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

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Marseille, France
<table>
<thead>
<tr>
<th>Speaker Name</th>
<th>Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Philippe Halfon</td>
<td>Nothing to declare</td>
</tr>
</tbody>
</table>

**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
- 1,095 anti-HCV positive
- 760 (69%) detectable Viral RNA

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

The HCV Toolbox: Change of paradigm with the DAA

Challenges:
- Genotype
- Subtype
- Cirrhosis
- Prior Tx/IL28B
- Race
- BMI
- HCV RNA

Treatment Duration:
- Nuc: High barrier to resistance
- PI: Modest barrier to resistance (esp to GT1a)
- NS5A: Low barrier to resistance (esp to GT1a)

IFN, RBV, NNI
The HCV Toolbox

Challenges

- Genotype
- Subtype
- Cirrhosis
- Prior Tx/IL28B
- Race
- BMI
- HCV RNA

Treatment Duration

- Nuc
  - High barrier to resistance
- PI
  - Modest barrier to resistance (esp to GT1a)
- NS5A
  - Low barrier to resistance (esp to GT1a)
- NNI

IFN
RBV

The HCV Toolbox: Mix and Match

Challenges
- Genotype
- Subtype
- Cirrhosis

Treatment Duration
- RBV
- Nuc
- PI
- NS5A
- NNI
Liver fibrosis is the common stage of liver damage from several different causes.

Fibrotic Liver Disease

- F0
- F1
- F2
- F3
- F4

Viral: HCV, HBV...
Alcohol
Metabolic
Genetic: HFE, Wilson...
Autoimmune Diseases

Hemorrhage | Liver Failure | Cancer
A progressif mechanism defined by 5 histological stages (METAVIR)

- **F0**: Normal Liver
- **F1**: Periportal Fibrosis
- **F2**: Septal Fibrosis
- **F3**: fibrosis septal with cirrhosis
- **F4**: Cirrhosis

Mild Hepatitis
F0, F1: 20 – 30%
F0, F1, F2: 70%
F3 – F4: 20 – 35%

In patients with viral hepatitis (including HIV/HCV), there are two clinically relevant endpoints:
- detection of significant fibrosis
- detection of cirrhosis. ++++++

F0 – F4: 20 to 35 years if progression
Risk for Liver Cancer even After SVR is Achieved

HCC Incidence Following SVR: by Cirrhosis

Results: HCC Incidence Rates in SVR vs no SVR

- The incidence rate of HCC in patients with SVR is 3.27/1000 PY (0.327% per year).
- The incidence rate of HCC in patients with no SVR was 13.2 per 1000 PY (1.32% per year).
- HR of 0.358 for SVR vs. no SVR.

Note: 0.1 is 10%
Fibrosis is a dynamic process

Reversible Process

Fibrogenèse

Fibrolyse
Progression of liver fibrosis

Poynard T et al, Lancet 1997; 349: 825  n=1157
Dynamique de la Fibrose hépatique
Progression exponentielle

Hypothèse linéaire
Hypothèse non linéaire

Aire de fibrose (%)
The relevance of Liver Biopsy in predicting fibrosis progression
The limits of liver biopsy

Size of liver biopsy at least 25 mm

Fibrosis area %)

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

Bedossa P et al Hepatology 2003; 38: 1449-1457
Regev A, el al. Am J Gastroenterol 2002; 97: 2614-2618
Liver Histology evaluation
Switch: From Invasive vs non-invasive process
Non-invasive tests for evaluation of liver disease severity and prognosis

Blood markers

Liver Stiffness Measurement
Serum BioMarkers of liver injury

Fibrotic Liver Disease

- F0
- F1
- F2
- F3
- F4

Hemorrhage | Liver Failure | Cancer

TIMP 1, PIIIINP

Hyaluronate

PT, Bilirubin, Albumin, Pugh, MELD, Maddrey

Alfa-Foeto Protein
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:

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

Non HCV specific

HBV specific

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

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Etiologies</th>
<th>Year</th>
<th>Patients (n)</th>
<th>F2 (%)</th>
<th>F4 (%)</th>
<th>Cut-offs</th>
<th>AUROC (%)</th>
<th>Se (%)</th>
<th>Sp (%)</th>
<th>CC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FibroTest® [21]</td>
<td>HCV</td>
<td>2001</td>
<td>339</td>
<td>80</td>
<td></td>
<td>&gt;0.48</td>
<td>0.87</td>
<td>75</td>
<td>85</td>
<td>46</td>
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<tr>
<td>Forns Index [22]</td>
<td>HCV</td>
<td>2002</td>
<td>476</td>
<td>26</td>
<td></td>
<td>&lt;4.2 &gt;6.9</td>
<td>0.81</td>
<td>30-94</td>
<td>51-95</td>
<td>45</td>
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<td>APRI [23]</td>
<td>HCV</td>
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<td>270</td>
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<td>0.80</td>
<td>41-91</td>
<td>47-95</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;1.0 &gt;2.0</td>
<td>0.89</td>
<td>57-89</td>
<td>75-93</td>
<td>72</td>
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<tr>
<td>FibroSpectII® [24]</td>
<td>HCV</td>
<td>2004</td>
<td>696</td>
<td>52</td>
<td></td>
<td>&gt;0.36</td>
<td>0.83</td>
<td>77</td>
<td>73</td>
<td>75</td>
</tr>
<tr>
<td>MP3 [25]</td>
<td>HCV</td>
<td>2004</td>
<td>194</td>
<td>45</td>
<td></td>
<td>&lt;0.3 &gt;0.4</td>
<td>0.82</td>
<td>35-65</td>
<td>85-96</td>
<td>n.a.</td>
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<tr>
<td>FPI [26]</td>
<td>HCV</td>
<td>2005</td>
<td>302</td>
<td>48</td>
<td></td>
<td>≤0.2 &gt;0.8</td>
<td>0.77</td>
<td>42-85</td>
<td>48-98</td>
<td>40-49</td>
</tr>
<tr>
<td>Hepascore® [27]</td>
<td>HCV</td>
<td>2005</td>
<td>211</td>
<td>57</td>
<td></td>
<td>≥0.5</td>
<td>0.82</td>
<td>63</td>
<td>89</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;0.84</td>
<td>0.89</td>
<td>71</td>
<td>89</td>
<td>n.a.</td>
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<tr>
<td>Lok index [28]</td>
<td>HCV</td>
<td>2005</td>
<td>1141</td>
<td>38</td>
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<td>0.81</td>
<td>40-98</td>
<td>53-99</td>
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<td>GUCl2 [29]</td>
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<td>2005</td>
<td>179</td>
<td>12</td>
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<td>&gt;0.1</td>
<td>0.85</td>
<td>80</td>
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<td>ViraHep-C [30]</td>
<td>HCV</td>
<td>2006</td>
<td>398</td>
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<td>≤0.22 &gt;0.55</td>
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<td>51-90</td>
<td>54-90</td>
<td>52</td>
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<tr>
<td>Fibroindex [31]</td>
<td>HCV</td>
<td>2007</td>
<td>360</td>
<td>50</td>
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<td>≤1.25 &gt;2.25</td>
<td>0.83</td>
<td>30-40</td>
<td>97-97</td>
<td>35</td>
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<tr>
<td>FIB-4 [32]</td>
<td>HCV</td>
<td>2007</td>
<td>830</td>
<td>17*</td>
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<td>&lt;1.45 &gt;3.25</td>
<td>0.85</td>
<td>38-74</td>
<td>81-98</td>
<td>68</td>
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<td>HAL T-C model [33]</td>
<td>HCV</td>
<td>2008</td>
<td>512</td>
<td>38</td>
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<td>&lt;0.2 &gt;0.5</td>
<td>0.81</td>
<td>47-88</td>
<td>45-92</td>
<td>48</td>
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<tr>
<td>Hui Score [36]</td>
<td>HBV</td>
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<td>235</td>
<td>25</td>
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<td>≤0.15 &gt;0.5</td>
<td>0.79</td>
<td>37-88</td>
<td>50-88</td>
<td>49</td>
</tr>
<tr>
<td>Zeng score [37]</td>
<td>HBV</td>
<td>2005</td>
<td>372</td>
<td>58</td>
<td></td>
<td>&lt;3.0 &gt;8.7</td>
<td>0.77</td>
<td>40-98</td>
<td>28-90</td>
<td>35</td>
</tr>
<tr>
<td>SHASTA [38]</td>
<td>HIV-HCV</td>
<td>2005</td>
<td>95</td>
<td>27</td>
<td></td>
<td>≤0.5 &gt;0.8</td>
<td>0.87</td>
<td>77-88</td>
<td>72-100</td>
<td>42</td>
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<tr>
<td>FIB-4 [39]</td>
<td>HIV-HCV</td>
<td>2006</td>
<td>832</td>
<td>22*</td>
<td></td>
<td>&lt;1.45 &gt;3.25</td>
<td>0.76</td>
<td>70</td>
<td>97</td>
<td>62</td>
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<tr>
<td>ELF® [34]</td>
<td>Mixed</td>
<td>2004</td>
<td>102/496**</td>
<td>40</td>
<td></td>
<td>0.102</td>
<td>0.78</td>
<td>87</td>
<td>51</td>
<td>n.a.</td>
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<tr>
<td></td>
<td></td>
<td>2005</td>
<td>12</td>
<td>n.a.</td>
<td></td>
<td></td>
<td>0.89</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
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<td>Fibrometer® [35]</td>
<td>Mixed</td>
<td>2007</td>
<td>598/503**</td>
<td>56</td>
<td></td>
<td>n.a.</td>
<td>0.89</td>
<td>80</td>
<td>84</td>
<td>82</td>
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<tr>
<td>NFS [40]</td>
<td>NAFLD</td>
<td>2008</td>
<td>733</td>
<td>27*</td>
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<td>&lt;1.455 &gt;0.676</td>
<td>0.82</td>
<td>43-77</td>
<td>97-97</td>
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<td>BARD score [41]</td>
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<td>2008</td>
<td>669</td>
<td>30*</td>
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<td>≥2</td>
<td>0.81</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
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</tbody>
</table>

EASL Clinical guidelines practices
## HIV-HCV patients : Non-invasive tests Diagnostic performances

<table>
<thead>
<tr>
<th>Test</th>
<th>Fibrosis (Metavir)</th>
<th>Cut-off</th>
<th>AUC [95% CI]</th>
<th>PPV</th>
<th>NPV</th>
<th>Référence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FibroTest®</strong></td>
<td>≥ F2</td>
<td>0,49</td>
<td>0,64 [0.58 ;0.70]</td>
<td>83%</td>
<td>35%</td>
<td>{Cacoub, 2008 #12}</td>
</tr>
<tr>
<td></td>
<td>F4</td>
<td>0,75</td>
<td>0,81 [0.76 ;0.85]</td>
<td>32%</td>
<td>97%</td>
<td>{Cacoub, 2008 #12}</td>
</tr>
<tr>
<td><strong>FibroMetre®</strong></td>
<td>≥ F2</td>
<td>0,50</td>
<td>0,70 [0.64 ;0.76]</td>
<td>80%</td>
<td>41%</td>
<td>{Cacoub, 2008 #12}</td>
</tr>
<tr>
<td></td>
<td>F4</td>
<td>-</td>
<td>0,84 [0.78 ;0.88]</td>
<td>-</td>
<td>-</td>
<td>{Cacoub, 2008 #12}</td>
</tr>
<tr>
<td><strong>Hepascore</strong></td>
<td>≥ F2</td>
<td>0,50</td>
<td>0,69 [0.63 ;0.74]</td>
<td>82%</td>
<td>39%</td>
<td>{Cacoub, 2008 #12}</td>
</tr>
<tr>
<td></td>
<td>F4</td>
<td>0,84</td>
<td>0,83 [0.78 ;0.88]</td>
<td>18%</td>
<td>98%</td>
<td>{Cacoub, 2008 #12}</td>
</tr>
<tr>
<td><strong>FibroScan®</strong></td>
<td>≥ F2</td>
<td>4.5 kPa</td>
<td>0.72 [0.60 ;0.84]</td>
<td>64%</td>
<td>63%</td>
<td>{de Ledinghen, 2006 #15}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5,9 kPa</td>
<td>0.85 [0.75 ;0.95]</td>
<td>91%</td>
<td>74%</td>
<td>{Miallhes, 2011 #13}</td>
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<tr>
<td></td>
<td></td>
<td>7,0 kPa</td>
<td>0.93 [0.85-1.00]</td>
<td>70%</td>
<td>81%</td>
<td>{Sanchez-Conde, 2010 #14}</td>
</tr>
<tr>
<td></td>
<td>F4</td>
<td>9,4 kPa</td>
<td>0.96 [0.92 ;1.00]</td>
<td>79%</td>
<td>98%</td>
<td>{Miallhes, 2011 #13}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11,8 kPa</td>
<td>0.97 [0.94 ;1.00]</td>
<td>81%</td>
<td>100%</td>
<td>{de Ledinghen, 2006 #15}.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14,0 kPa</td>
<td>0.99 [0.97 ;1.00]</td>
<td>57%</td>
<td>100%</td>
<td>{Sanchez-Conde, 2010 #14}</td>
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<tr>
<td></td>
<td></td>
<td>14,5 kPa</td>
<td>0.97 [0.94 ;1.00]</td>
<td>88%</td>
<td>96%</td>
<td>{de Ledinghen, 2006 #15}</td>
</tr>
</tbody>
</table>
Measurement of Liver Stiffness

Fibroscan: Transient Elastography
ARFI: Acoustic Radiation Force Impulse Elastography
SWE: Supersonic shear wave imaging
MR elastography
Fibroscan: Transient Elastography

- FibroScan values ranged from 2.4 to 75.4 kilopascals.
- 7.1 kPa for F ≥ 2
- 9.5 kPa for F ≥ 3
- 12.5 kPa for F4

(Castera et al. Gastroenterology 2005; 128: 343-50.)
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

**F0**

**F1**

**F2**

**F3**

**F4**

**Indication for antiviral treatment**

**Screening for Eosophageal varices**

**Screening for Hepatocellular carcinoma**
Cirrhosis Complication

N=711 patients (cirrhosis 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 : Force Impulse Elastography  shear wave imaging  MR elastography
Respective advantages and disadvantages of currently available non-invasive methods in patients with chronic liver diseases

<table>
<thead>
<tr>
<th>Serum biomarkers</th>
<th>Measurement of liver stiffness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td><strong>Transient elastography</strong></td>
</tr>
<tr>
<td>• Good reproducibility</td>
<td>Most widely used and validated technique: standard to be beaten</td>
</tr>
<tr>
<td>• High applicability (95%)</td>
<td>User-friendly (performed at bedside; rapid, easy to learn)</td>
</tr>
<tr>
<td>• No cost and wide availability (non-patented)</td>
<td>High range of values (2-75 kPa)</td>
</tr>
<tr>
<td>• Well validated</td>
<td>Quality criteria well defined</td>
</tr>
<tr>
<td>• Can be performed in the outpatient clinic</td>
<td>Good reproducibility</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td><strong>ARFI (pSWE)</strong></td>
</tr>
<tr>
<td>• Non-specific of the liver</td>
<td>Requires a dedicated device</td>
</tr>
<tr>
<td>• Unable to discriminate between intermediate stages of fibrosis</td>
<td>ROI cannot be chosen</td>
</tr>
<tr>
<td>• Performance not as good as TE for cirrhosis</td>
<td>Unable to discriminate between intermediate stages of fibrosis</td>
</tr>
<tr>
<td>• Cost and limited availability (proprietary)</td>
<td>Applicability (80%) lower than serum biomarker: (obesity, ascites, operator experience)</td>
</tr>
<tr>
<td>• Limitations (hemolysis, Gilbert syndrome, inflammation...)</td>
<td>False positive in case of acute hepatitis, extrahepatic cholestasis, liver congestion, food intake and excessive alcohol intake</td>
</tr>
<tr>
<td></td>
<td>Prognostic value in cirrhosis?</td>
</tr>
</tbody>
</table>
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)
Proposed algorithm for the use of non-invasive tests in treatment naive patients with Hepatitis C with or without HIV coinfection
Recommandations

La maladie hépatique est sévère

<table>
<thead>
<tr>
<th>PBH antérieure F3 ou F4</th>
<th>Traitement à court terme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ou Fibroscan ≥ 9,5 kPa</td>
<td></td>
</tr>
<tr>
<td>Ou FibroTest ≥ 0,59</td>
<td></td>
</tr>
<tr>
<td>Ou FibroMètre ≥ 0,63</td>
<td></td>
</tr>
</tbody>
</table>

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 | La maladie hépatique est sévère |
| ou Fibroscan 5,6 – 9,4 kPa et FibroMètre ≥ 0,63 | Traitement à court terme |

| FibroTest 0,27 – 0,58 et Fibroscan ≥ 9,5 kPa | La maladie hépatique est peu sévère, Surveillance annuelle. Le traitement à court terme n'est pas nécessaire. |
| ou FibroMètre 0,33 – 0,62 et Fibroscan ≥ 9,5 kPa | |

| Fibroscan < 7,1 kPa et Fibrotest < 0,48 | Surveillance à un an et envisager un traitement à moyen terme (2 à 3 ans) |
| ou Fibroscan < 7,1 kPa et FibroMètre < 0,41 | |

Dans les autres cas
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
Trends in Liver Biopsy practice in HCV vs HBV from 2000 -2013

Courtesey Pierre Bedossa
“Back to the future with Australia Antigen”
Liver Histological assessment

Plasma HBsAg: Measurement
- Virions: 42 nm
- Filaments: 22 nm
- Spherical particles: 22 nm

HBV Viral Load

cccDNA Correlation

Treatment Indication

Definition of Response

Monitoring antiviral Therapy

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

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).
HBsAg is a reliable marker
HBs Inactive carrier definition

EASL 2009

- ALT < N
- DNA < 2 000 UI/ml

Survey: 3 – 6 mois

EASL 2012

- AgHBe-
- ALT < N
- DNA < 20 000 UI/ml

Non invasive test <F1

DNA < 2 000
3 – 6 month

2 000 – 20 000
/ 3 month- 3 year

« inactive carriers with high viral load »
Histological lesions risk

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

- DNA VHB < 2000
  - Fibrosis > 1: 1.4%
  - Activity > 1: 0.7%
- 2000 < DNA HBV < 20000
  - Fibrosis > 1: 7%
  - Activity > 1: 10%

N= 142, 73

Papatheodoridis et al, J Hepatol 2012
Inactive Carriers Prognosis

Incidence of HBsAg spontaneous loss

- HBsAg < 100 IU/ml
- HBsAg 100-999 IU/ml
- HBsAg > 1000 IU/ml

Tseng et al, Gastroenterology 2011
Tseng Algorithm from REVEAL cohort

- **Asian HBsAg (-) HBV carriers**
  - **HBV DNA**
    - <2000 IU/mL → **Normal**
    - ≥2000 IU/mL → **Abnormal**
  - **ALT**
    - <2000 IU/mL → **Normal**
    - ≥1000 IU/mL → **Intermediate**
  - **HBsAg**
    - <1000 IU/mL → **Minimal**
    - ≥1000 IU/mL → **High**

**Risk level**
- **High** → ≤3 months or start treatment
- **Intermediate** → 3-6 months
- **Low** → 6-12 months
- **Minimal** → 12 months

**Follow-up interval or management**
HCC risk Prediction

REVEAL Study: n = 3411

Initial HBV DNA /HBsAg

- $10^2$+/1000+
- $10^2$+100-999
- $10^2+$/<100
- $10^2$-<100 / 1000+
- $10^2$-100-999
- $10^4-$ / 100-999
- $10^4$/ 100+
- $10^4$/ 100-999
- $10^4$/ <100

Cumulative incidence of HCC (%) over time:
- HBV DNA <2000 UI/ml
- HBV DNA ≥2000 UI/ml

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…
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 HBcAg-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

- Pegasys 180 µg for 48 weeks
- Analogues for 48 weeks, followed by 96 weeks
- Analogues for 144 weeks

Assessment of HBsAg loss at 30 centers

Add-on of peg interferon to a stable nucleoside regimen

Bourliere M AASLD 2014
Add-on of peg interferon to a stable nucleoside regimen

Loss of HBsAg at W48

<table>
<thead>
<tr>
<th></th>
<th>Analogue</th>
<th>PEG-IFN + analogue</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss HBsAg ITT</td>
<td>1/93 (1 %)</td>
<td>7/90 (8 %)</td>
<td>0,0327</td>
</tr>
<tr>
<td>Loss HBsAg in patients with complete dosage</td>
<td>1/91 (1 %)</td>
<td>7/82 (9 %)</td>
<td>0,0276</td>
</tr>
</tbody>
</table>

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
- 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

- HBV DNA ≤10⁹ copies/mL
- HBeAg <100 PEIU/mL

- ETV 0.5 mg QD (N=200)
  - ~ 9–36 months

  \[\text{Switch to PegIFNα-2a 180 μg/week for 48 weeks (n=100)}\]

  \[\text{ETV 0.5 mg QD for 8 weeks}\]

  \[\text{ETV 0.5 mg QD for 48 weeks (n=100)}\]

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

- **HBV DNA <1000 copies/mL**
  - PegIFN-α2a (n=97): 63.9%
  - ETV (n=100): 90.0%
  - **p<0.0001**

- **HBeAg seroconversion**
  - PegIFN-α2a (n=97): 15.5%
  - ETV (n=100): 6.0%
  - **p=0.0314**

- **HBsAg loss**
  - PegIFN-α2a (n=97): 9.3%
  - ETV (n=100): 0%
  - **p=0.0014**

- **HBsAg seroconversion**
  - PegIFN-α2a (n=97): 4.1%
  - ETV (n=100): 0%
  - **p=0.0569**

* 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)

HBeAg seroconversion and HBsAg loss

<table>
<thead>
<tr>
<th></th>
<th>&lt;1500 IU/mL</th>
<th>≥1500 IU/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg loss</td>
<td>37.5%</td>
<td>6.9%</td>
</tr>
<tr>
<td>HBeAg-positive</td>
<td>16.7%</td>
<td>13.0%</td>
</tr>
</tbody>
</table>

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

p = 0.03

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>48 w</th>
<th>96 w</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA &lt; 2000 UI/ml</td>
<td>6/51</td>
<td>15/52</td>
</tr>
<tr>
<td>HBsAg seroclearance</td>
<td>0/51</td>
<td>3/52</td>
</tr>
<tr>
<td>HBsAg &lt; 10 UI/ml</td>
<td>0/51</td>
<td>5/52</td>
</tr>
</tbody>
</table>

Lampertico P et al. GUT 2012
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:

[Diagram showing time in weeks (12, 24, 48, 96, 72) with fluctuations representing treatment periods]
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.
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.

An 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 HBsAg 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 recommendatons.
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, writes: “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 around 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 insulating 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 attributing 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-Blasco defend the systemic, clairvoyant, and grotesquely irrational system of certifying the works of their father. To their own benefit, and with catastrophic results: thousands of false works, and the subsequent 1958 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”, limply remained silent in the face of the grotesque system of certifying its virgility.

José Ruiz Blasco, 1896. Oil on canvas, atributed to Picasso.

Hepatologists Party Like it’s 1999.

This report contains 250 pages and certifies that Piccsio 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联谊 to the “P” of Pablo, and was unknowingly and deleteriously assumed by Pablo Ruiz Picasso.” As 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 and 1917.

What did Concepción Ruiz Walter, Claude, and Paloma Ruiz Glax know? This circumstance, would not worry us if it were not for the fact that the appraiser was compelled to register the irregularities before the Madrid Court of Instruction of November 10th 2003 and 15th July 2004, and to be the separation of the works of both artists, father and son. This separation is compulsory by law.

As 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 Solana, opens the present system for valuing Picassos as “Authentications by the descendents 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 Daix, Marilyn McCully; Henry Gild, Douglas Cooper, Premises, Catherine Morley, Helmut Gernsheim; and several others.

This report was made by the expert calligraphers Ms. Rosa Torres Boleu and Ms. Silvia Tarrago Goané, from Barcelona, Spain.

Former President Bush indicted for War Crimes

Rómulo-Antonio Tenés, Spain, a researcher and artist, is the author of the book “Lolch Picasso. He takes to Goya’s New Caprices Exhibition for proof in the National Library of Spain, Madrid. He Vanguard, 11.8.81. He achieved the removal of a false painting attributed to Daub de Ragonos from the Prado Museum news flash by HERNET and El Pais. He published a study on Picasso’s plagiarism: the horse in the Guernica, which was paired by Ricardo Marin, Nuevo Mundo in Madrid.