BASL treatment guidelines for hepatitis B and C

Prof Dr Anja Geerts

Secretary BASL

VPHB meeting 7-8 nov 2017
Brussels

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Hepatitis B

- No specific update recommendations from BASL

Colle et al. **Acta Gastroenterologica Belgica 2007**; 70: 389-420

EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection

Pietro Lampertico, Kosh Agarwal, Thomas Berg, Maria Buti, Harry L.A. Janssen, George Papatheodoridis, Fabien Zoulim, Frank Tacke
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Journal of Hepatology
Volume 67, Issue 2, Pages 370-398 (August 2017)
DOI: 10.1016/j.jhep.2017.03.021

Goals of Hepatitis B Treatment

- Prevention of long-term negative clinical outcomes (cirrhosis, HCC, death) by durable suppression of HBV DNA
- Primary treatment endpoint
  - Sustained decrease in serum HBV DNA level to low or undetectable
- Secondary treatment endpoints
  - Decrease or normalize serum ALT
  - Improve liver histology
  - Induce HBeAg loss or seroconversion
  - Induce HBsAg loss or seroconversion

EASL guidelines 2017
Indications for treatment

Chronic hepatitis B, eAg + or –

- HBV DNA > 2000 IU/ml
- ALT: above upper limit of N
- Biopsy: moderate to severe active necroinflammation and/or at least fibrosis

Compensated cirrhosis: treat if HBV detectable, even below 2000 IU/ml

Decompensated cirrhosis: rapid and profound viral suppression is necessary + LTx

EASL Guidelines 2017: Management of chronic HBV.

Current Guideline Recommendations for First-line Therapy

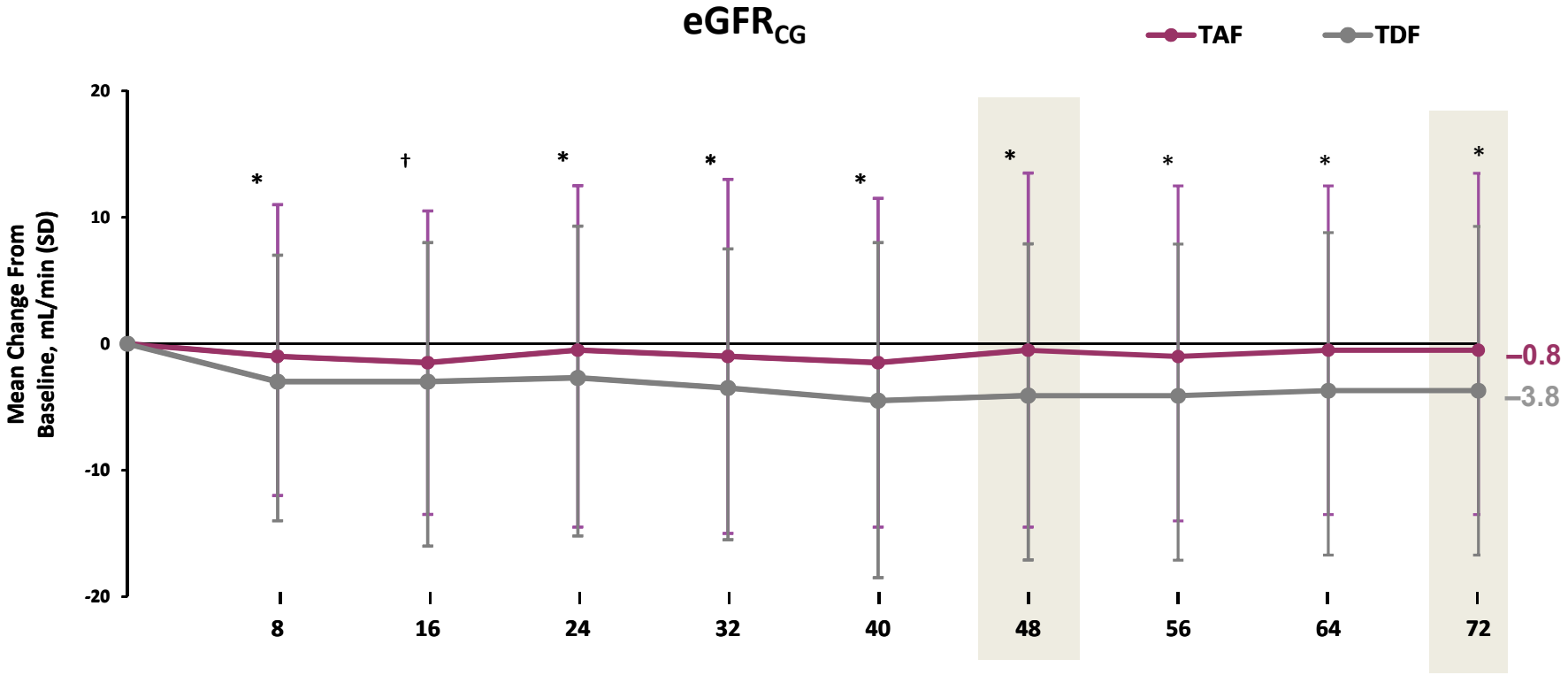
- Entecavir 0.5 mg/ 1mg (Baraclude)
- Tenofovir disoproxil fumarate 300mg (Viread)
- Tenofovir alafenamide 25 mg (Vemlidy, since Nov 1st 2017)

- Pegylated interferon (high serum ALT, HBV genotype A/B, high activity on biopsy)

EASL. J Hepatol. 2009;50:227-242. J Hepatol 2017
Liaw YF, et al. Hepatol Int. 2008;2:263-283.
Lok AS, et al. Hepatology. 2009;50:661-662.

Study 108 and 110: Phase 3 CHB Studies: TAF vs TDF

Renal Laboratory Parameters in CHB Patients Treated with TAF or TDF



TAF treatment had statistically significant less effect on eGFR compared to TDF at 72 weeks

***p<0.001**
†p<0.01

Agarwal, AASLD 2016, Poster 1844

Reimbursement criteria Belgium

Example: Vemlidy® reimbursement

- Treatment of chronic active hepatitis B in
  - Adults
  - Adolescents aged ≥ 12 years

Conditions	Presence of HbsAg for more than 6 months
	With or without HbeAg
	HBV DNA ≥2000 IU/mL
	2 times ALT > ULN
	Liver inflammation and/or fibrosis proven at biopsie (no biopsie required in hemophilia patients or patients treated with anticoagulants)

Riziv Website; http://ondpanon.riziv.fgov.be/SSPWebApplicationPublic/nl/Public/ProductSearch; consulted 2017/11/06

Conclusions
Treatment options hepatitis B

+ availability of drugs with high efficacy and low resistance rate
+ treatment option for adolescents
- Need to change reimbursement criteria for some indications like: cirrhosis with low DNA, solid or hematological transplant (reimbursement only Lamivudine available)
- No updated Belgian recommendations

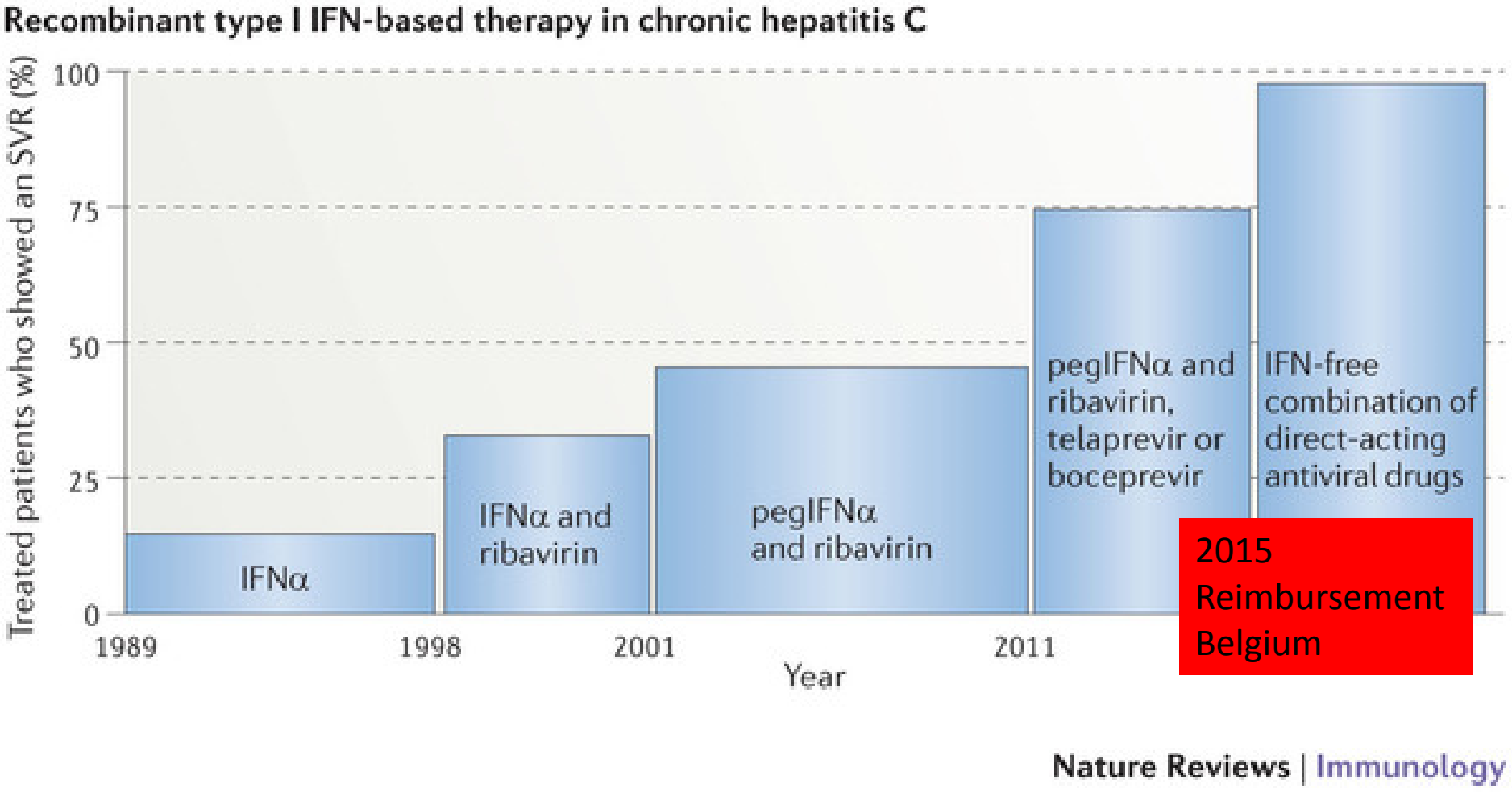
Hepatitis C

- Recommendations from BASL

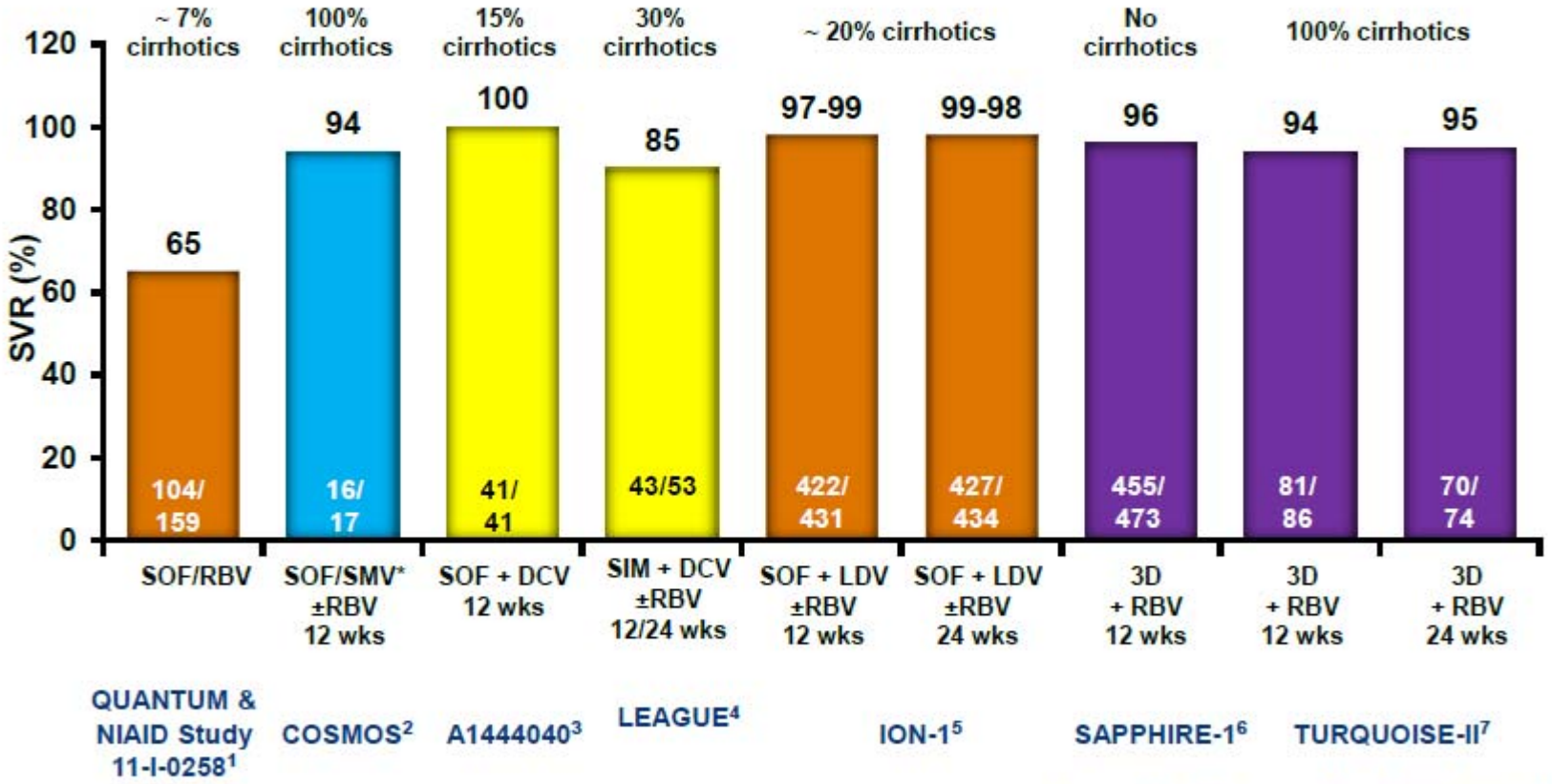
  First version January 1st 2015

  Second version January 1st 2017

Evolution in treatment HCV



IFN free regimens in genotype 1 treatment-naïve patients



Cross comparison of studies cannot be carried out

1. Sofosbuvir EU SmPC 2. Lawitz E, et al. EASL 2014. O165;
3. Sulkowski M, et al. NEJM 2014;370:211–21;
4. Zeuzem S et al. CROI 2014. Oral presentation 28LB
5. Afdhal N, et al. N Engl J Med. 2014; 370: 1889–98
6. Feld JJ, et al. N Engl J Med 2014; 370:1594-1603
7. Poordad F, et al. N Engl J Med 2014; 370:1973–82

Now hepatitis C can be cured with all-oral treatment [4–9]

All-oral treatment achieves **cure rates of >95%**[5–9]

Treatment now takes approximately 2–3 months with **all-oral treatment**[5–9]

No interferon.
No complicated regimens.

4. Man s MP *et al. Nat Rev Drug Discov* 2007;6:991–1**5.** SOVALDI Summary of Product Characteristics, February 2016. **6.** DAKLINZA Summary of Product Characteristics, February 2016. **7.** HARVONI Summary of Product Characteristics, January 2016. **8.** OLYSIO Summary of Product Characteristics, February 2016. **9.** VIEKIRAX Summary of Product Characteristics, February 2016.

HCV treatment options in Belgium

- January 1st 2015 :

  Chronic hepatitis C with F3 and F4 fibrosis stage

  Sofosbuvir and Simeprevir

- From 2015 till 2017 :

  Daclatasvir + Sofosbuvir

  Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir

  Sofosbuvir/Ledipasvir

- From january 1st 2017:

  Chronic hepatitis C from F2 and special populations

  Sofosbuvir/velpatasvir

  Grazoprevir/elbasvir

New HCV reimbursement criteria 01-2017

- Chronic hepatitis C with ≥ F2 fibrosis stage

- Chronic hepatitis C regardless of fibrosis stage if:
  - HIV-HCV coinfection
  - HBV-HCV coinfection
  - Listed for or post-solid organ transplantation
  - Listed for or post hematopoietic stem cell/bone marrow transplantation
  - Severe extrahepatic manifestation: diffuse large cell lymphoma B, immunomediated vasculitis, renal disease related to mixed cryoglobulinemia
  - Patient on dialysis
  - Hemophilia or other coagulation disorder

New HCV reimbursement criteria 01-2017

- Presciption by a Specialist in Gastroenterology or Internal Medicine
  - Attached to an academic centre if 580, 588 or 987
  - Attached to academic **or** non academic hospital if 650, 651 or 659
  - Training in Hepatology (**15 CME/year**)
  - Agrees to record follow-up data of treated patients
- Reimbursement trough e-health platform

METAVIR F2-F3-F4 criteria consensus

(agreed at RIZIV-INAMI 01.12.2016)

EITHER A LIVER BIOPSY, or

EITHER 1 ELASTOGRAPHY TEST (CUT-OFFS SEE NEXT SLIDE)

+ 1 BIOLOGICAL FIBROSIS SCORE (CUT-OFFS SEE NEXT SLIDE)

MAXIMUM AGE OF ELASTOGRAPHY AND LAB VALUES TO BE USED FOR BIOLOGICAL TESTS = 1 YEAR

RESULTS TO BE KEPT IN FILE OF PATIENT (SCORES & LAB VALUES USED FOR TEST)

Fibrosis evaluation

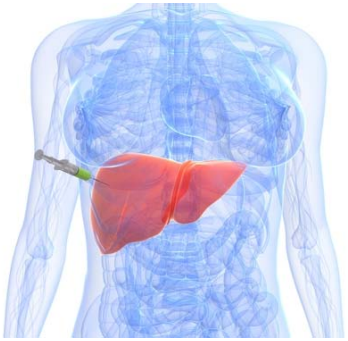
- ***Transient elastography (Fibroscan®)***

  Device designed to measure liver elasticity, which is related to liver fibrosis

- ***Radiological technique***

  Shear Wave Elastography (Philips) or Acoustic Radiation Force Impulse Imaging (Siemens) using ultrasound device

- ***Liver biopsy***



cut-offs of *ELASTOGRAFY for fibrosis assesment F2-F3-F4 chronic hepatitis C*

(agreed at RIZIV-INAMI 01.12.2016)

1. *FIBROSCAN*[1]

Valid if 10 correct measurements, success rate > 60%, IQR < 30%

F2 ≥ 7.1 kPA
F3 ≥ 9.5 kPA
F4 ≥ 12.5 kPA

2. *SHEAR WAVE ELASTOGRAFIE*[2]

F2 ≥ 7.1 kPA
F3 ≥ 8.7 kPA
F4 ≥ 10.4 kPA

3. *ACOUSTIC RADIATION FORSE IMPULSE (ARFI, SIEMENS TECHNIQUE)*[3,4]

F2 ≥ 1.22 m/s
F3 ≥ 1,55 M/S
F4 ≥ 1,80 M/S

[1]Castera et al. Gasteroenterology 2005
[2]Ferraioli et al Hepatology 2012
[3]Friedrich-Rust et al J Viral Hepat 2012
[4]Ferraioli et al J Ultrasound Med 2014

Fibrosis evaluation

- ***Composite serum markers***

FIB-4

$$= \frac{age \times AST}{Platelet\ count \times ALT^{\frac{1}{2}}}$$

APRI

$$= \frac{\frac{AST\ Level\ (\frac{IU}{L})}{AST\ Upper\ Limit\ of\ Normal\ (\frac{IU}{L})}}{Platelet\ counts\ (\frac{10^9}{L})} \times 100$$

FibroTest®

patented algorithm using α2 macroglobulin, haptoglobin, apolipoprotein A1, total bilirubin, GGT

Holmberg *et al*, Clin Infect Dis 2013; 57(2):240-6
Martinez *et al*, Aliment Pharmaco Ther 2011; 33(1):138-48
Poynard *et al*, J. Hepatol 2014; 60(4):706-14
Vallet-Pichard *et al*, Hepatology 2007 ;46(1):32-6
Wai CT *et al*, Hepatology 2003; 38 (2) :518-26

cut-offs of *BIOLOGICAL FIBROSIS-SCORES for assesment F2-F3-F4 in chronic hepatitis C*

(agreed at RIZIV-INAMI 01.12.2016)

1. *FIBROTEST (BIOPREDICTIVE)*:

Elements : α2 macroglobulin, haptoglobin, apolipoprotein A1, total bilirubin, GGT

F2 : ≥ 0.49

F3: 0.59-0.72

F3-F4: 0.73-0.74

F4: ≥0.75

2. *APRI (AST-PLATELET RATIO)*

In a pure HCV cohort

F2: APRI not to use for detection of F2

F3: ≥ 1

F4: ≥ 1.6

Reference: Holmberg, Clin Infect Dis 2013

3. *FIB-4* (age, AST,ALT, platelets)

F2 ≥ 1.45

F3: ≥ 2.1

F3-F4: ≥ 3.25

F4: ≥ 3.85

References: Vallet-Pichard, Hepatology 2007, Holmberg, Clin Infect Dis 2013, Martinez APT 2011

DAA available in Belgium

(8 nov 2017)

- Sofosbuvir/Velpatasvir (Epclusa, Gilead): pangenotypic
- Grazoprevir/elbasvir (Zepatier, MSD): genotype 1a/1b and 4 (+ renal impairment)
- Sofosbuvir/Ledipasvir (Harvoni, Gilead): genotype 1,4,5,6
- Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir (Viekirax + Exviera, Abbvie): genotype 1a/1b (+renal impairment)
- Ombitasvir/paritaprevir/ritonavir (Viekirax, Abbvie) :

  genotype 4 (+ renal impairment)
- Sofosbuvir/Daclatasvir (Sovaldi + Daklinza, Gilead, BMS): genotype 1,2,3,4,5

Conclusions
Treatment options Hepatitis C

- + Availability of several DAA's
- + Free choice in DAA in treatment decision
- - - Restricted reimbursement criteria
- - - No data of treated patients: number of patients treated, response rates, …. Trough ehealth system?
- - - Lack of estimation of number HCV patients in Belgium?

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Treatment options for antiviral therapy in Belgium
Update 01-2017

	Genotype 1a	Genotype 1b
Non-cirrhotic	`Sofosbuvir + Daclatasvir 12 wk Ritonavir-boosted Paritaprevir + Ombitasvir + Dasabuvir + RBV 12 wk Ledipasvir/Sofosbuvir 12 wk* Velpatasvir/Sofosbuvir 12 wk Elbasvir/Grazoprevir 12 wk** *consider 8 wk if naïve and HCVRNA < 6.10^6 IU/mL **consider 16 wk + RBV if HCVRNA>800.000 IU/mL or if baseline NS5a RAs	Sofosbuvir + Simeprevir 12 wk Sofosbuvir + Daclatasvir 12 wk Ritonavir-boosted Paritaprevir + Ombitasvir + Dasabuvir 12 wk ** Ledipasvir/Sofosbuvir 12 wk* Velpatasvir/Sofosbuvir 12 wk Elbasvir/Grazoprevir 12 wk *consider 8 wk if naïve and HCVRNA < 6.10^6 IU/mL **consider 8 wk if naïve
Cirrhotic compensated	Sofosbuvir + Daclatasvir + RBV 12 wk* Ledipasvir/Sofosbuvir + RBV 12 wk* Ritonavir-boosted Paritaprevir + Ombitasvir + Dasabuvir + RBV 24 wk Velpatasvir/Sofosbuvir 12 wk Elbasvir/Grazoprevir 12 wk** *In case of poor RBV tolerance, prolonge to 24 wk without RBV **consider 16 wk + RBV if HCVRNA>800.000 IU/mL or if baseline NS5a RAs	Sofosbuvir + Simeprevir +/- RBV 12 wk* Sofosbuvir + Daclatasvir +/- RBV 12 wk* Ritonavir-boosted Paritaprevir + Ombitasvir + Dasabuvir 12 wk Ledipasvir/Sofosbuvir +/- RBV 12 wk* Velpatasvir/Sofosbuvir 12 wk Elbasvir/Grazoprevir 12 wk *In case of poor RBV tolerance, prolonge to 24 wk without RBV
PI experienced	Sofosbuvir + Daclatasvir + RBV 12 wk Ledipasvir/Sofosbuvir + RBV 12 wk Velpatasvir/Sofosbuvir + RBV 12 wk Consider 24 wk + RBV in F3-F4 patients	Sofosbuvir + Daclatasvir + RBV 12 wk Ledipasvir/Sofosbuvir + RBV 12 wk Velpatasvir/Sofosbuvir + RBV 12 wk Consider 24 wk + RBV in F3-F4 patients
NS5a experienced	Sofosbuvir + Simeprevir +RBV 24 wk* Velpatasvir + Sofosbuvir +RBV 24 wk* *based on few evidence, testing for Ras has to be considered on a case by case discussion	Sofosbuvir + Simeprevir +RBV 24 wk* Velpatasvir + Sofosbuvir +RBV 24 wk* *based on few evidence, testing for Ras has to be considered on a case by case discussion

Treatment options for antiviral therapy in Belgium
Update 01-2017

Cirrhotic decompensated	Sofosbuvir + Daclatasvir + RBV 12 wk* Ledipasvir/Sofosbuvir + RBV 12 wk* Velpatasvir/Sofosbuvir + RBV 12 wk* *In case of poor RBV tolerance, prolonge to 24 wk without RBV consider treating after Tx if MELD > 18	Sofosbuvir + Daclatasvir + RBV 12 wk* Ledipasvir/Sofosbuvir + RBV 12 wk* Velpatasvir/Sofosbuvir + RBV 12 wk* *In case of poor RBV tolerance, prolonge to 24 wk without RBV consider treating after Tx if MELD > 18
Post-organ transplant	Same recommendations than non transplanted patients RBV should be considered in all patients. However, the need for RBV in non-cirrhotic patients has not been established However, potential drug-drug interactions with immunosuppressant agents requires careful selection of agents	Same recommendations than non transplanted patients RBV should be considered in all patients. However, the need for RBV in non-cirrhotic patients has not been established However, potential drug-drug interactions with immunosuppressant agents requires careful selection of agents
HIV-HCV coinfected	Same recommendations than monoinfected HCV patients However, potential drug-drug interactions in patients receiving antiretroviral agents requires careful selection of agents	Same recommendations than monoinfected HCV patients However, potential drug-drug interactions in patients receiving antiretroviral agents requires careful selection of agents

Treatment options for antiviral therapy in Belgium
Update 01-2017

	Genotype 2
Non-cirrhotic	Sofosbuvir + Velpatasvir 12 weeks Sofosbuvir + Daclatasvir 12 weeks If previous failure of Sofosbuvir + Ribavirin: Sofosbuvir + Velpatasvir or Daclatasvir + Ribavirin 12 weeks
Cirrhotic compensated	Sofosbuvir + Velpatasvir 12 weeks Sofosbuvir + Daclatasvir 12 weeks If previous failure of Sofosbuvir + Ribavirin: Sofosbuvir + Velpatasvir or Daclatasvir + Ribavirin 24 weeks
PI experienced	Not applicable
NS5a experienced	Sofosbuvir + Velpatasvir + Ribavirin for 24 weeks *based on few evidence, testing for Ras has to be considered on a case by case discussion. Alternatively, patients without an urgent need for treatment can wait until more data and/or alternative therapeutic options become available

Treatment options for antiviral therapy in Belgium
Update 01-2017

	Genotype 2
Cirrhotic decompensated	Sofosbuvir + Velpatasvir + Ribavirin 12 weeks Sofosbuvir + Daclatasvir + Ribavirin 12 weeks *In case of poor RBV tolerance, prolonge to 24 wk without RBV consider treating after Tx if MELD > 18
Post-organ transplant	Same recommendations than non transplanted patients RBV should be considered in all patients. However, the need for RBV in non-cirrhotic patients has not been established However, potential drug-drug interactions with immunosuppressant agents requires careful selection of agents
HIV-HCV coinfected	Same recommendations than monoinfected HCV patients However, potential drug-drug interactions in patients receiving antiretroviral agents requires careful selection of agents

Treatment options for antiviral therapy in Belgium
Update 01-2017

	Genotype 3
Non-cirrhotic	Sofosbuvir + Daclatasvir 12 wk Velpatasvir/Sofosbuvir 12 wk both for treatment-experienced (IFN) or –naive patients
Cirrhotic compensated	Sofosbuvir + Daclatasvir + RBV 24 wk* ** Velpatasvir/Sofosbuvir 12 wk* + RBV** *treatment naive **treatment experienced (IFN)
PI experienced	Not applicable
NS5A experienced	Velpatasvir/Sofosbuvir + RBV 24 wks *based on few evidence, testing for Ras has to be considered on a case by case discussion. Alternatively, patients without an urgent need for treatment can wait until more data and/or alternative therapeutic options become available

Treatment options for antiviral therapy in Belgium
Update 01-2017

	Genotype 3
Cirrhotic decompensated	Sofosbuvir + Daclatasvir + RBV 24 wk Velpatasvir/Sofosbuvir + RBV 12 wk consider treating after Tx if MELD > 18
Post-organ transplant	Same recommandations than non transplanted patients RBV should be considered in all patients. However, the need for RBV in non-cirrhotic patients has not been established Potential drug-drug interactions with immunosuppressant agents requires careful selection of agents
HIV-HCV coinfected	Same recommandations than monoinfected HCV patients Potential drug-drug interactions in patients receiving antiretroviral agents requires careful selection of agents

Treatment options for antiviral therapy in Belgium
Update 01-2017

	Genotype 4
Non-cirrhotic	Sofosbuvir + Simeprevir 12 wk Sofosbuvir + Daclatasvir 12 wk Ritonavir-boosted Paritaprevir + Ombitasvir + RBV 12 wk Ledipasvir/Sofosbuvir 12 wk Velpatasvir/Sofosbuvir 12 wk Elbasvir/Grazoprevir 12 wk
Cirrhotic compensated	Sofosbuvir + Simeprevir 12 wk Sofosbuvir + Daclatasvir 12 wk Ritonavir-boosted Paritaprevir + Ombitasvir + RBV 12 wk Ledipasvir /Sofosbuvir 12 wk Velpatasvir/Sofosbuvir 12 wk Elbasvir/Grazoprevir 12 wk
PI experienced	Sofosbuvir + Daclatasvir + RBV 12 wk Ledipasvir/Sofosbuvir + RBV 12 wk Velpatasvir/Sofosbuvir + RBV 12 wk Consider 24 wk + RBV in F3-F4 patients
NS5a experienced	Sofosbuvir + Simeprevir +RBV 24 wk* Velpatasvir + Sofosbuvir +RBV 24 wk* *based on few evidence, testing for Ras has to be considered on a case by case discussion. Alternatively, patients without an urgent need for treatment can wait until more data and/or alternative therapeutic options become available

Treatment options for antiviral therapy in Belgium
Update 01-2017

	Genotype 4
Cirrhotic decompensated	Sofosbuvir + Daclatasvir + RBV 12 wk* Ledipasvir/Sofosbuvir + RBV 12 wk* Velpatasvir/Sofosbuvir + RBV 12 wk* *In case of poor RBV tolerance, prolonge to 24 wk without RBV consider treating after Tx if MELD > 18
Post-organ transplant	Same recommendations than non transplanted patients RBV should be considered in all patients. However, the need for RBV in non-cirrhotic patients has not been established However, potential drug-drug interactions with immunosuppressant agents requires careful selection of agents
HIV-HCV coinfected	Same recommendations than monoinfected HCV patients However, potential drug-drug interactions in patients receiving antiretroviral agents requires careful selection of agents

Treatment options for antiviral therapy in Belgium
Update 01-2017

	Genotype 5	Genotype 6
Non-cirrhotic	Sofosbuvir+Velpatasvir 12 weeks Sofosbuvir+Ledipasvir 12 weeks Sofosbuvir+Daclatasvir 12 weeks	Sofosbuvir+Velpatasvir 12 weeks Sofosbuvir+Ledipasvir 12 weeks Sofosbuvir+Daclatasvir 12 weeks
Cirrhotic compensated	Sofosbuvir+Velpatasvir 12 weeks Sofosbuvir+Ledipasvir 12 weeks Sofosbuvir+Daclatasvir 12 weeks	Sofosbuvir+Velpatasvir 12 weeks Sofosbuvir+Ledipasvir 12 weeks Sofosbuvir+Daclatasvir 12 weeks
PI experienced	Sofosbuvir+Velpatasvir 12 weeks Sofosbuvir+Ledipasvir 12 weeks Sofosbuvir+Daclatasvir 12 weeks	Sofosbuvir+Velpatasvir 12 weeks Sofosbuvir+Ledipasvir 12 weeks Sofosbuvir+Daclatasvir 12 weeks
NS5a experienced	Sofosbuvir+Velpatasvir+RBV 24 weeks based on few evidence, testing for Ras has to be considered on a case by case discussion. Alternatively, patients without an urgent need for treatment can wait until more data and/or alternative therapeutic options become available	Sofosbuvir+Velpatasvir+RBV 24 weeks based on few evidence, testing for Ras has to be considered on a case by case discussion. Alternatively, patients without an urgent need for treatment can wait until more data and/or alternative therapeutic options become available

Treatment options for antiviral therapy in Belgium
Update 01-2017

	Genotype 5	Genotype 6
Cirrhotic decompensated	Sofosbuvir+Velpatasvir+RBV* 12 weeks Sofosbuvir+Ledipasvir+RBV* 12 weeks Sofosbuvir+Daclatasvir+RBV*12 weeks *In case of poor RBV tolerance, prolonge to 24 wk without RBV consider treating after Tx if MELD > 18	Sofosbuvir+Velpatasvir+RBV* 12 weeks Sofosbuvir+Ledipasvir+RBV* 12 weeks Sofosbuvir+Daclatasvir+RBV*12 weeks *In case of poor RBV tolerance, prolonge to 24 wk without RBV consider treating after Tx if MELD > 18
Post-organ transplant	Same recommandations than non transplanted patients RBV should be considered in all patients. However, the need for RBV in non-cirrhotic patients has not been established However, potential drug-drug interactions with immunosuppressant agents requires careful selection of agents	Same recommandations than non transplanted patients RBV should be considered in all patients. However, the need for RBV in non-cirrhotic patients has not been established However, potential drug-drug interactions with immunosuppressant agents requires careful selection of agents
HIV-HCV coinfected	Same recommandations than monoinfected HCV patients However, potential drug-drug interactions in patients receiving antiretroviral agents requires careful selection of agents	Same recommandations than monoinfected HCV patients However, potential drug-drug interactions in patients receiving antiretroviral agents requires careful selection of agents