EASL AND AASLD 2014 RECOMMENDATIONS FOR HEPATITIS C

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Advances in Diagnosis and Management of Viral Hepatitis, ESCMID Postgraduate Education Course
6 - 7 March 2015, Tunis, Tunisia

DIFFERENCES BETWEEN EASL AND AASLD RECOMMENDATIONS

- **Date of publications**
  - in April 2014 for EASL (at a time where ledipasvir was no yet available).
  - in December 2014 for AASLD
- **Main differences:**
  - **EASL :** PegIFN/RBV with a DAA (SOF) remained the main option

    Many alternative options
  - **AASLD :** Peg IFN has disapear (except for difficult to treat cases)

    Once daily sofosbuvir/ledipasvir for 12 weeks : main choice for G 1, 4 and 6
- **G1a not similar to G1b :** more difficult to treat

SIMILARITIES BETWEEN EASL AND AASLD RECOMMENDATIONS

- Treatment prioritized to the most severe patients: cirrhosis, severe fibrosis, extra hepatic manifestations
- Sosfosbuvir: pillar of the therapeutic regimen
- Duration of therapy shortened to
  - 12 weeks in most of the cases
  - 24 weeks for genotype 3 and cirrhosis
- Decompensated cirrhosis : immediate treatmenT without peg IFN
- Genotype 2: SOF+ RBV

SIMILARITIES BETWEEN EASL AND AASLD RECOMMENDATIONS

- **Recommendations for Patients Who are Initiating Therapy by HCV Genotype**
- **Rating of recommendations**
  - Strength
  - Level of evidence

EASL RECOMMENDATIONS: LONDON 2014

April 2014

WHO TO TREAT?

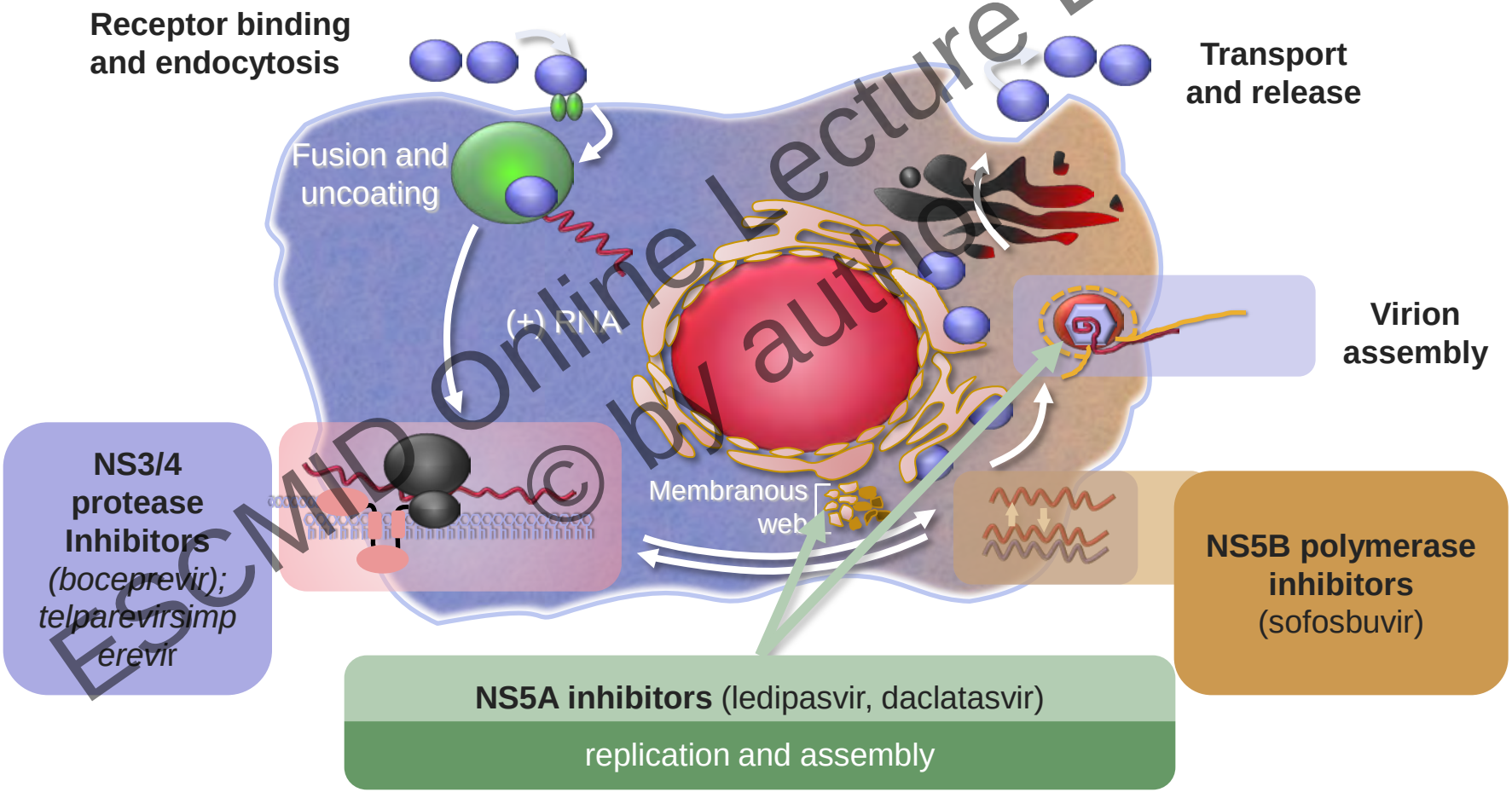
2014 EASL recommendations: who to treat ?

- All treatment-naïve and -experienced patients with compensated disease due to HCV should be considered for therapy **(Recommendation A1)**
- Treatment should be prioritized for patients with significant fibrosis (METAVIR score F3 to F4) **(Recommendation A1)**
- Treatment is justified in patients with moderate fibrosis (METAVIR score F2) **(Recommendation A2)**
- In patients with no or mild disease (METAVIR score F0-F1), the indication for and timing of therapy can be individualized **(Recommendation B1)**
- Patients with decompensated cirrhosis who are on the transplant list should be considered for IFN-free, ideally ribavirin-free therapy **(Recommendation A1)**

EASL CPG. J Hepatol 2014;60:392-420.

HOW TO TREAT?

HCV Life Cycle: Targets for Direct-Acting Antivirals (DAAs)



Adapted from Manns MP, et al. Nat Rev Drug Discov. 2007;6:991–1000.

Abbreviations

- PR : Peg IFN + Ribavirin
- RBV : ribavirin
- SOF : sofosbuvir
- SMV : siméprevir
- DVC : daclatasvir
- LDV : lédipasvir

2014 EASL recommendations: how to treat ?

	Genotype 1#	Genotype 4*	Genotypes 5-6*
Option 1	**SOF+PR** 12 w	**SOF+PR** 12 w	**SOF+PR** 12 w
Option 2	**SMV+PR** 24-48 w	**SMV+PR** 24-48 w	**SOF+RBV** 24 w **(in case of intolerance to IFN)**
Option 3	**DCV+PR** 24 sem **(if G1b)**	**DCV+PR** 24 w	
Option 4	**SOF+RBV** 24 w (in case of intolerance /contraindication to IFN)	**SOF+RBV** 24 w (in case of intolerance /contraindication to IFN)	
Option 5	**SOF+SMV** 12 sem	**SOF+SMV** 12 sem	
Option 6	**SOF+DCV** 12-24 sem	**SOF+DCV** 12-24 sem	

If SOF non available, TPV or BOC acceptable.
* If SOF non available, PEG-IFN+RBV 24 acceptable.

2014 EASL recommendations: how to treat ?

	Genotype 2*	Genotype 3*
Option 1	**SOF+RBV** Naive:12 w NR or cirrhosis: 16-20 w	**SOF+PR** 12 w
Option 2	SOF+PR 12 w (if cirrhosis or NR)	**SOF+RBV** 24 w
Option 3		**SOF+DCV** Nave : 12 w NR : 24 w

* # If SOF non available, PegIFN+RBV for 24 weeks is an option

EASL CPG. J Hepatol 2014;60:392-420.

MONITORING OF TREATMENT EFFICACY

Monitoring of treatment efficacy

- • Real-time PCR-based assay with a lower limit of
- detection of <15 IU/ml

- HCV RNA should be measured :
  - at baseline,
  - week 2 (assessment of adherence),
  - week 4,
  - end of treatment
  - and 12 or 24 weeks after the end of therapy

Post treatment follow-up

- **Non-cirrhotic patients with SVR**
  - should be retested for ALT and HCV RNA at 48 weeks post-treatment,
  - then discharged if ALT is normal and HCV RNA is negative

- **Cirrhotic patients with SVR**
  - should undergo surveillance for HCC every 6 months by means of ultrasound
  - Guidelines for management of portal hypertension and varices should be implemented

- **Monitoring for HCV reinfection**, **following SVR**,
  - through annual HCV RNA assessment should be undertaken on PWID or MSM with on-going risk behaviour

RECOMMENDATIONS FOR TESTING, MANAGING AND TREATING PEOPLE WITH HCV INFECTION

By a panel of HCV experts in the fields of hepatology and infectious diseases

December 2014

Full report

- INTRODUCTION
- METHODS
- HCV TESTING AND LINKAGE TO CARE
- WHEN AND IN WHOM TO INITIATE HCV THERAPY
- INITIAL TREATMENT OF HCV INFECTION
- RETREATMENT OF PERSONS IN WHOM PRIOR THERAPY HAS FAILED
- MONITORING PATIENTS ON TREATMENT, OR HAVING COMPLETED THERAPY
- UNIQUE PATIENT POPULATIONS: HIV/HCV COINFECTION, DECOMPENSATED CIRRHOSIS , RECURRENT HCV INFECTION POST–LIVER TRANSPLANTATION, RENAL IMPAIRMENT
- MANAGEMENT OF ACUTE HCV INFECTION
- REFERENCES

Recommendations for pretreatment assessment

- **An assessment of the degree of hepatic fibrosis, using noninvasive testing or liver biopsy, is recommended** (Rating: I, A)

- ***Recommendation for repeat liver disease assessment***
  - **Ongoing assessment of liver disease is recommended for persons in whom therapy is deferred** (Rating: I, C)

AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

AASLD

IDSA

Infectious Diseases Society of America

When and in Whom to Initiate HCV Therapy ?

In Whom to Initiate HCV Therapy

- **Highest priority patients**
  - settings in Which HCV Treatment is Most Likely to Provide the Most Immediate and Impactful Benefits
- **High Priority patients**
  - Owing to High Risk for Complications
- **Persons At Elevated Risk of HCV Transmission**
  - in whom Treatment May Yield Transmission Reduction Benefits

Highest priority patients :

- **advanced fibrosis (Metavir F3),**
- **compensated and decompensared cirrhosis (Metavir F4),**
- **liver transplant recipients,**
- **patients with severe extrahepatic hepatitis C**

=> Immediate treatment is assigned for these patients

Based on available ressources, immediate treatment should be prioritized as necessary so that patients at high risk for liver-related complications and severe extrahepatic hepatitis C complications are given high priority.

Ratings refer to the strength and level of evidence with regard to benefits of treatment in these settings

High Priority for Treatment Owing to High Risk for Complications

- **Fibrosis (Metavir F2)** (rating: 1B)
- **HIV-1 coinfection** (rating: 1B)
- **HBV coinfection** (rating: IIa, C)
- **Other coexistent liver disease (eg, NASH)** (rating: IIa, C)
- **Debilitating fatigue**(rating: IIa, B)
- **Type 2 Diabetes mellitus (insulin resistant)** (rating: IIa, B)
- **Porphyria cutanea tarda**(rating: IIa, B)
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Persons At Elevated Risk of HCV Transmission and in whom Treatment May Yield Transmission Reduction Benefits

- **Men who have sex with men (MSM) with high-risk sexual practices**
- **Active injection drug users**
- **Incarcerated persons**
- **Persons on long-term hemodialysis**
- **HCV-infected women of child-bearing potential wishing to get pregnant**
- Rating: Class IIa, Level C

Patients at substantial risk of transmitting HCV should be counseled on ways to decrease transmission and minimize the risk of reinfection.

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HOW TO TREAT?

AASLD recommendations: naïve patients

3 options of similar efficay	Genotype 1a	Genotype 1b	Genotype 4
Option 1	**SOF+LDV** 12 w (I, A)	**SOF+LDV** 12 w (I, A)	**SOF+LDV** 12 w (I,I B)
Option 2	**paritaprevir/ritonavir /ombitasvir + dasabuvir + RBV*** 12 w(no cirrhosis) or 24 w (cirrhosis) (I, A)	**paritaprevir/ritonavir /ombitasvir + dasabuvir** 12 w Addition RBV* if cirrhosis) (I, A)	**paritaprevir/ritonavir /ombitasvir + dasabuvir** + RBV* 12 w (I, B)
Option 3	**SOF+SMV** +/- RBV 12 w (no cirrhosis) or 24 w (cirrhosis) (I, A)	**SOF+SMV** 12 w (no cirrhosis) or 24 w (cirrhosis) (I, A)	**SOF+RBV*** 24 w IIa, B)

****weight-based RBV (1000 mg [<75kg] to 1200 mg [≥75 kg])**

Regimens NOT recommended for treatment-naive patients with HCV genotype 1

G1 : Regimens NOT recommended

- **Sofosbuvir + RBV for 24 weeks** (Rating: IIb, A)
- **PEG-IFN + RBV +/- sofosbuvir, simeprevir, telaprevir, or boceprevir for 12 weeks to 48 weeks** (Rating: IIb, A)
- **Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral** (Rating: III, A)

G 4 : Regimens NOT recommended

- **PEG-IFN + RBV with or without simeprevir for 24 weeks to 48 weeks**
- **Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral**
- **Telaprevir- or boceprevir-based regimens**

AASLD recommendations: naïve patients

	Genotype 2	Genotype 3
Option 1	**SOF+RBV*** Naive;12 w (I, A) 16 w if cirrhosis: (IIb, C)	**SOF+ RBV** 24 w (I, B)
Option 2	No alternative regimen	**SOF+PEG+ RBV*** 12 w

* **weight-based RBV (1000 mg [<75kg] to 1200 mg [≥75 kg])

AASLD recommendations, Dec 2014.

Recommended regimen for treatment-naive patients with HCV genotype 3 infection

- ***G2 : the following regimens are NOT recommended:***
  - **PEG-IFN and RBV for 24 weeks**
  - **Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral**
  - **Telaprevir-, boceprevir-, or ledipasvir-containing regimens**

- ***G3 : the following regimens are NOT recommended:***
  - **PEG-IFN + RBV for 24 weeks to 48 weeks**
  - **Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral Telaprevir-, boceprevir-, or simeprevir-based regimens**

AASLD recommendations: naïve patients

	Genotype 5	Genotype 6
Option 1	**SOF+RBV*+PEG** ;12 w	**SOF+ LDV** 12 w (IIa, B)
Option 2	**PEG RBV** 48 w	**SOF+PEG+ RBV*** 12 w (Iia, B)

* ***weight-based RBV (1000 mg [<75kg] to 1200 mg [≥75 kg])

AASLD recommendations, Dec 2014.

Regimens NOT recommended for HCV genotype 5 or 6 infection.

- **Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral** (Rating: III, A)
- **Telaprevir- or boceprevir-based regimens** (Rating: Class III, Level A)

How to treat patients who failed HCV therapy ?

Regimens NOT recommended for genotype 1 infection, after failure of treatment with an HCV protease

- **Any interferon-free regimen containing an HCV protease inhibitor**
  - **Simeprevir**
  - **Paritaprevir** (Rating: IIb, A)
- **Any regimen containing PEG-IFN,**
  - **Including or not including RBV, Simeprevir, Sofosbuvir, Telaprevir or boceprevir** (Rating: IIb, A)
- **Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral** (Rating: III, A)

SPECIFICITIES OF HIV HCV CO INFECTED PATIENTS

HIV/HCV-coinfected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications

Managing interactions with antiretroviral medications

- Complex drug interactions can occur between DAAs and antiretroviral medications is required.

- **For HIV antiretroviral management of these drug** interactions, **expert consultation is recommended.**

- **Antiretroviral drug switches, when needed, should be done in collaboration with the HIV practitioner.**

BACK UP

Goal of treatment of HCV-infected persons

- **to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma,**
- **by the achievement of virologic cure as evidenced by an SVR.**
- **Rating:** Class I, Level A

Factors Associated with Accelerated Fibrosis Progression

Host Viral	Viral
Non-Modifiable Fibrosis stage Inflammation grade Older age at time of infection Male sex Organ transplant **Modifiable** Alcohol consumption Nonalcoholic fatty liver disease Obesity Insulin resistance	Genotype 3 Coinfection with HBV or HIV

Salmon, ESCMID course, 2015, Tunis, EASL and AASLD recommendations