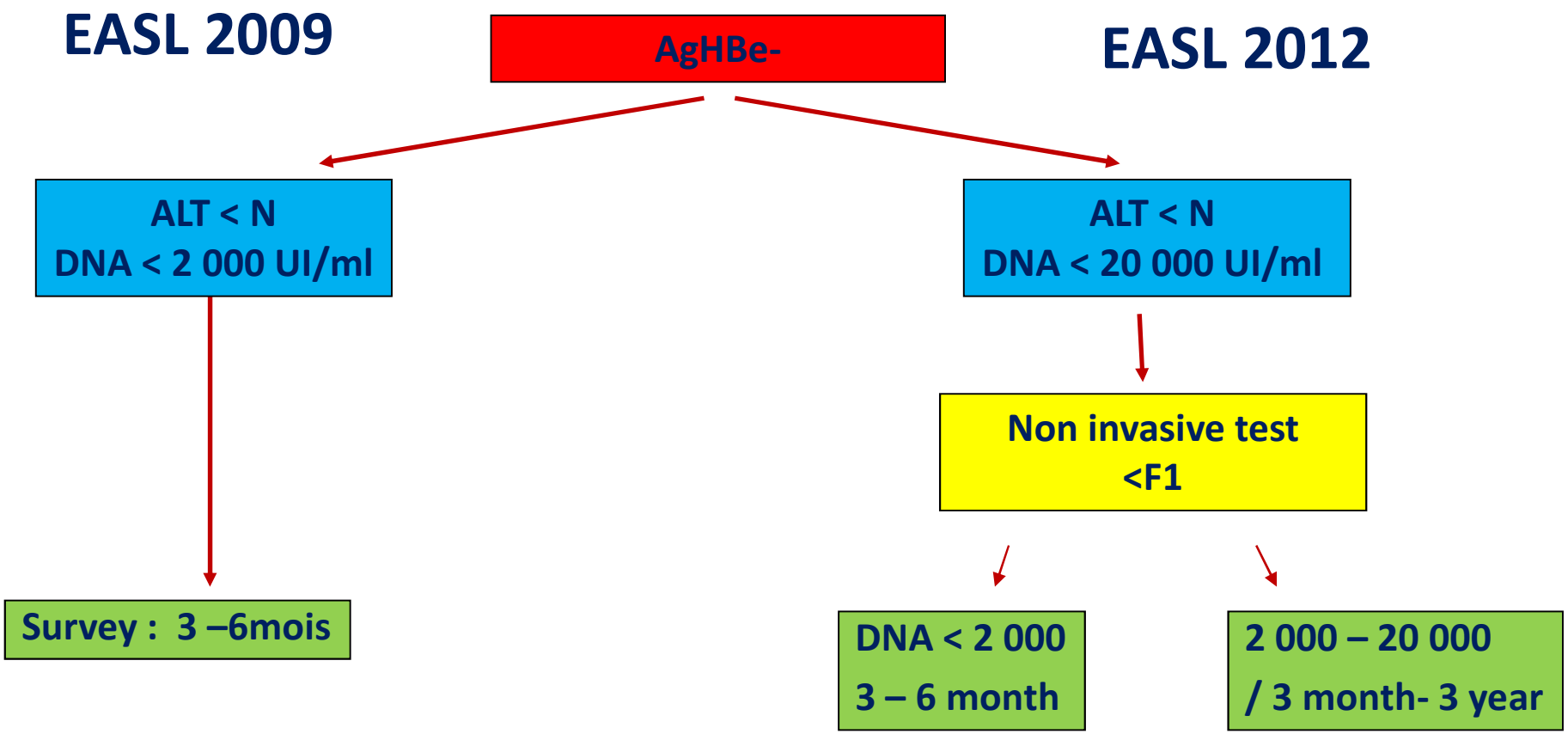
HBsAg is a reliable marker



Martinot-Peinoux Liver International 2013:125:132

Martinot-Peignoux et al. J Clin Virol 2013

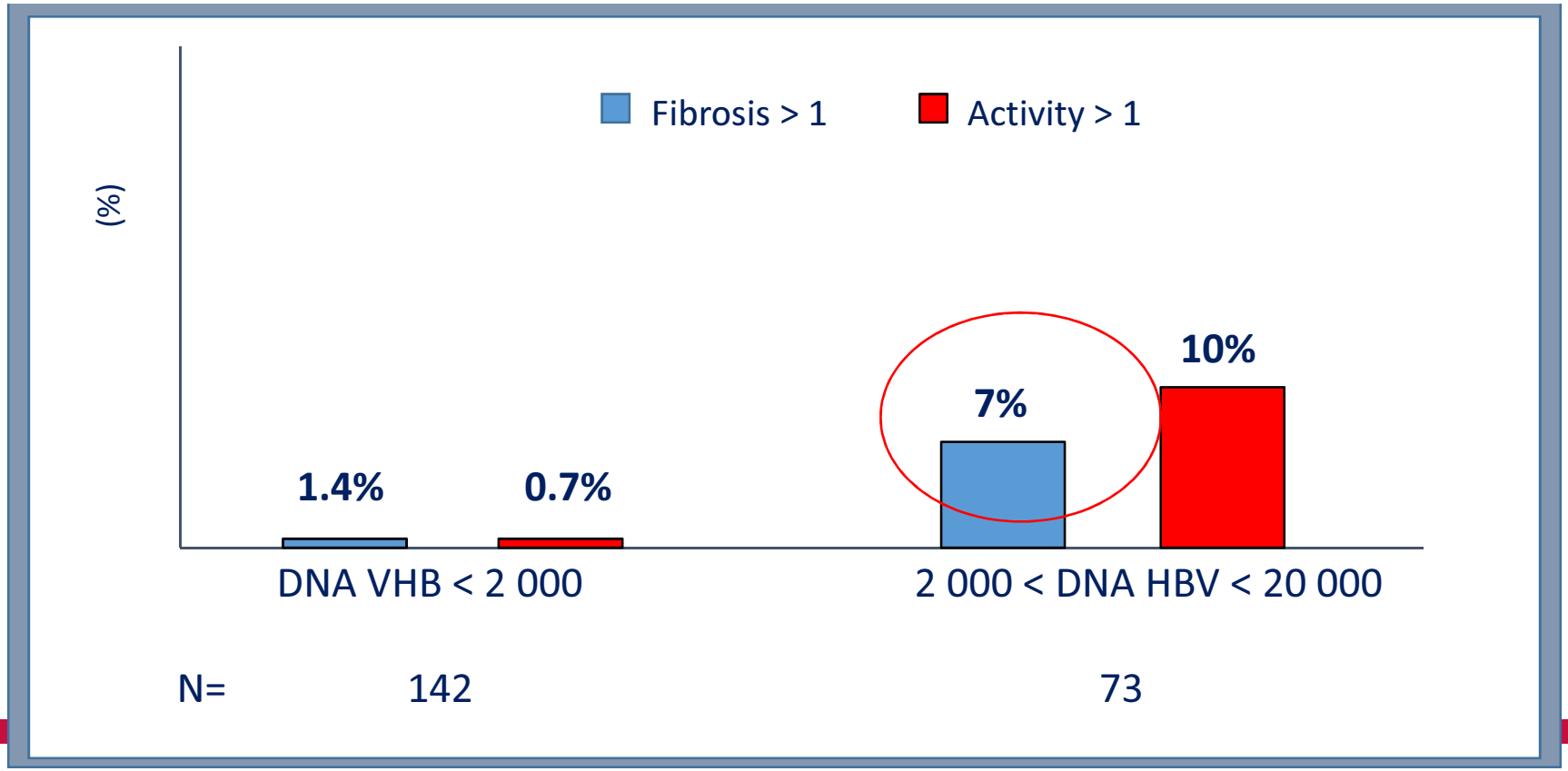
HBs Inactive carrier definition



« inactive carriers with high viral load »

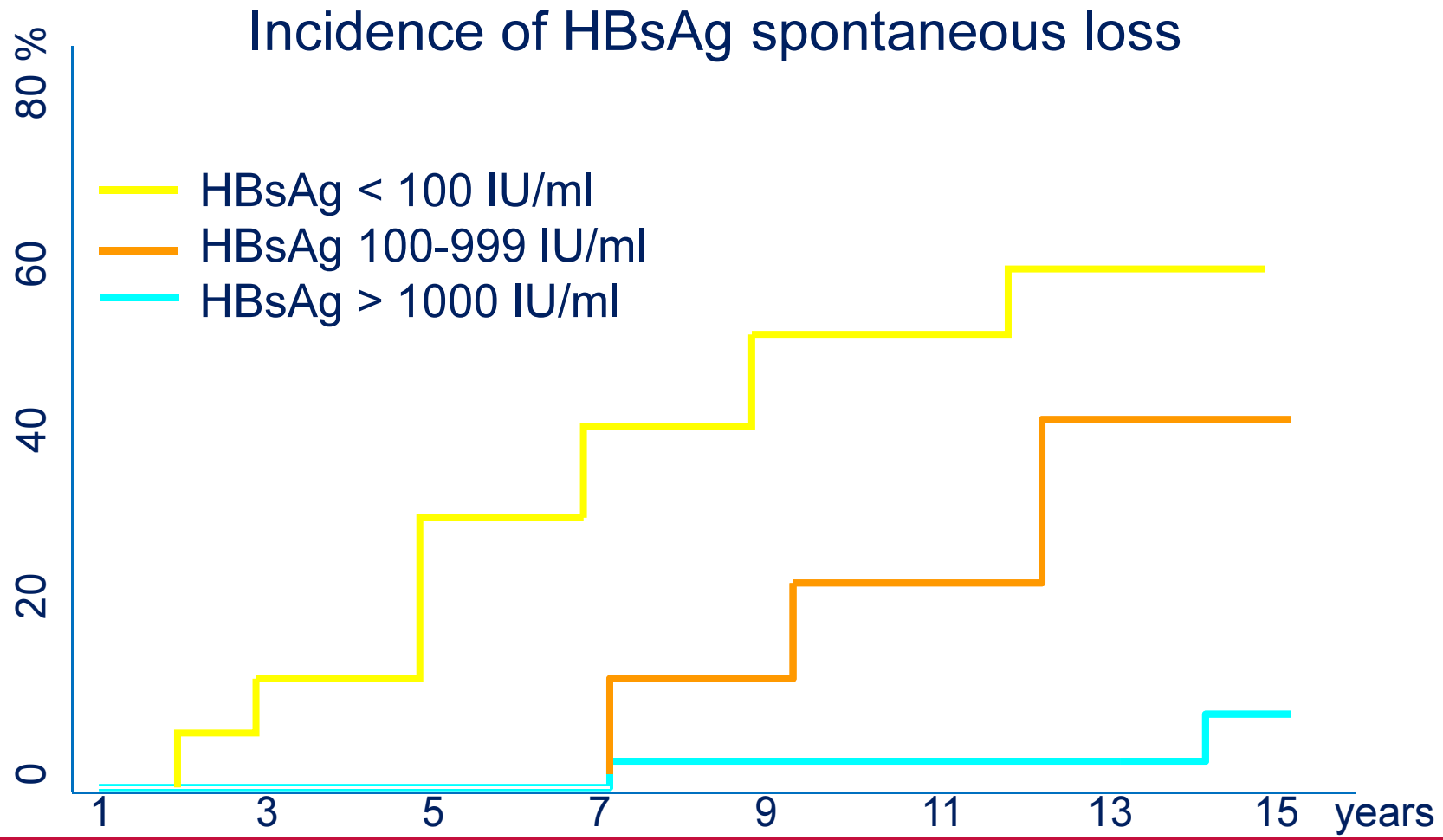
Histological lesions risk

- **Meta-analysis : 6 studies, 335 patients with normal ALT / Liver biopsies**



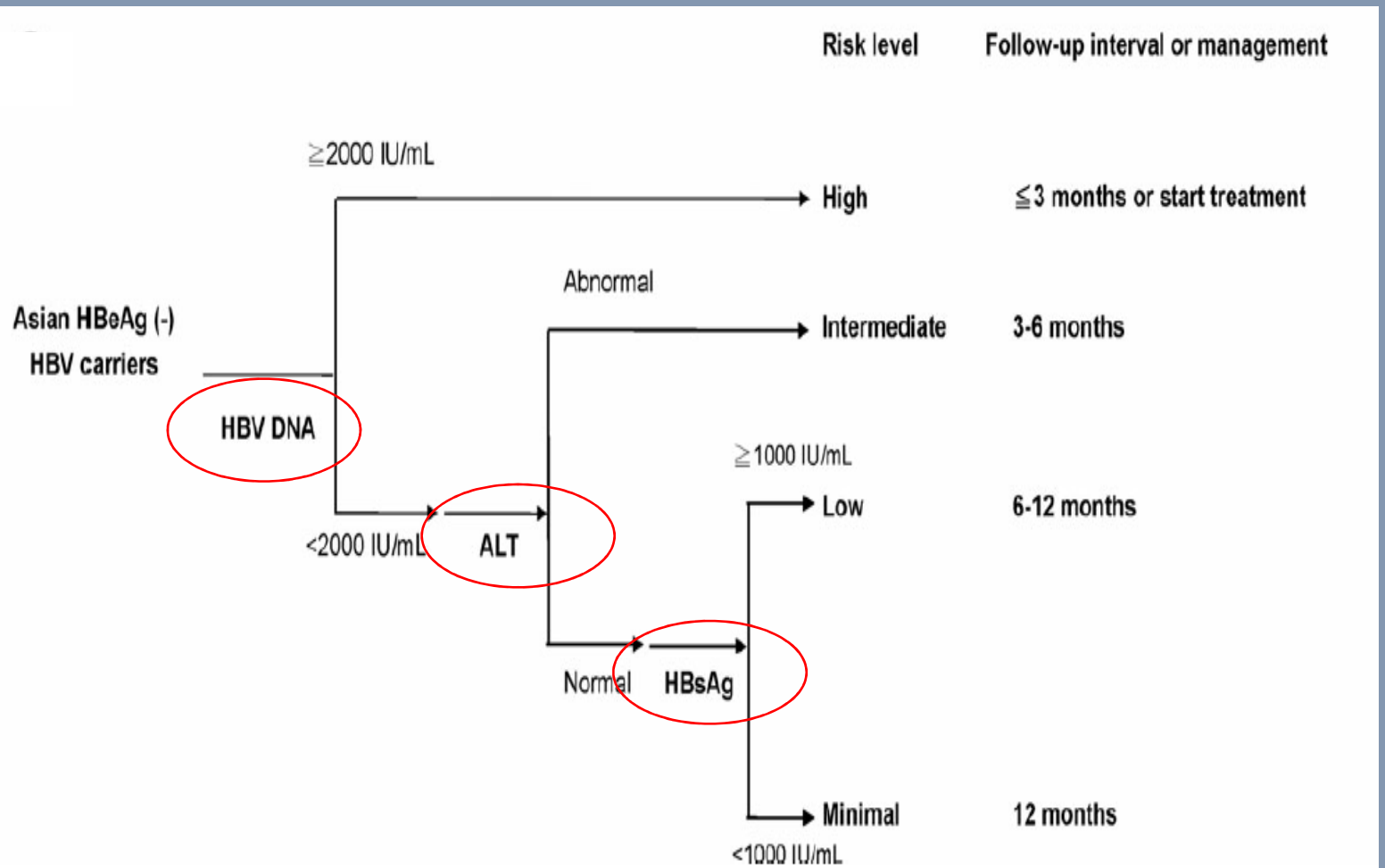
Papatheodoridis et al, J Hepatol 2012

Inactive Carriers Prognosis



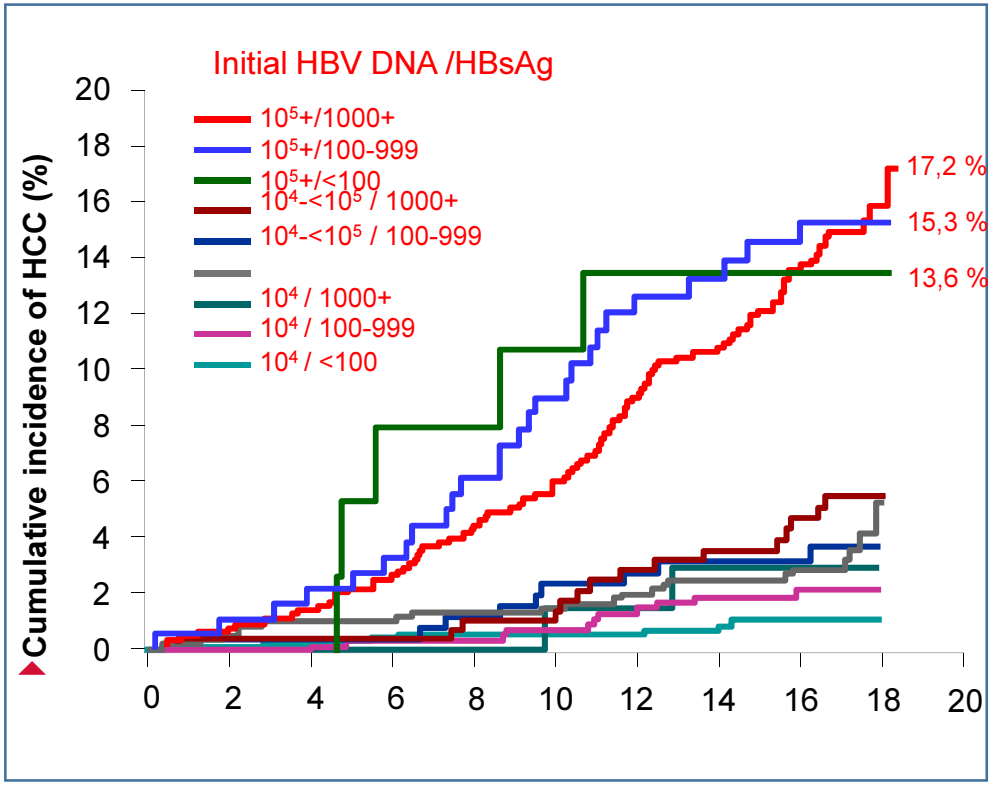
Tseng et al, Gastroenterology 2011

Tseng Algorithm from REVEAL cohort



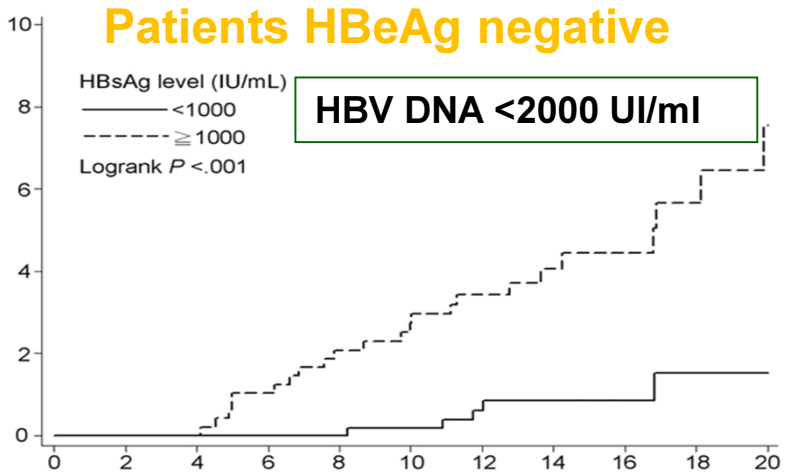
HCC risk Prediction

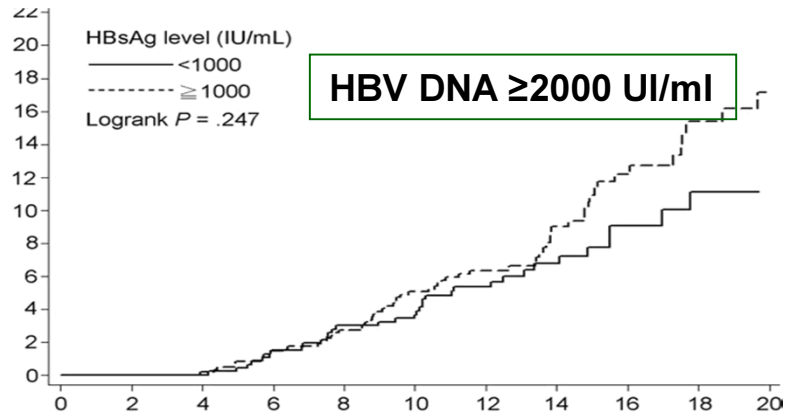
REVEAL Study :n = 3 411



ERADICATE-B : n=2688

Patients HBeAg negative



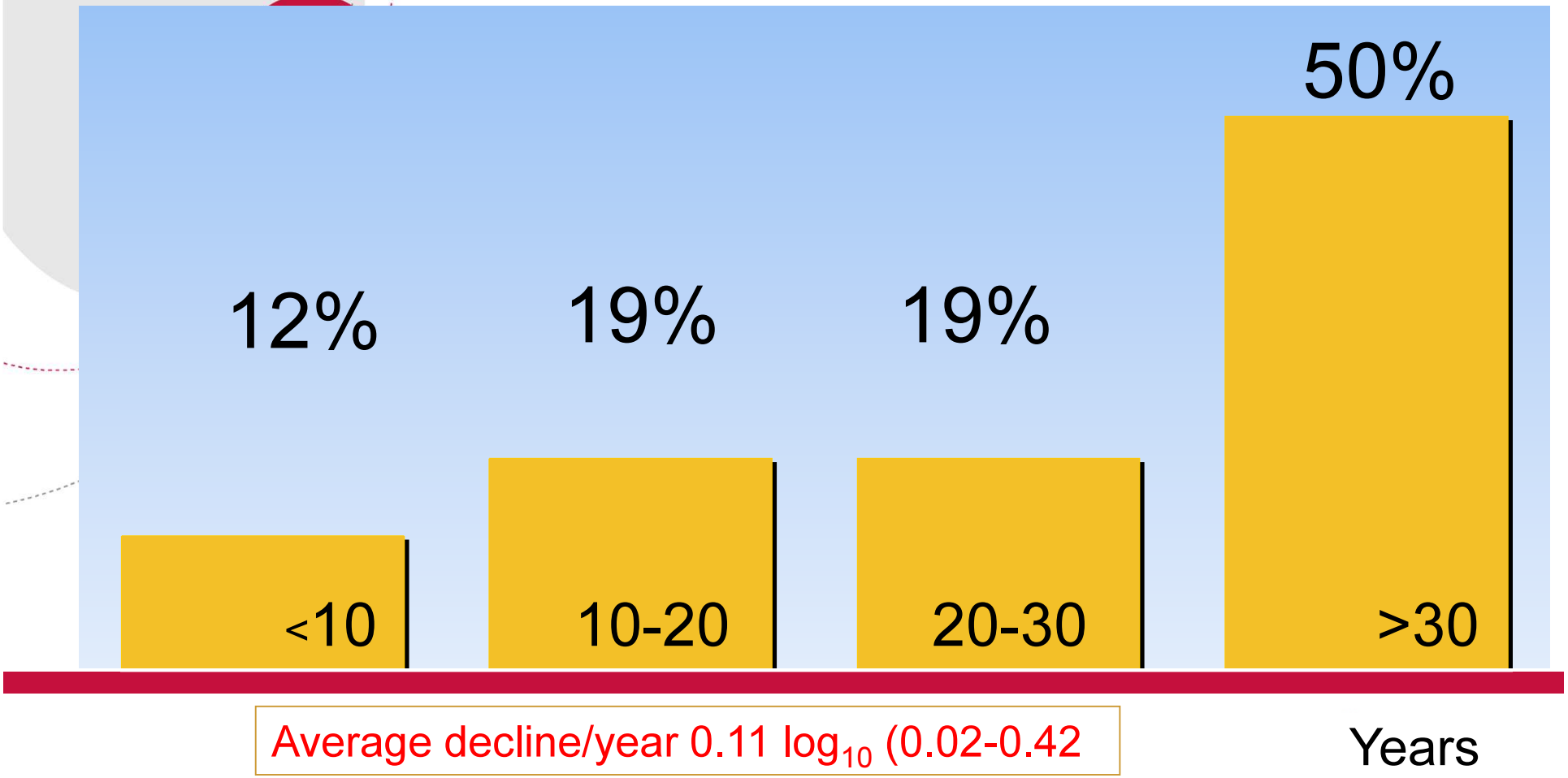


CHC minimal risk HBsAg <1000 UI/ml and DNA <2000 UI/ml

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

Finite treatment duration unlikely

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



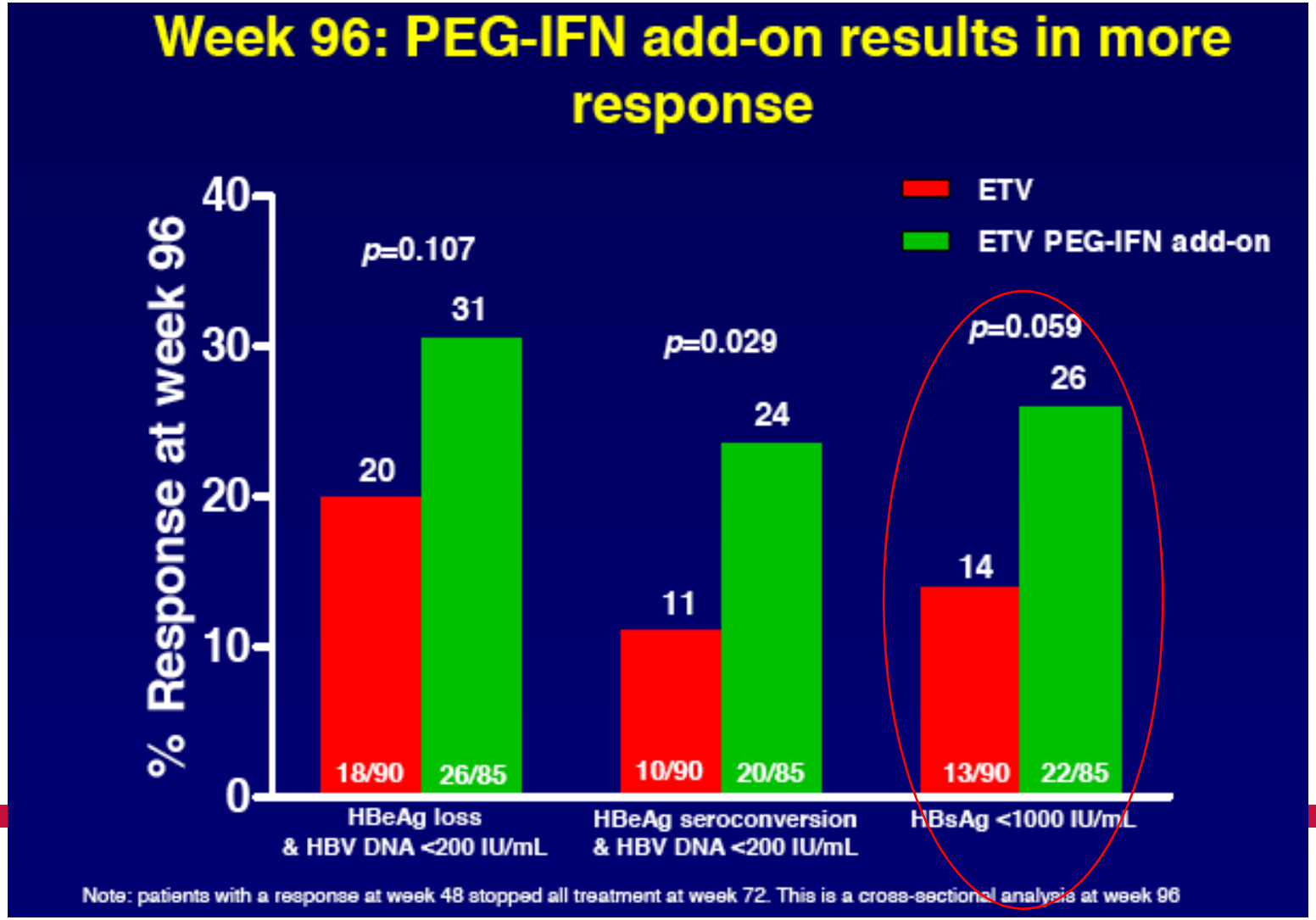
Average decline/year 0.11 $\log_{10}$ (0.02-0.42


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

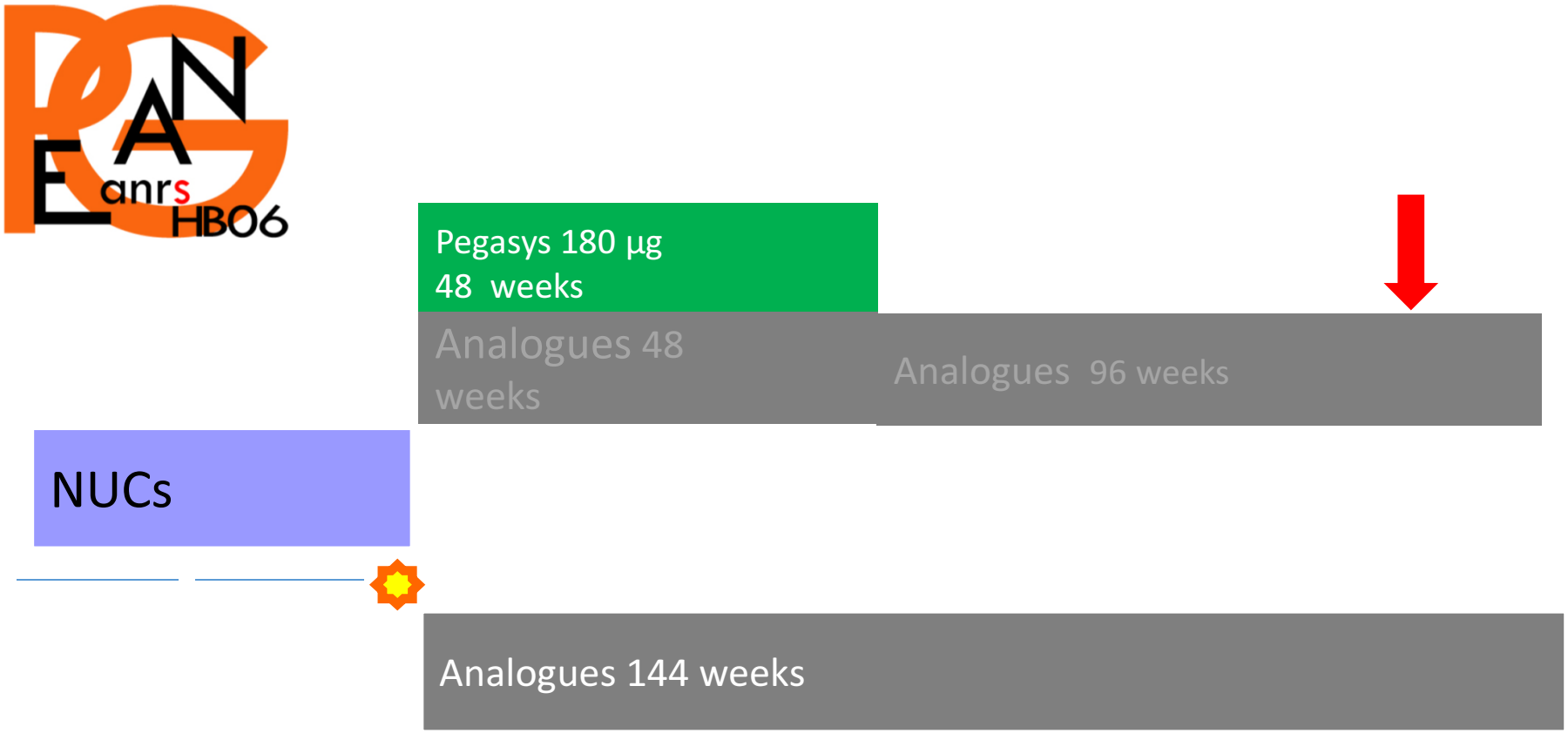
How find a solution for alternative to indefinite nucleos(t)ide analogue (NA) therapy in patients chron hepatitis B, two concepts were developed

- Add-on Therapy
- Swiching 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)



Add-on of peg interferon to a stable nucleoside regimen



Add-on of peg interferon to a stable nucleoside regimen

Loss of HBsAg at W48

	Analogue	PEG-IFN + analogue	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

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

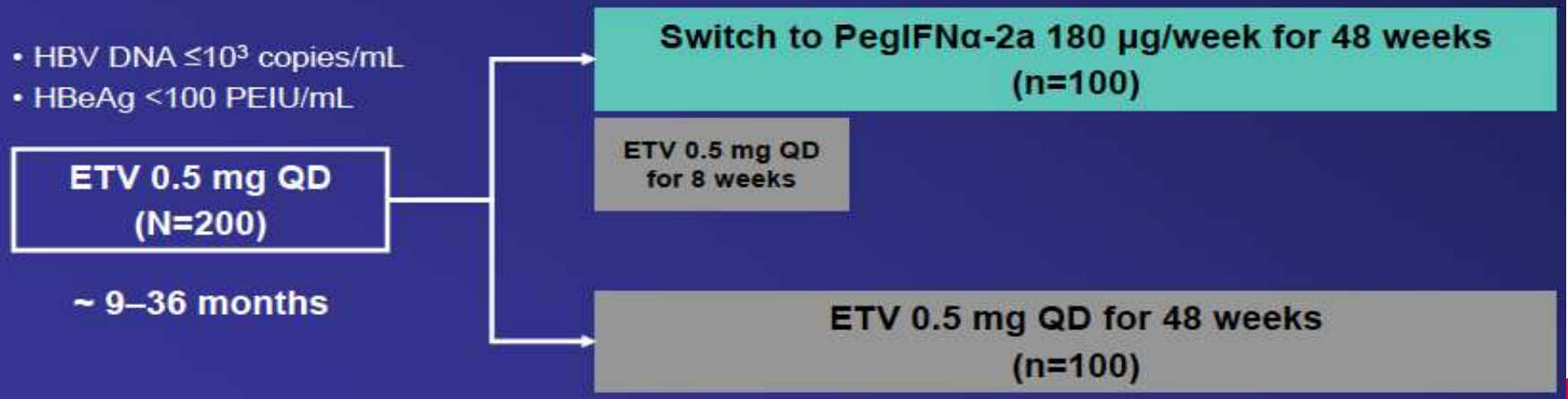
- Add-on Therapy

- Swiching 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

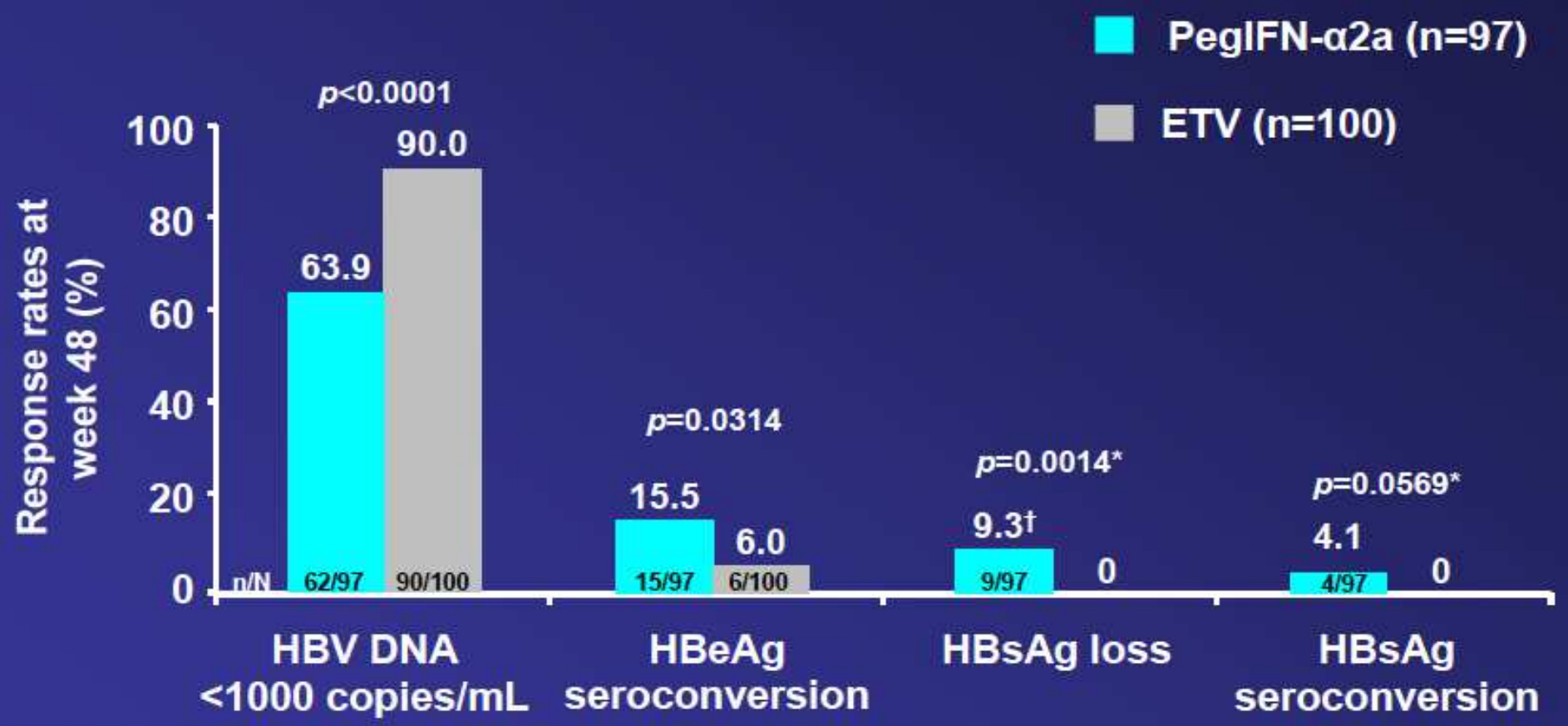
- Randomized, multicenter, open-label study
- Primary endpoint: HBeAg seroconversion at end of treatment (week 48)
- Secondary endpoint: HBsAg loss at week 48



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

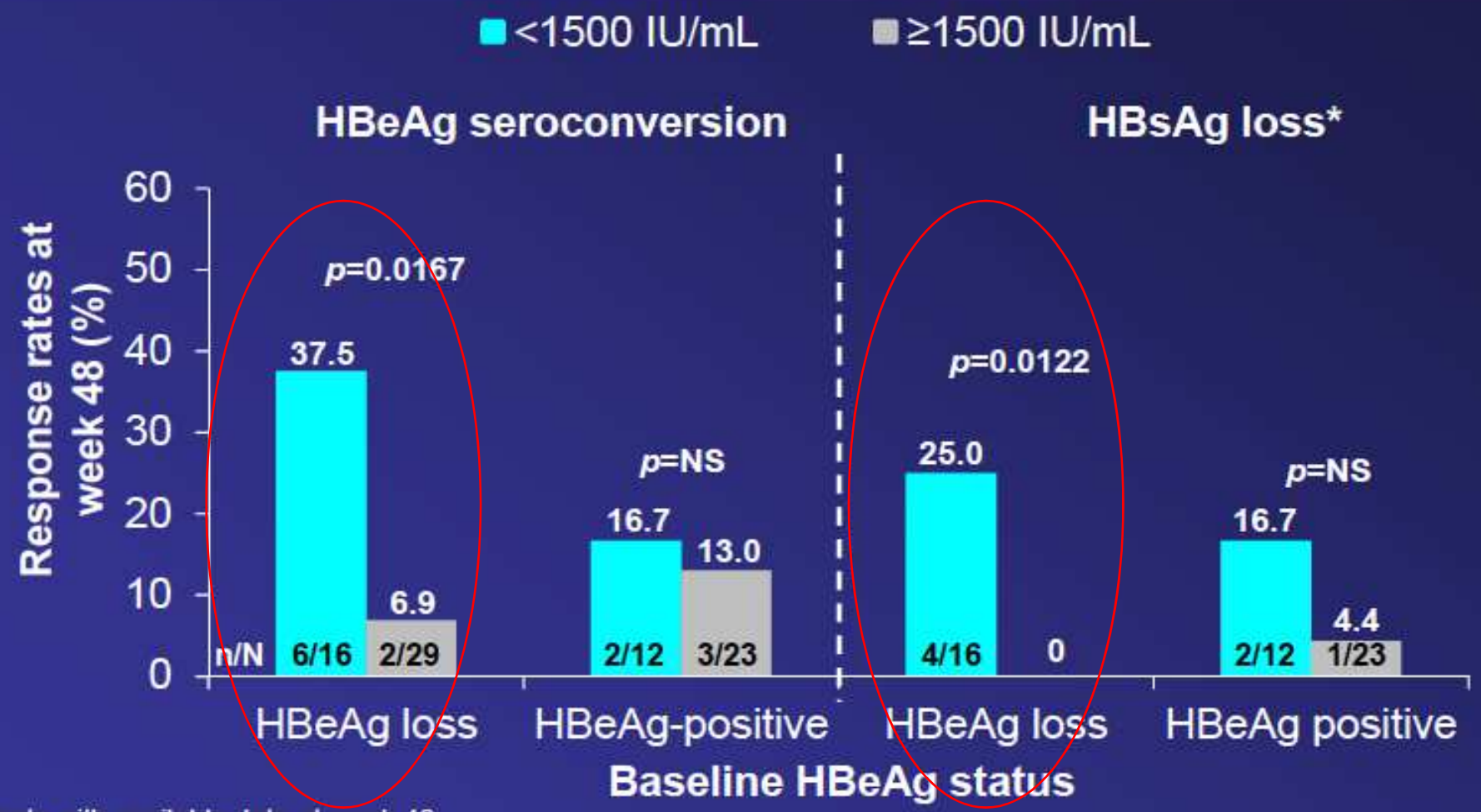
Ning et al J Hepatol 2014

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

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

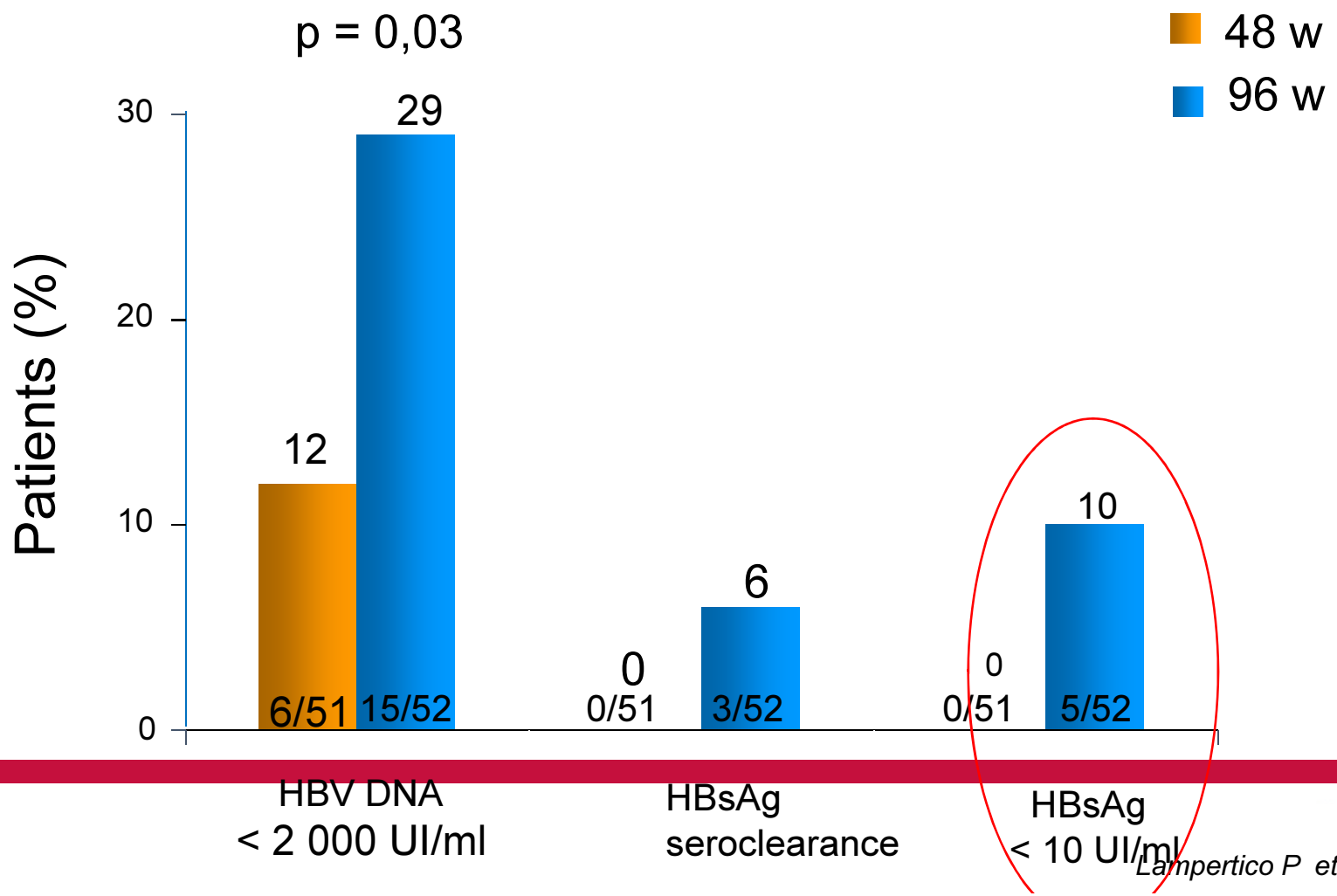
This cut-off is updated from time of abstract submission

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

- Add-on Therapy
- Swiching 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



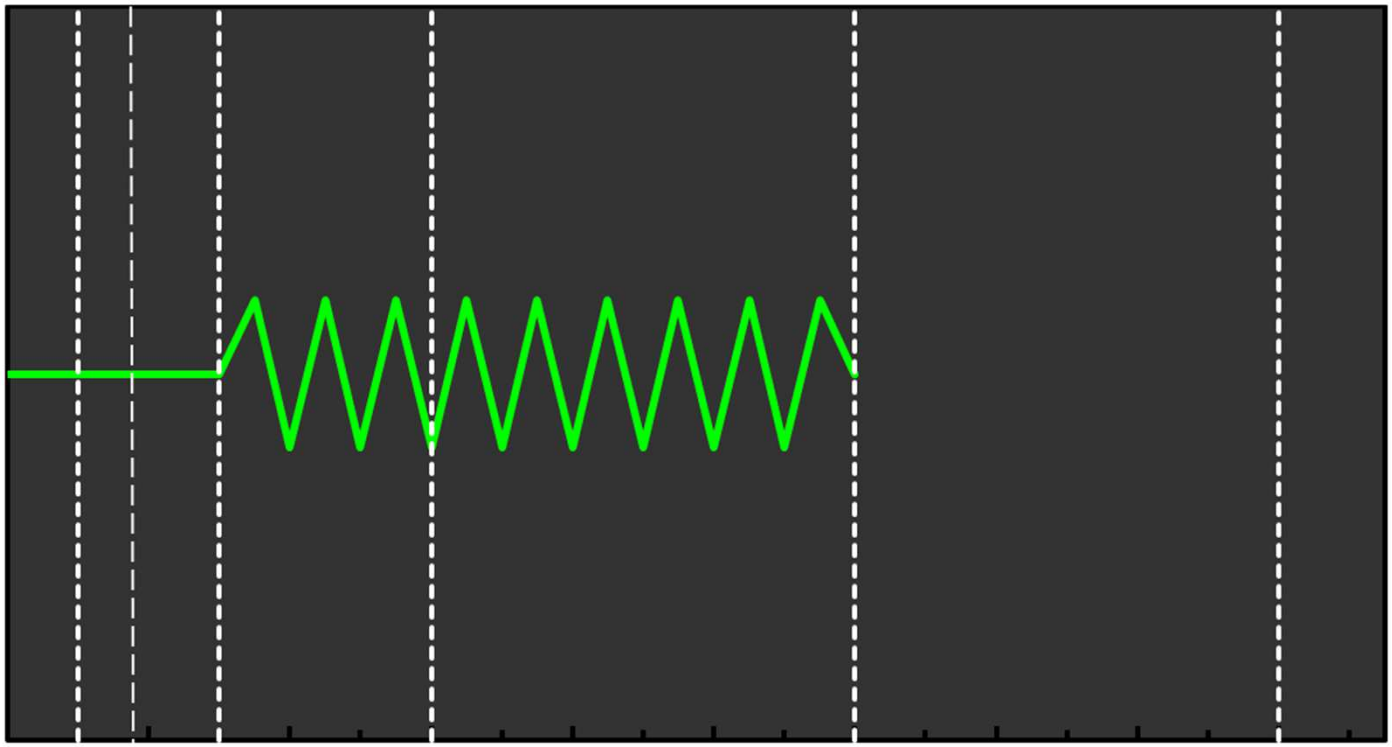
Lampertico P et al .GUT 2012

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

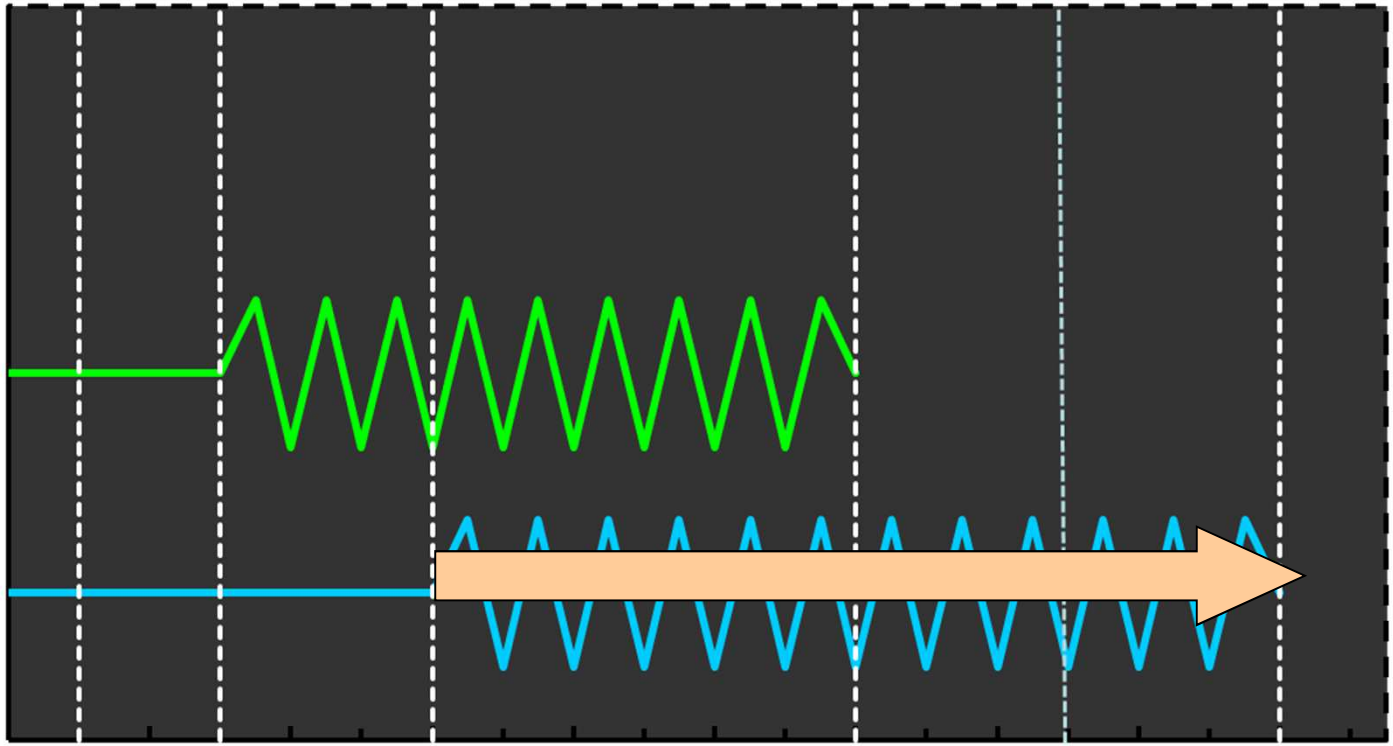
Halfon P. J Hepatol 2014

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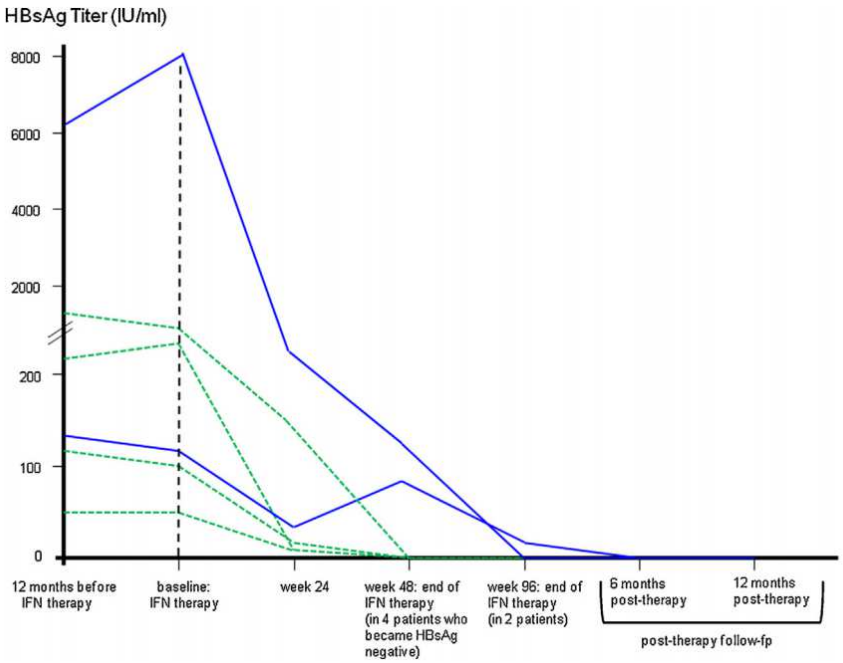
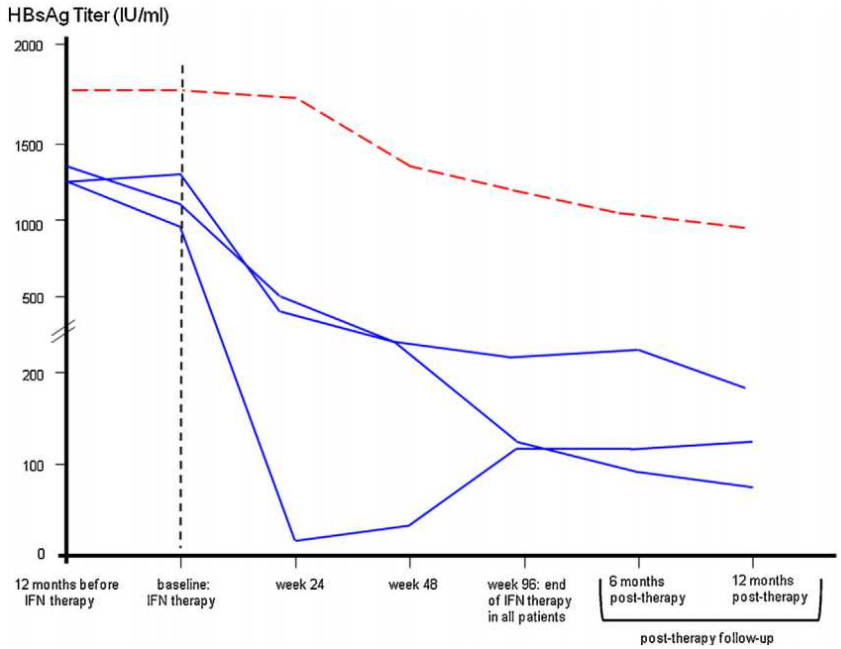
Add-on peg-interferon leads to loss of HBsAg in patients with HBeAg-negative chronic hepatitis and HBV DNA fully suppressed by long-term nucleotide analogs

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





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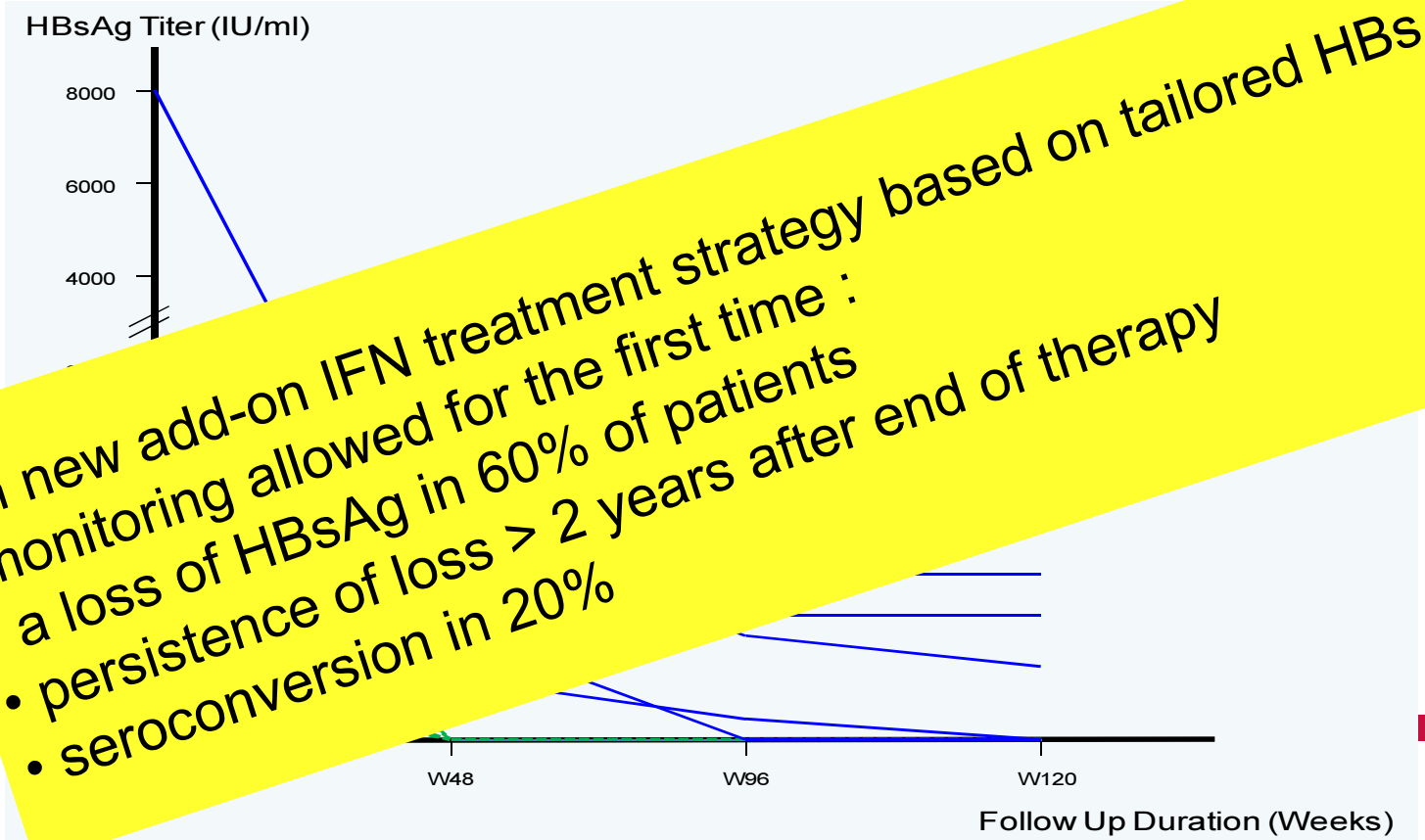
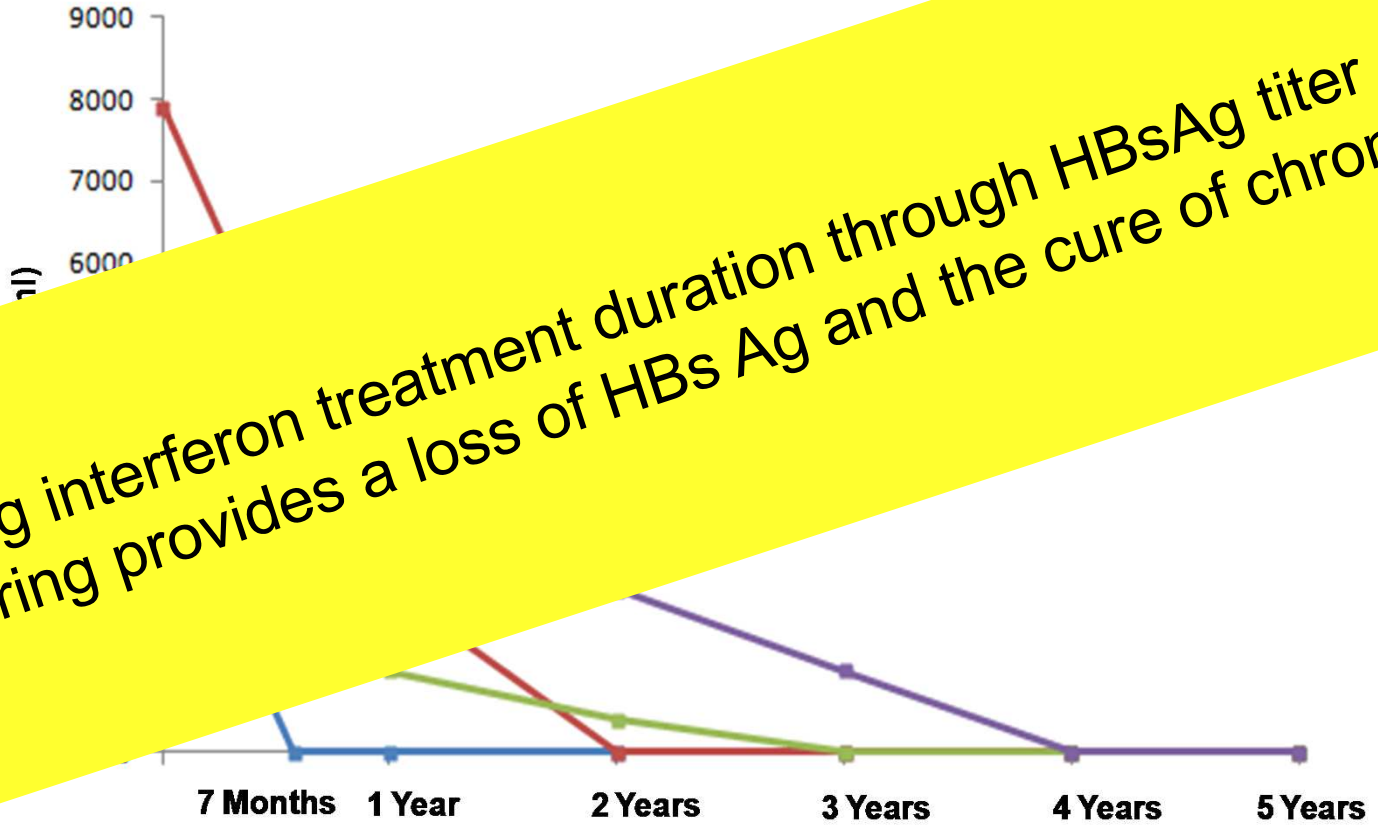


An new add-on IFN treatment strategy based on tailored HBsAg monitoring allowed for the first time :

- a loss of HBsAg in 60% of patients
- persistence of loss > 2 years after end of therapy
- seroconversion in 20%

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

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

Home Messages : Non Invasive tests

- Non-invasive tests should always be interpreted by specialists in liver disease, **according to the clinical context**, considering the results of other tests (biochemical, radiological and endoscopic) and taking into account the recommended quality criteria for each test and its possible pitfalls
- **Serum biomarkers can be used in clinical practice due to their high applicability (>95%) and good interlaboratory reproducibility**. However, they should be preferably obtained in fasting patients (particularly those including hyaluronic acid) and following the manufacturer's recommendations for the patented tests
- **TE is a fast, simple, safe and easy to learn procedure that is widely available**. Its main limitation is the impossibility of obtaining results in case of ascites or morbid obesity and its limited applicability in case of obesity and limited operator experience

Conclusions : The usefulness of quantitative HBsAg

- Decisional algorithms based on HBsAg and HBV DNA kinetics leading to response guided therapy are needed
- Stopping rules should be defined at a specific time point using an optimal HBsAg cut-off or HBsAg Kinetics
- “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

"All the News That's Fit to Print"

The New York Times

Late Edition

Today: Hot. Really hot. Global warming hot. Highs: 96, Lows: 97. Tomorrow: 80% Chance of hurricane; 90% Chance of flood. Yesterday Tropical Storm Florence ravaged Brooklyn an Manhattan. Weather Map on page D18.

VOL. CLIV NO 53,011 MONDAY, MAY 15, 2023 12 DOLLARS

HCV ELIMINATED FROM PLANET

Deadly bloodborne virus cured. Joins list of unintimidating diseases; polio, consumption, scurvy, cabin fever.

By Rómulo A. Tenés

Voltaire, in his Dictionnaire Philosophique said:

"What? A rigorous test is requested to affirm that the surface of a sphere is equal to that of the quadruple of the surface of the circle round its central point..." and yet does it not have to be rigorous, for example, in certifying the whole of Picasso's false work between 1891 and 1897 which was undoubtedly made by his father. José Ruiz Blasco? Or the centenary canvas, 1903 "Dama en Eden Concert" as a true one?

Well, dear investors in art, that is how it is. In insulting arbitrariness, contrary to the most elemental common sense, and to the exclusive benefit of unscrupulous art merchants, science is not used in certifying Picasso's work.

A grotesque example of this is Josep Palau i Fabre, "biographer", whose only merit resides in idolizing Picasso to his own benefit. A clumsy hearing aid to his ear, he pretends to listen, expecting the paintings to speak. He is deaf. Fine.

Cure Attributed to Stem Cell Research

But, surprise! Concepción, Claude, and Paloma Ruiz-Picasso defend the esoteric, clumsy, and grotesquely irrational system of certifying the work of their father. To their own benefit, and with catastrophic results: thousands of false works, and the subsequent loss of credit.

Would an investor in art allow such an individual to enter his company entrusted with its management, or as an instructor for his children?

Why then does he accept him in his investments in art? why does he not demand modern, rigorous, scientific certificates?

"Dama en Eden Concert", timidly remained silent in the face of the grotesque system of certifying its virginity.

José Ruiz Blasco. 1895. Oil on canvas, attribu-

Photo. Béatrice HATALA

"Dama en Eden Concert", oil on canvas, 80x59 cm. Picasso 1903. Signed in the top right-hand corner, with scientific certificates issued by Doctor Marianne Tauber from the Swiss Institute for Art Research, Phd. in Chemical Engineering, Francesc Servera, from Lausanne and Barcelona University; and by Historian and friend of Picasso, Pierre de Champris. Pierre Deix says in his Dictionary that "We owe Champris the best study on Picasso's pictorial sources, written about in his book *Ombre et soleil, Paris 1960*. Analysed by X-Ray, appearing on the sub-layer, is the father of the artist reading. Picasso marked the frame with the numbers "323" and "323".

rarchy, which is verified in a Calligraphy Report dated 27th December 2002 by the expert calligraphers Ms. Rosa Torrents Boley and Ms. Silvia Tarrago Goarré, from Barcelona, Spain.

Hepatologists Party Like it's 1999.

This report contains 298 pages and certifies that Picasso had taken over by deceitful means all the works whose author was undoubtedly his father, José Ruiz Blasco in the period between 1892 and 1897. Specifically, the "J" of José Ruiz had been falsified to the "P" of Pablo, and was unlawfully and deceivingly assumed by Pablo Ruiz Picasso; this lie was made worse with the fraudulent Picasso donation in 1970 to Barcelona City Council: a donation which contained all the works of José Ruiz between 1892-1897.

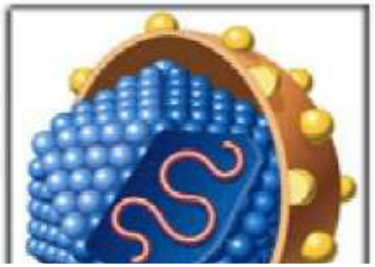
What did Concepción Ruiz Walter, Claude, and Paloma Ruiz Gilot know?

This circumstance, would not worry us if it were not for the fact that the researcher was compelled to register the irregularities before the Central Courts of Instruction of Madrid on 10th June 2003 and 15th July 2004 and request by Law the separation of the work of both artists, father and son. This separation is compulsory by Law.

As a result, the successors of Picasso must lose all their rights regarding the works of their grandfather, José Ruiz Blasco.

The chief Curator of the Prado Museum of Madrid, Antonio Solano, concerning the present system for valuing Picassos affirms: "Authentications by the descendants of painters should not be accepted. Some are so discredited, it is embarrassing".

However, we see what has been done by Christian Zervos, 1932, John Richardson, Pierre Deix, Marilyn McCully, Henry Gidel, Douglas Cooper, Penrose, Catherin Hutin-Blay, William Rubin, Renata Proper, María Teresa Ocaña, Josep Palau i Fabre and Norman Mailer, 1995, one of the latest writers



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Former President Bush indicted for War Crimes

Rómulo-Antonio Tenés, Spain, a researcher and artist, is the author of the book **Fraud Picasso**. He takes to Cou Goya's New Caprices Exhibition for prove fraud at the National Library of Spain, L Vanguardia, 11.8.81-. He achieved the removal of a false painting attributed t Darío de Regoyos from the Prado Museum news flash by REUTER and EFE Worl Press Agencys 20.09.1989. He participate in the Homage to Picasso 1981 at Skira A Gallery along with Henry Moore, Chillid Tapies, Miró, Rafael Alberti, Canoga Oleiza, Saura, and other famous artists. I La Vanguardia, dated 8-03-1983, he publis hed a study on Picasso's plagiarisme o the horse in the Guernica, which was pai ted by Ricardo Marín, Nuevo Mundo