HBV Inactive chronic carrier

JP ZARSKI
Clinique universitaire d'Hépato-gastroentérologie
Pole Digi-Dune
CRI INSERM U-823
CHU de Grenoble
France

Observation

- Men
- Native of Senegal
- 51 year old now
- Past history:
  - Tubercular pleurisy (1977)
  - Duodenal bulbar ulcer (1995)
- 1997: 37 year old
  - HBs antigen (+), anti-HBc (+), anti-Hbe (+), HBV DNA (-), ALT <N
- No symptoms
- Physical examen: normal
- Ultrasound sonography: normal

Observation

- Follow-up
- Every year
- ALT<N
- HBV DNA
  - 2007/March: 548 IU/mL or 2.74 Log IU/ml or 3.5 Log copies/mL
  - 2009/April: 267 IU/mL or 2.43 log IU/mL or 3.19 log Copies/ml

Question?

- The good follow-up for this patient:
- ALT and HBV DNA
  - Every year
  - 2 times/year
  - 3 times /year
  - 4 times/year

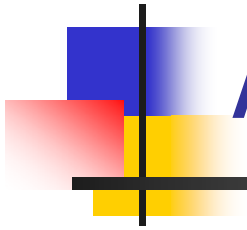
AASLD Guidelines

- ALT levels every 3 months during the first year
- Then every 6-12 months

Lok and McMahon, Hepatology 2007

Observation

- 2010/January:
  - ALT:31 IU/L
  - HBV DNA: 1593 UI/ml or 3,2Log UI/ml
- 2010/ June:
  - ALT:35IU/L
  - HBV DNA: 3170 UI/ml
- Diagnosis:
  - Inactive chronic carrier
  - Or HBe antigen (-) chronic hepatitis B



ALT level?

ALT levels and HBV DNA: risk of CHB

ALT<30IU/L (men) ALT<19IU/L (women) HBV DNA<20 000UI/mL	ALT>30IU/l (men) ALT>19IU/L (women) HBV DNA>20 000UI/mL
5%	86%

*19 ICC

Assy et al, World J gastroenterol 2009

Factors associated with high-normal serum ALT level*

1. Male sex: 1.82 [1.10-3.01]
2. Increasing age
    1. <30 years:1
    2. 30-39 years:2.43 [1.18-5.05]
    3. 40-49 years:4.22 [1.99-8.93]
    4. ≥50 years:4.06 [1.69-9.78]
3. Serum HBV DNA >10^4 copies/ml:1.83 [1.07-3.13]

*ALT levels:
Low-normal:0-0.5
High-normal:0.5-1.0

Lin et al, Hepatology 2007

HBV DNA: cut-off?

Levels of HBV DNA?

Table 3. HBV DNA Levels in Inactive Carriers With Persistently Normal ALT Levels (≤30 U/L for Males and ≤19 U/L for Females)

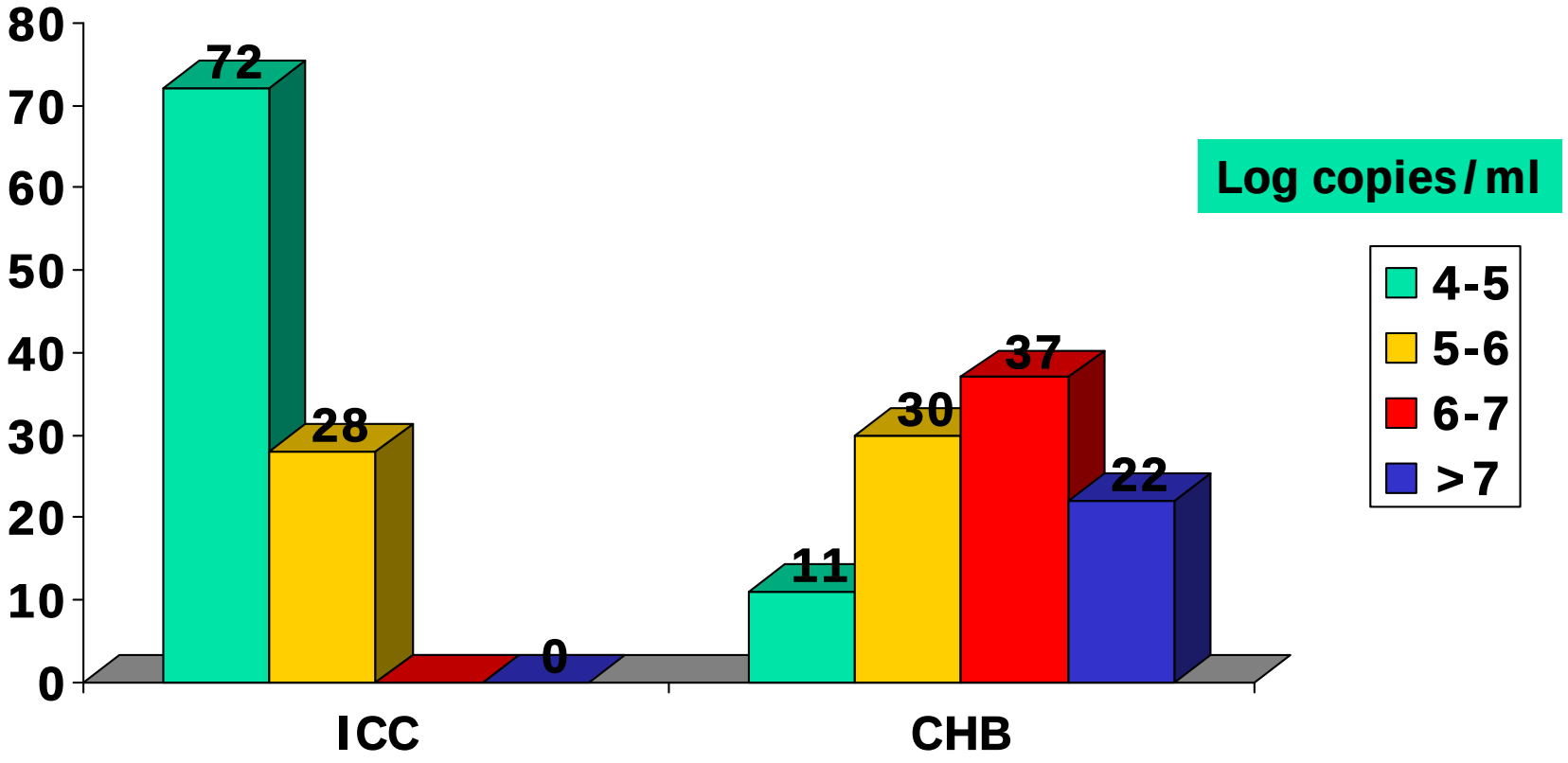
HBV DNA levels, log_{10} copies/mL[a]	Total (n = 75)	Males (n = 52)	Females (n = 23)	*P*
<2.3 (undetectable)	9 (12)	6 (12)	3 (13)	.85
2.3–2.99	8 (7)	6 (12)	2 (9)	.71
3–3.99	26 (35)	15 (29)	11 (48)	.11
4–4.99	24 (32)	20 (38)	4 (17)	.071
5–5.99	8 (11)	5 (10)	3 (13)	.66
Median (range)	3.81 (<2.3 to 5.45)	3.95 (<2.3 to 5.45)	3.76 (<2.3 to 5.45)	.72

NOTE. Data are given as number (%).
[a]5.26 copies/mL = 1 IU/mL.

Follow-up:>10 years

Chu et al, Clinical Gastroenterol Hepatol, 2010

HBV DNA



250 ICC
Normal ALT levels>10 years

Chu et al, Clin Gastoenterol Hepatol 2010

HBV DNA>10^4copies/ml

Taiwan	Hong Kong	Greece
34%	7%	0%

Characteristics of patients?

Table 4. Comparison of Clinical and Virologic Features Between Inactive Carriers With HBV DNA Levels of 10^4 Copies/mL or More and Patients With HBeAg-Negative Chronic Hepatitis

Data	Inactive carriers (n = 90)	Chronic hepatitis (n = 90)	*P*
Age, *y*	50.7 ± 8.9	51.1 ± 7.8	.75
Male:female ratio	30:60	72:18	<.0001
HBV DNA levels, $\log_{10}$ copies/mL[a]	4.72 ± 0.56	6.24 ± 1.12	<.0001
	4.63 (4.01–5.98)	6.24 (4.09–9.18)	
4–4.99	65 (72)	10 (11)	
5–5.99	25 (28)	27 (30)	
6–6.99	0 (0)	33 (37)	
≥7	0 (0)	20 (22)	
Genotype			
B	80 (89)	67 (74)	.015
C	10 (11)	23 (26)	
Precore A1896 mutant	75 (83)	74 (82)	.84
Basal core promoter T1762/A1764 mutant	13 (14)	39 (43)	<.0001

NOTE. Data are given as mean ± SD, median (range), or number (%).
[a]5.26 copies/mL = 1 IU/mL.

Chu et al, 2010

Factors correlated with active hepatitis

Factors	OR (95%CI)	p
Sex:		<0.0001
Female	1	
Male	8.2(3.4-20.0)	
HBV DNA levels:		
4-5 logs cp/mL	1	
>5 logs cp/mL	21.5 (8.4-55.4)	<0.0001
Génotype:		
B	1	
C	1.8 (0.5-5.8)	0.34
Basal core promoter:		
T1762/A1764		
Mutant		
No	1	
Yes	3.5 (1.3-9.3)	0.011

Do you use surrogate markers of fibrosis?

- We performed:
  1. Fibrotest: A1/F1-F2 (0.41)
  2. FibroScan: 7,8 kPa (IQR:0.9, TDR=60%)

- Chronic hepatitis B:?

Main blood tests: Significative fibrosis (F≥2)

	AUROC		
	HBV	**HCV**	**p**
Fibrometer	0,81	0,82	ns
Fibrotest	0,78	0,81	ns
Hépascore	0,77	0,79	ns

Leroy, Zarski, submitted

Discordances

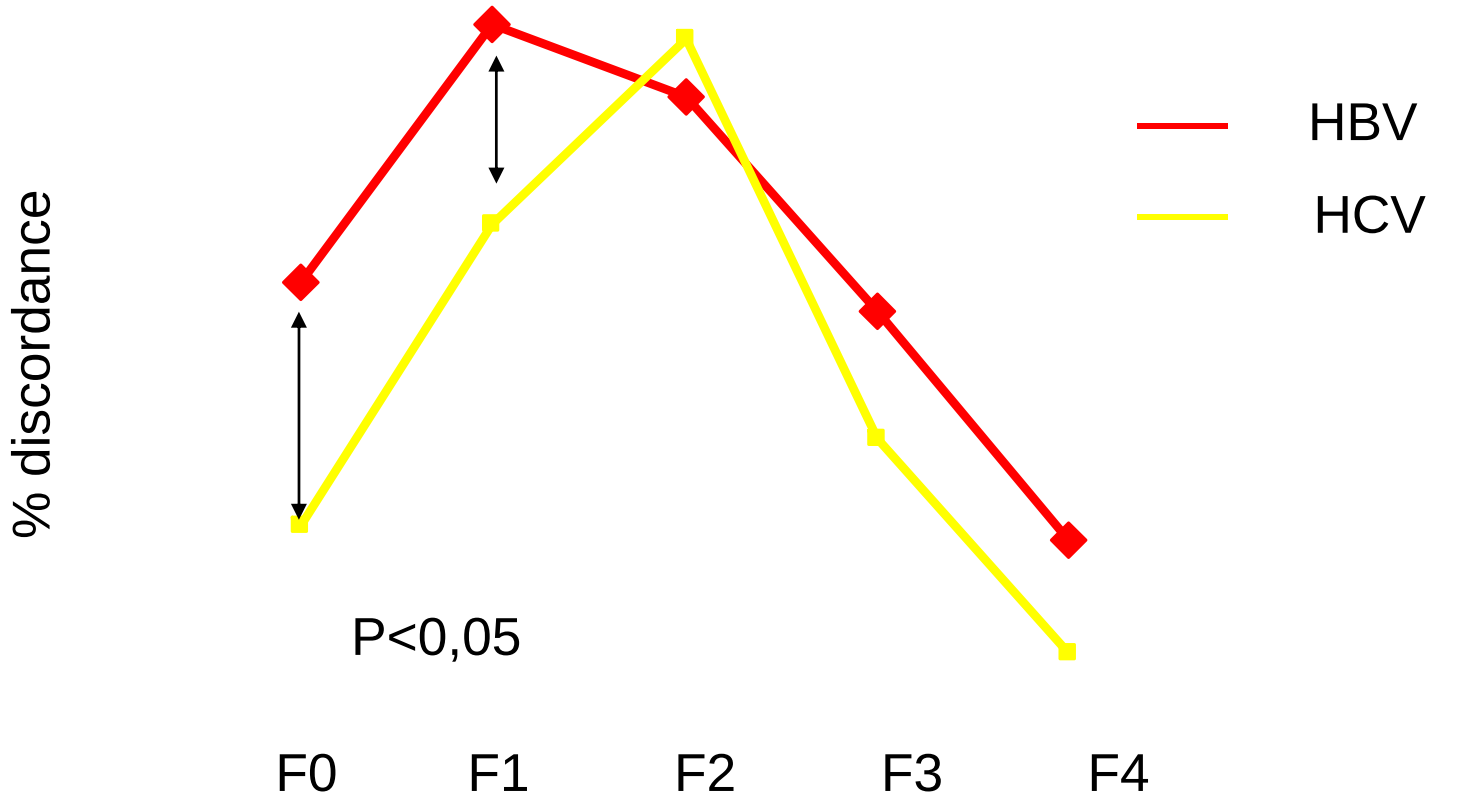
	F≥2		F≥3	
	HBV	**HCV**	**HBV**	**HCV**
Fibrometer	26%	20%	11%	10%
Fibrotest**	37%	28%	17%	17%

p<0,05

* Cut-offs

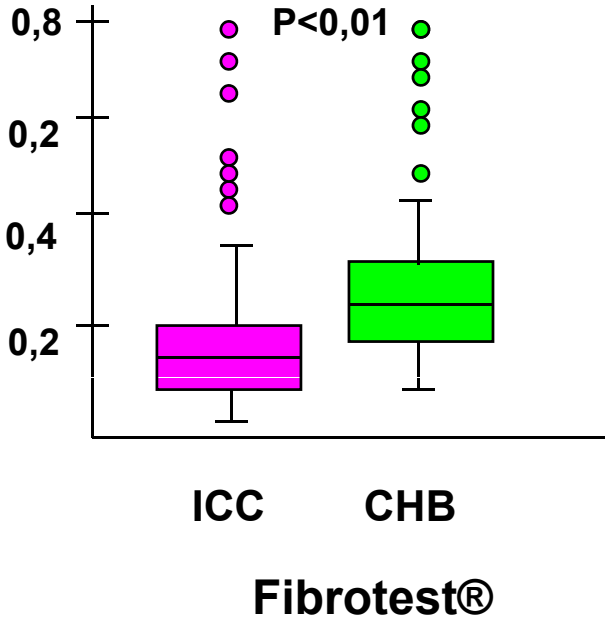
** Cut-off bioprédictive

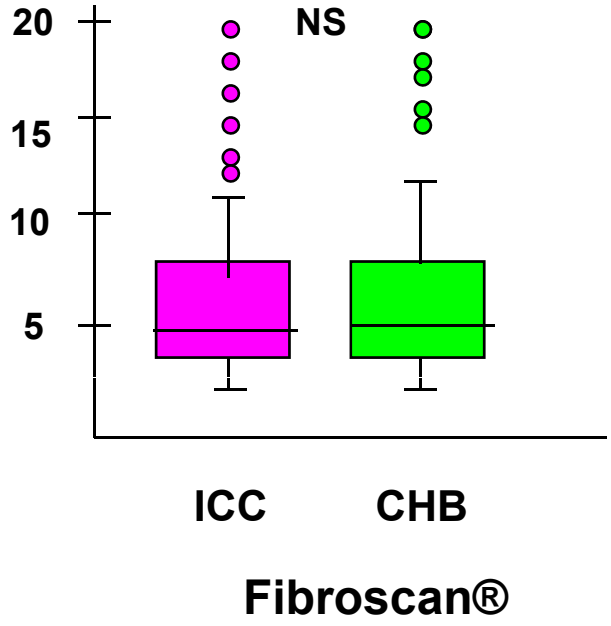
Fibrotest: discodances



Inactive chronic carriers

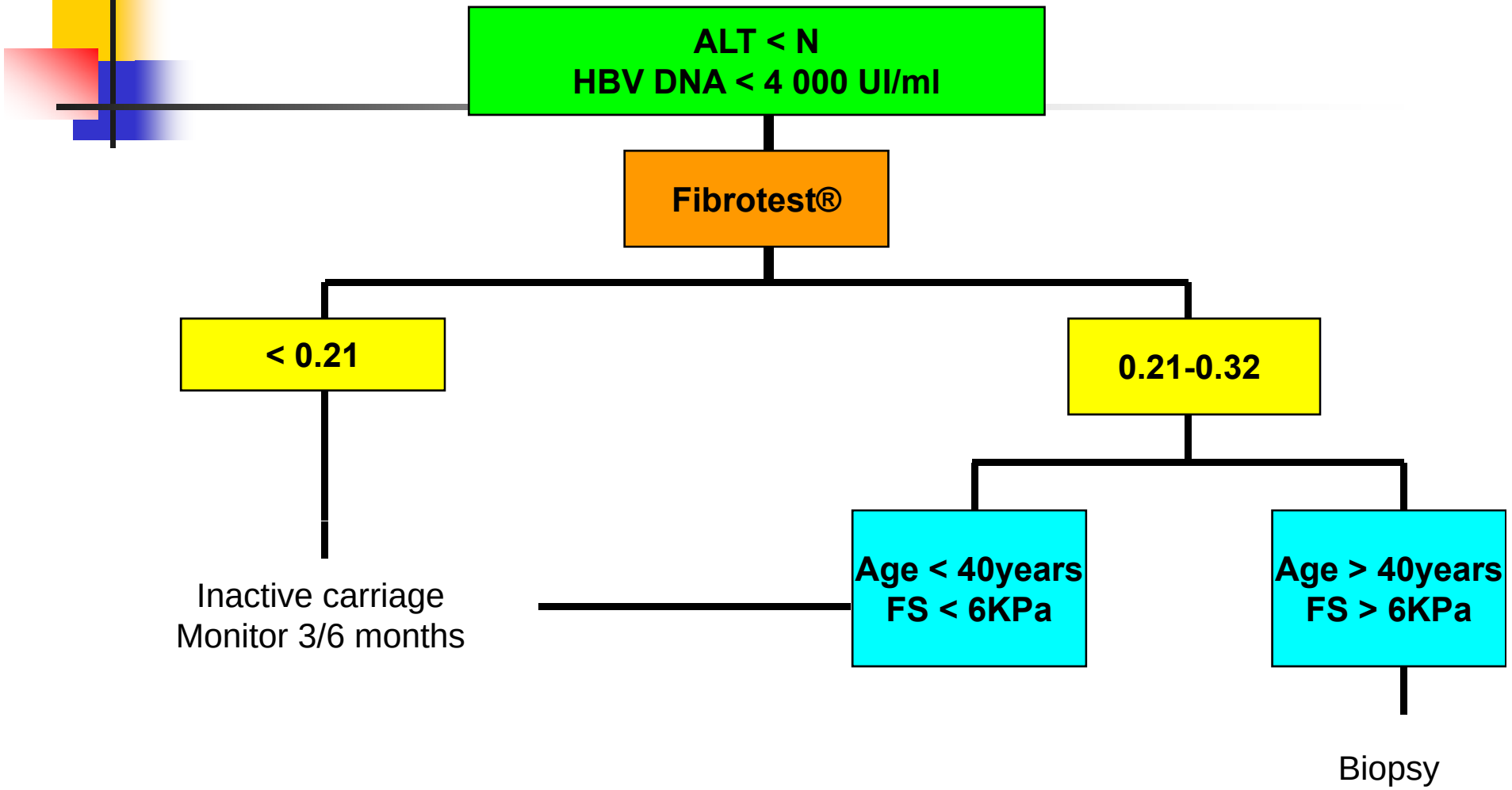
- 145 ICC (ALAT < N, HbeAg -, HBV DNA < 4000IU/mL)
- Compared to 122 HbeAg (–) chronic hepatitis F0F1 (LB)
- Performance of Fibrotest® and Fibroscan®





Leroy et al, submitted

Diagnosis of inactive carrier state

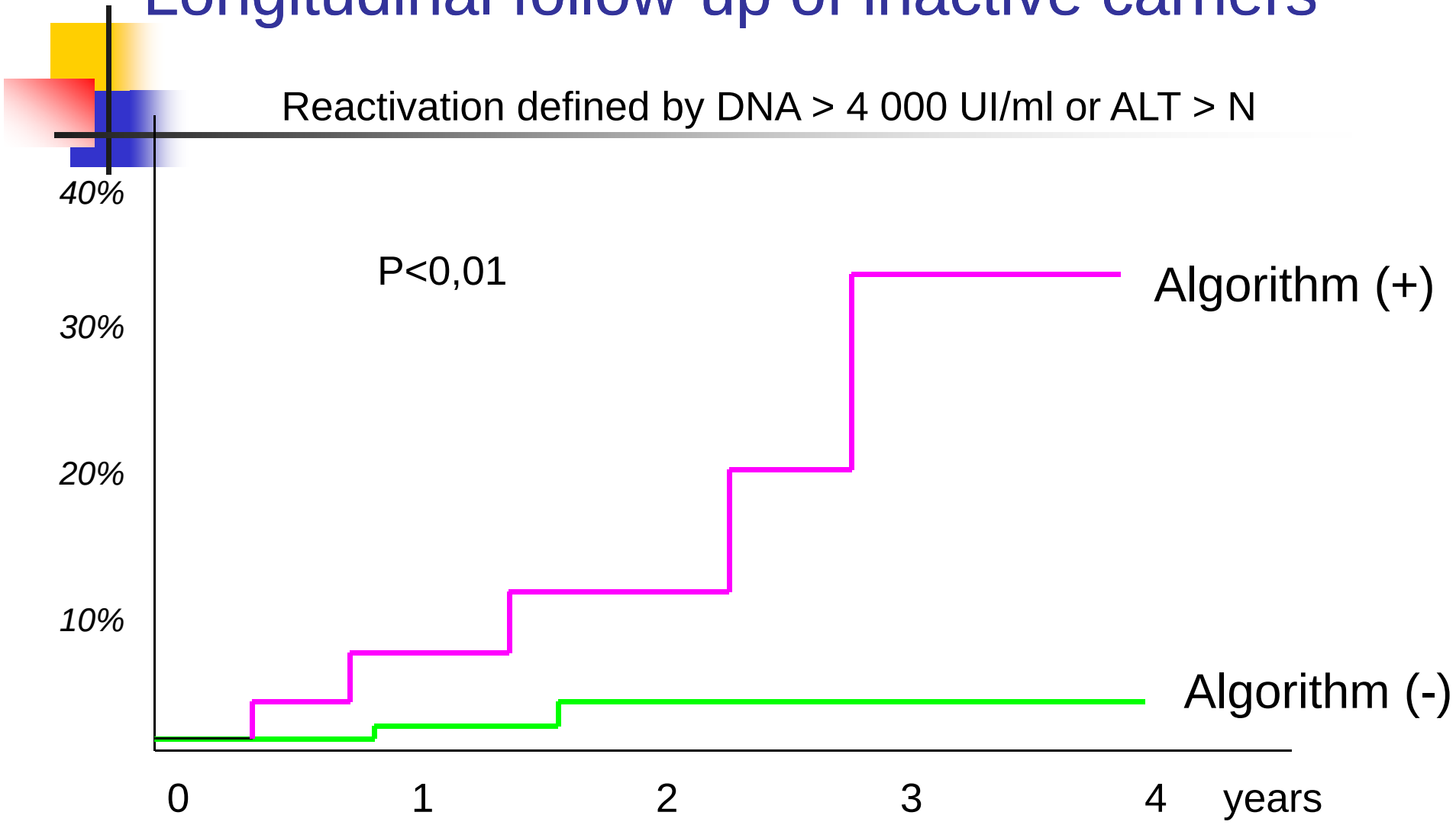


* HBV DNA < 2 000 IU/ml : 80% of patients

** Fibrotest < 0.21 : 75% of patients

Leroy et al, submitted

Longitudinal follow-up of inactive carriers



- Biopsy at reactivation : A2F1 maximum
- HBV DNA < 2 000 IU/ml = viral load 2 000 – 4 000 IU/ml

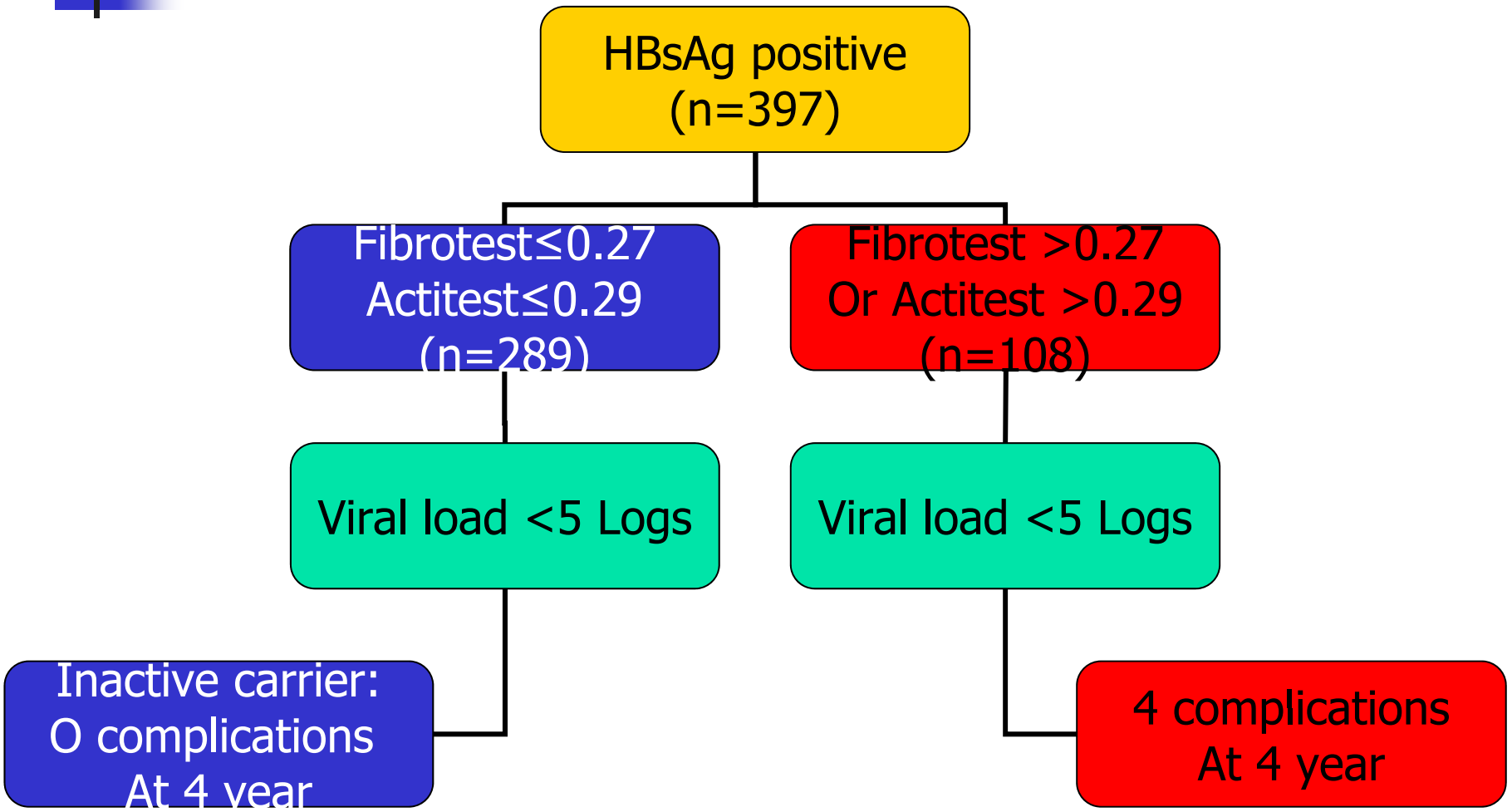
Leroy et al, submitted

Liver stiffness

- 125 inactive chronic carriers
- 95 anti-HBe CHB
- Mean stiffness:
  - Inactive chronic carrier: 4.83±1.2kPa
  - Chronic hepatitis: 8.53±6.0kPa ($p<0.01$)

Maimone et al, J Viral Hepatitis 2009

Combination of biomarkers and viral load?

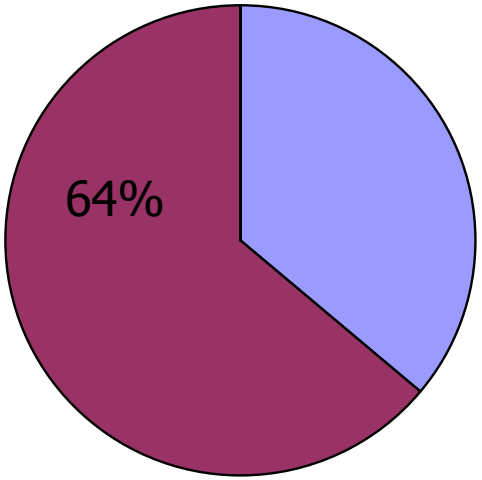


Poynard et al, PLOSone 2008

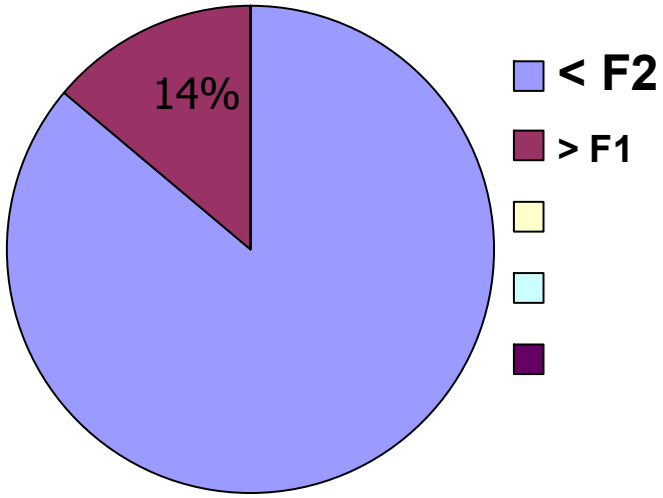
Observation

- Liver biopsy:
  - 26 mm
  - 11 portal tracts
  - A0 F1
  - Steatosis: 10%
  - Iron deposit+++

Histological lesions: HBeAg-



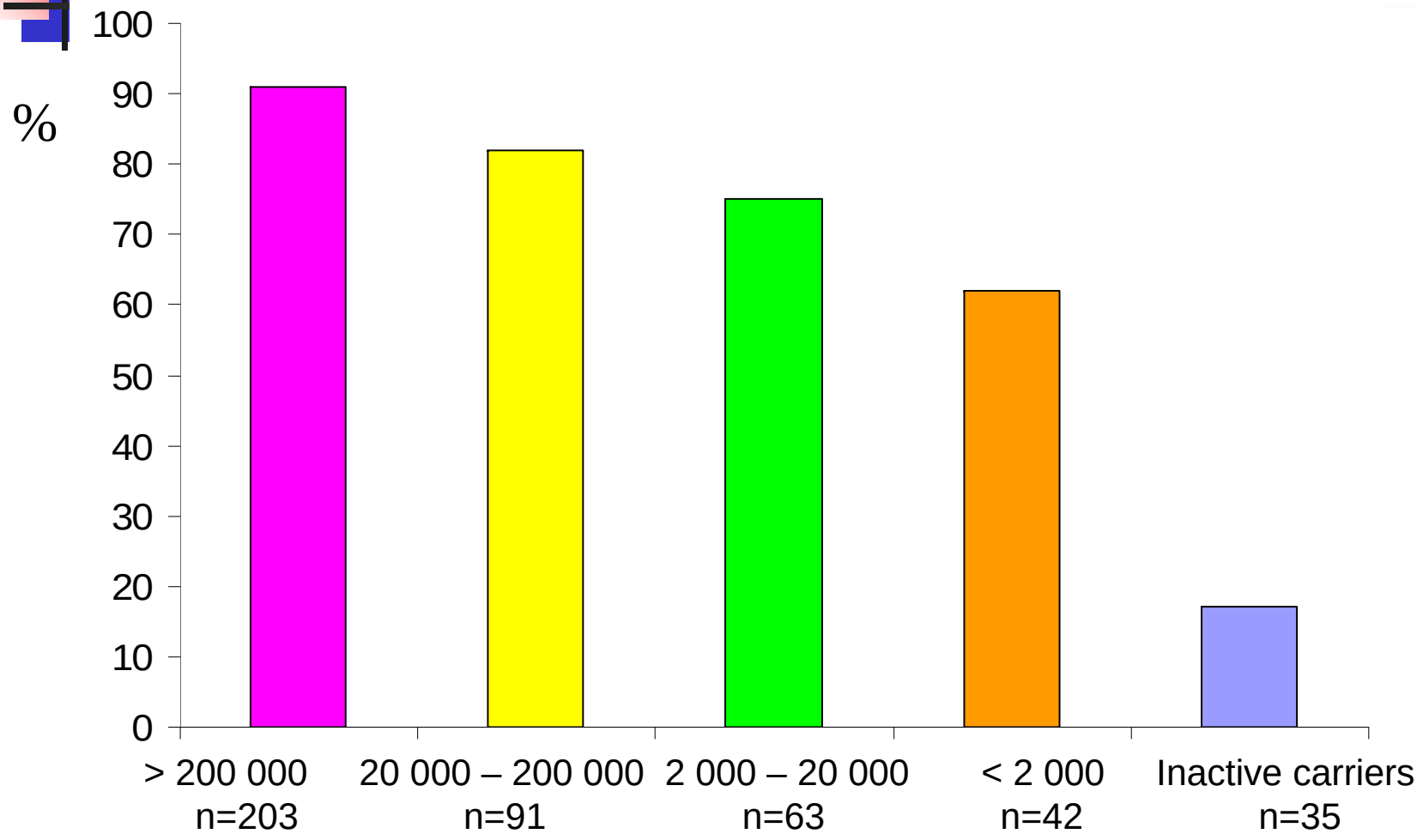
ALAT > N



ALAT < N

Kumar et al, Gastroenterology 2008

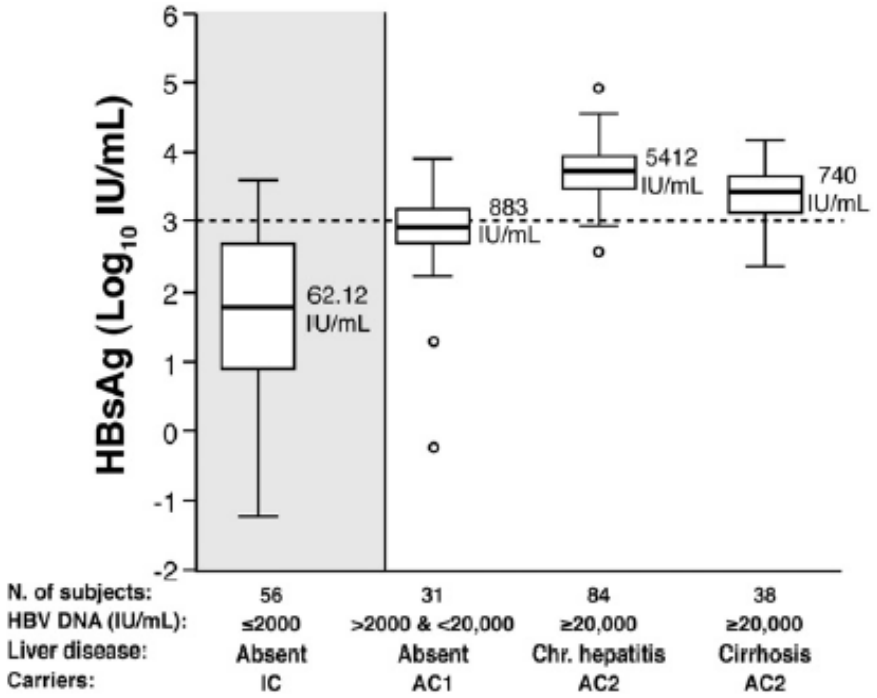
Prévalence of histological lesions > A1F1



Papatheodoridis et al, Hepatology 2008

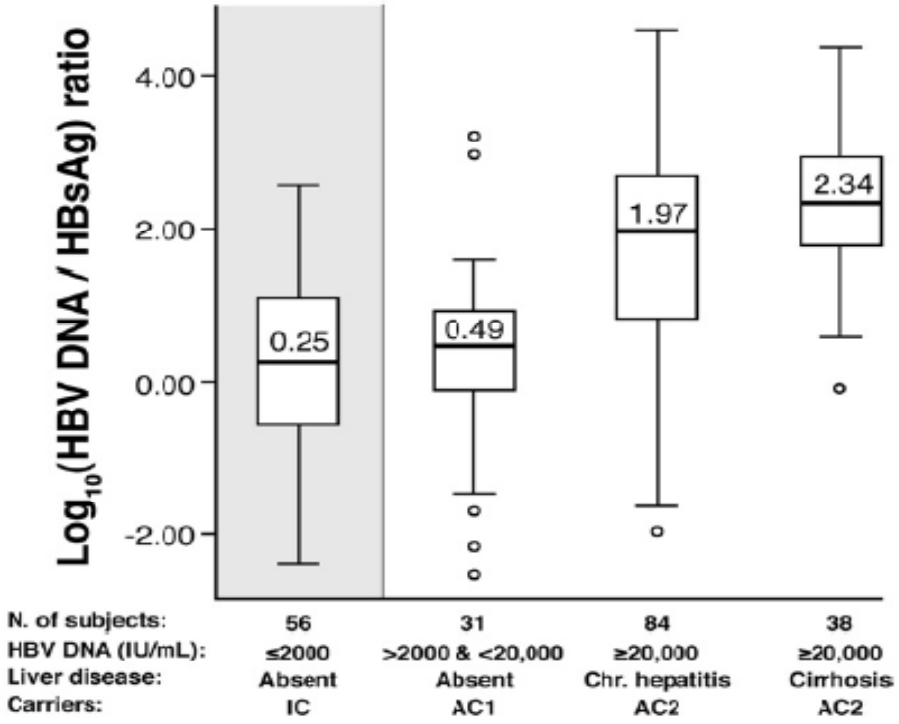
HBs Ag quantification?
Another marker

HBsAg title



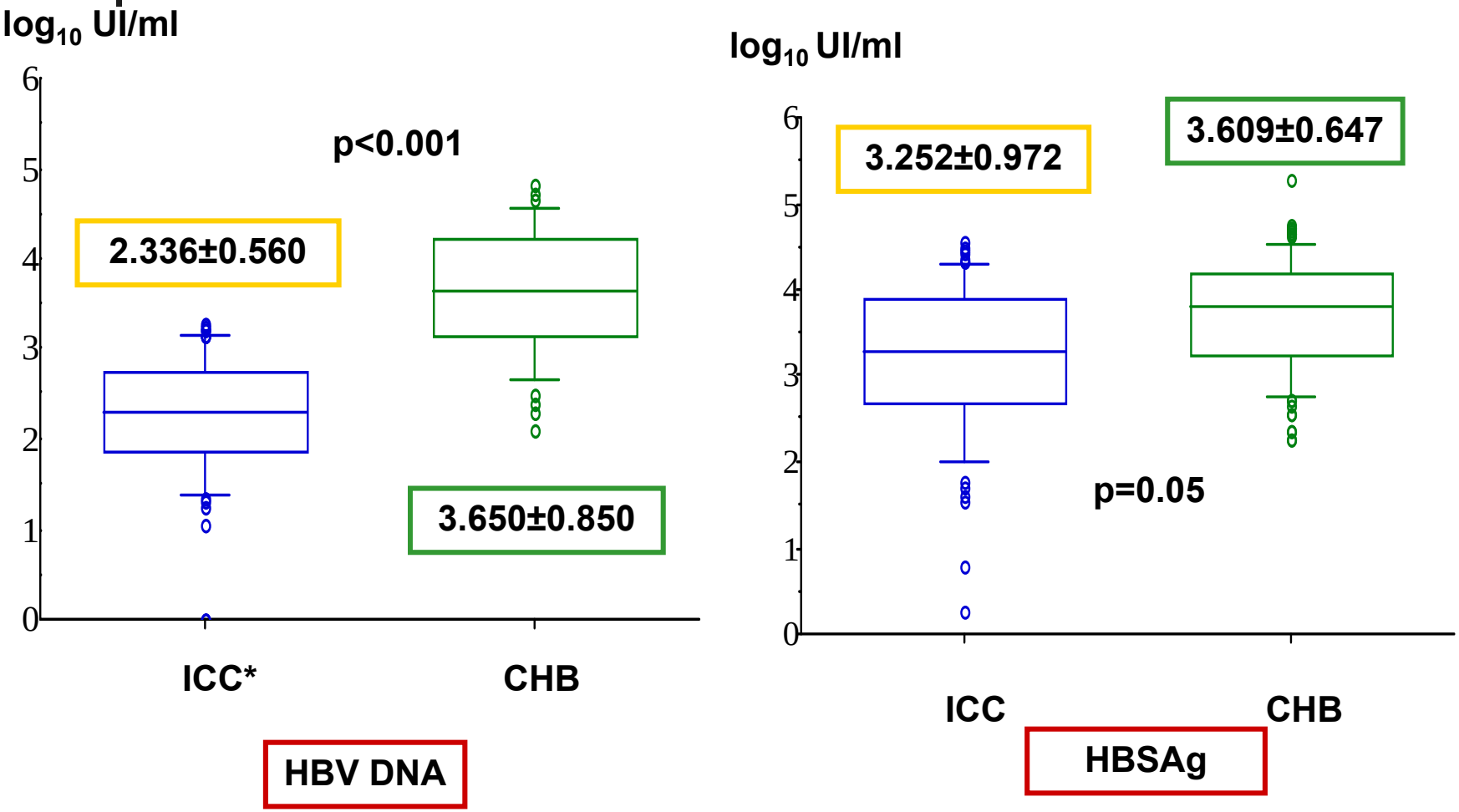
Brunetto et al, Gastroenterology 2010

HBV DNA/HBs Ag ratio



Brunetto et al, Gastroenterology 2010

HBsAg and HBV DNA



* 4 étaient ADN VHB non détectable

Martinot-Peignoux et al. AASLD 2010

Ratio HBV DNA/HBsAg

	ICC	CHB
Ratio DNA/HBsAg	0.696±0.303*	1.043±0.282*
≤ 0.70**	45 (56%)	5 (11%)
Year decrease**	0.115±0.148***	0.096±0.202***

* p<0.01 ** PPV90% ***M±SD log_{10} IU/ml ***p= ns

PPV of cut-offs

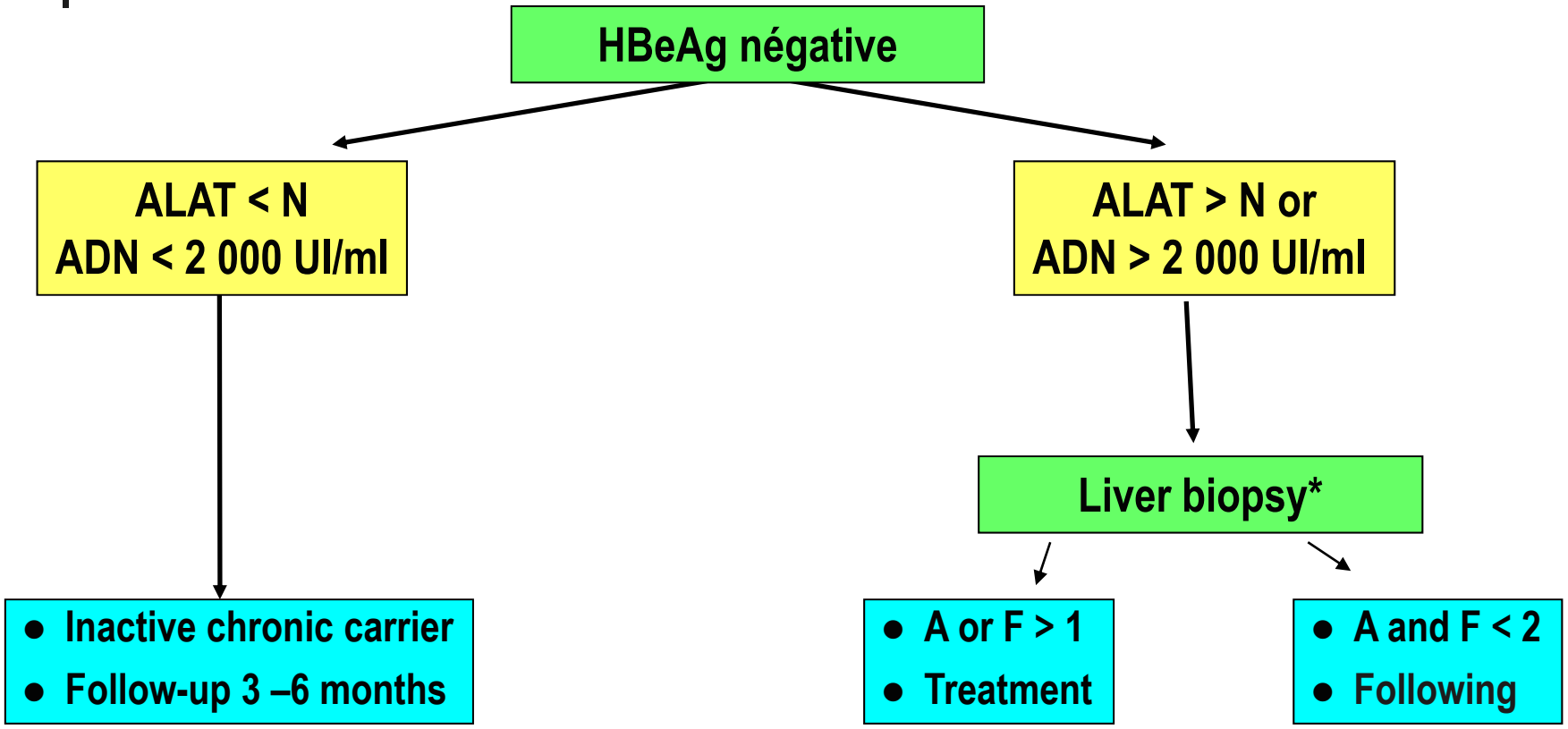
Cut-off	HBsAg	HBV DNA	HBV DNA/HBsAg
< 2000 UI/ml	67 %	87 %	90 %
< 1000 UI/ml	73 %	87 %	93 %

Martinot-Peignoux et al. AASLD 2010

Conclusions

- The barrier between ICC and CHB is sometimes difficult to define
- A long follow-up is mandatory to clearly differentiate these situations
- We can use:
  - ALT levels
  - HBV DNA
  - Blood tests of fibrosis
- And maybe in the future the ratio HBV DNA/HbsAg
- We have to carefully follow-up:patients
  - Men
  - Age, especially after 40 years
  - HBV DNA>2000IU/ml

Algorithm EASL 2009



1 UI = 5 cop/mL

*no if evident cirrhosis