Position Paper of the Italian Association for the Study of the Liver for the rational use of anti-HCV drugs available in Italy

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Updated on June, 20, 2018

Screening for HCV infection

Screening for HCV is required to identify infected individuals and engage them in care and treatment.

Screening for HCV is strongly recommend in **high risk groups** as :

- people who had blood transfusions, blood products transfusions or solid organ trasplant
- injection drug users, including those who may have used drugs once many years ago
- people who had major surgical procedures
- people who had injection with non disposable syringes
- people who had unregulated tatooing or body piercing
- chronic hemodialysis patients
- HIV infected patients
- prisoners o people who live in community
- people who have shared toothbrushes, razors and other personal items with a family member that is HCV-infected
- people who have a risk sex life, particularly men who have sex with men(MSM)
- born from HCV infected mother
- people who had abnormal serum transaminases levels

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Endpoints of HCV therapy

- The primary goal of HCV therapy is to cure the infection achieving the sustained virological response (SVR) which is defined as undetectable HCV-RNA 12 weeks after treatment completion, as assessed by a sensitive molecular method with a lower limit of detection ≤ 15 IU/mL.

- The SVR corresponds to cure the infection with very low chance of relapse. The SVR is associated with improvement or disappearance of necroinflammation and fibrosis, improvement survival and quality of life. Patients with advanced fibrosis or cirrhosis remain at risk of life-treating complications, however hepatic fibrosis may regress and the risk of complication is reduced in patients who cleared HCV compared to untreated patients.

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AIFA Criteria (1)

1. Treatment of patients with Child Pugh A or B class cirrhosis with or without treated HCC without indication for liver transplant and with prognosis related to liver disease.

2. Treatment of recurrent Hepatitis C in liver transplant recipients with clinical stable conditions and optimal immunosuppression.

3. Treatment of patients with chronic hepatitis C with virus-related extra-epatic manifestations (Crioglobulynemia syndrome with organ involvement, B-cell Lynfoproliferative syndromes)

4. Treatment of patients with chronic hepatitis C and advanced fibrosis (Metavir F3 or corresponding Ishak score)

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AIFA Criteria (2)

5. Treatment of patients in waiting list for liver transplant with cirrhosis MELD score < 25 with or without HCC but inside Milan criteria and with an expected time to liver transplantation of at least 2 months.

6. Treatment of solid organ or bone marrow transplanted patients with chronic hepatitis C with stable clinical conditions and optimal immunosuppression.

7. Treatment of patients with chronic hepatitis C and fibrosis METAVIR F2 (or corresponding by Ishak score) with or without comorbidities (HBV or HIV coinfection, chronic hepatitis of other aetiology, diabetes, obesity, hemoglobinopathies or bleeding disorders).

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AIFA Criteria (3)

8. Treatment of patients with chronic hepatitis C and fibrosis METAVIR F0-F1 (or corresponding by Ishak score) with or without comorbidities (HBV or HIV coinfection, chronic hepatitis of other aetiology, diabetes, obesity, hemoglobinopathies or bleeding disorders).

9. Treatment of HCV infected health workers.

10. Treatment of patients with chronic hepatitis C with or without cirrhosis and renal impairment, including haemodialysis patients.

11. Treatment of patients with chronic hepatitis C in waiting list for solid organ (other than liver) or bone marrow transplant.

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Who should be treated?

- All patients with HCV infection who are willing to be treated and who have no controindication must be considered for therapy indipendently of age.

- Treatment is generally not recommended in patients with limited life expectancy because of non –liver-related comorbidities.

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HCV DAA approved in Italy

Genotype	Pangenotypic regimens			Genotype-specific regimens
	SOF/VEL	GLE/PIB	SOF/VEL/VOX*	GZR/EBR
Genotype 1	Yes	Yes	Yes	Yes
Genotiype 2	Yes	Yes	Yes	No
Genotype 3	Yes	Yes	Yes	No
Genotype 4	Yes	Yes	Yes	Yes
Genotype 5	Yes	Yes	Yes	No
Genotype 6	Yes	Yes	Yes	No

*** approved for failure to DAA-regimens patients only**

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HCV Direct antiviral Drugs: general considerations

- All the “green” treatment schedules are recommended by AISF
- Patient’s characteristics, liver disease severity and virological profile should be assessed before treatment regimen’s choice.
- Whenever possible (same efficacy and safety) Ribavirin-free regimens are preferred.
- When more than one treatment schedule with same efficacy and safety are available the treatment choice should be discussed with the patient.

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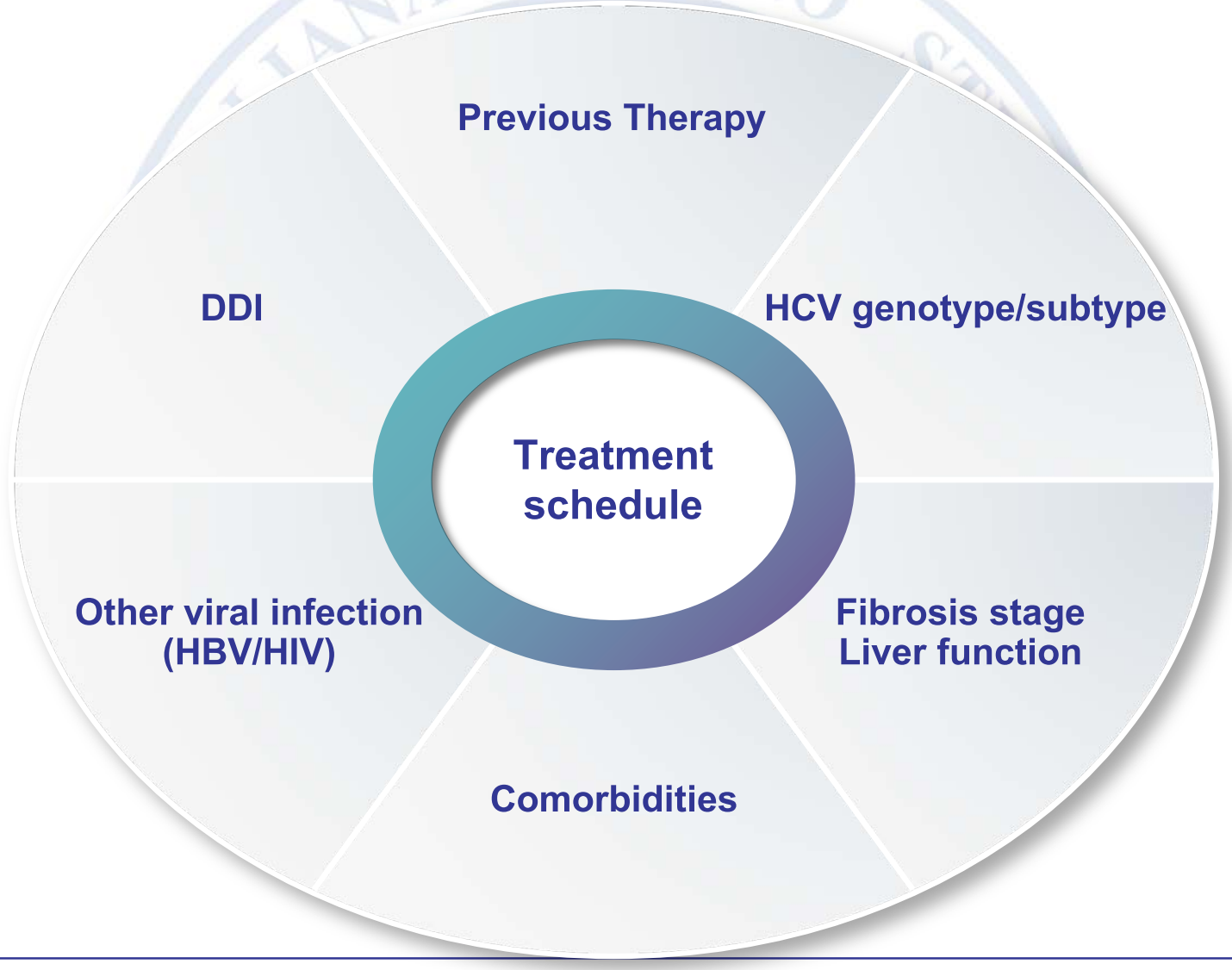
Pre-terapeutic assessment



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Pre-terapeutic assessment: main recommendations (1)

- Protease inhibitors-containing regimens (Glecaprevir, Grazoprevir and Voxilaprevir) are contraindicated in patients with decompensated cirrhosis (Child Pugh B or C class)

- Protease inhibitors-containing regimens (Glecaprevir, Grazoprevir and Voxilaprevir) should be used under strict clinical monitoring in:
  - patients with cirrhosis Child-Pugh A6 class
  - patients with previous liver decompensation
  - old patients or patients with relevant comorbidities

- Sofosbuvir should be used with caution in patients with severe renal impairment (GFR<30 ml/min) and in patients with end-stage renal disease on haemodialysis.

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Pre- therapeutic assessment: main recommendations (2)

- Patients coinfected with HCV and HBV fulfilling the criteria for HBV treatment should receive HBV antiviral therapy according to AISF recommendations.

- In HBsAg positive patients with no indication to HBV antiviral therapy, serum ALT levels and HBV DNA should be tested during and after anti-HCV therapy in order to exclude HBV reactivation. Such patients may receive a nucleos(t)ide analogue prophylaxis at least until week 12 post anti-HCV.

- In HBsAg negative, HBcAb positive, HBsAb postive/negative, HBs Antigen e HBV DNA should be tested in case of ALT elevation with unknown aetiology, particularly in immunosuppressed patients or transplant recipients.

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AIFA Criteria 1 (CPT A5)

Genotype	Pangenotypic regimens		Genotype-specific regimens
	SOF/VEL	GLE/PIB	GZR/EBR
Genotype 1a	12 weeks	12 weeks	12 weeks if HCVRNA <800.000 IU/Ml and no significant RAS in NS5a
Genotype 1b	12 weeks	12 weeks	12 weeks
Genotype 2	12 weeks	12 weeks	No
Genotype 3	12 weeks ±RBV	12-16 weeks	No
Genotype 4	12 weeks	12 weeks	12 weeks if HCV RNA <800.000 IU/Ml
Genotype 5	12 weeks	12 weeks	No
Genotype 6	12 weeks	12 weeks	No

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AIFA Criteria 1 (CPT A6-B9)

Genotype	Pangenotypic regimens		Genotype-specific regimens
	SOF/VEL	GLE/PIB	GZR/EBR
Genotype 1a	12 weeks + RBV	No	No
Genotype 1b	12 weeks + RBV	No	No
Genotype 2	12 weeks + RBV	No	No
Genotype 3	12 weeks + RBV	No	No
Genotype 4	12 weeks + RBV	No	No
Genotype 5	12 weeks + RBV	No	No
Genotype 6	12 weeks + RBV	No	No

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AIFA Criteria 2

Genotype	Pangenotypic regimens	
	SOF/VEL+	GLE/PIB*
Genotype 1a	12 weeks	12 weeks
Genotype 1b	12 weeks	12 weeks
Genotype 2	12 weeks	12 weeks
Genotype 3	12 weeks	12-16 weeks
Genotype 4	12 weeks	12 weeks
Genotype 5	12 weeks	12 weeks
Genotype 6	12 weeks	12 weeks

- This regimen is contraindicated in Child A6 and Child B patients with previous history of ascites or in patients with significant portal hypertension

+ Ribavirin treatment regimen should be use in Child B patients

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AIFA Criteria 5

Genotype	Pangenotypic regimens		Genotype-specific regimens
	SOF/VEL+	GLE/PIB*	GZR/EBR*
Genotype 1a	12 weeks	12 weeks	12 weeks if HCVRNA <800.000 IU/Ml and no significant RAS in NS5a
Genotype 1b	12 weeks	12 weeks	12 weeks
Genotype 2	12 weeks	12 weeks	No
Genotype 3	12 weeks	12-16 weeks	No
Genotype 4	12 weeks	12 weeks	12 weeks if HCV RNA <800.000 IU/Ml
Genotype 5	12 weeks	12 weeks	No
Genotype 6	12 weeks	12 weeks	No

- This regimen is contraindicated in Child A6 and Child B patients with previous history of ascites or in patients with significant portal hypertension

+ Ribavirin treatment regimen should be use in Child B patients

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AIFA Criteria 6

Genotype	Pangenotypic regimens	
	SOF/VEL+	GLE/PIB*
Genotype 1a	12 weeks	12 weeks
Genotype 1b	12 weeks	12 weeks
Genotype 2	12 weeks	12 weeks
Genotype 3	12 weeks	12-16 weeks
Genotype 4	12 weeks	12 weeks
Genotype 5	12 weeks	12 weeks
Genotype 6	12 weeks	12 weeks

- This regimen is contraindicated in Child A6 and Child B patients with previous history of ascites or in patients with significant portal hypertension

+ Ribavirin treatment regimen should be use in Child B patients

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AIFA Criteria 10

Genotype	Pangenotypic regimens		Genotype-specific regimens
	SOF/VEL	GLE/PIB*	GZR/EBR*
Genotype 1a	No	8-12 weeks	12 weeks if HCVRNA <800.000 IU/Ml and no significant RAS in NS5a
Genotype 1b	No	8-12 weeks	12 weeks
Genotype 2	No	8-12 weeks	No
Genotype 3	No	8-12-16 weeks	No
Genotype 4	No	8-12 weeks	12 weeks if HCV RNA <800.000 IU/Ml
Genotype 5	No	8-12 weeks	No
Genotype 6	No	8-12 weeks	No

*Contraindicated in Child B

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AIFA Criteria 11

Genotype	Pangenotypic regimens		Genotype-specific regimens
	SOF/VEL	GLE/PIB	GZR/EBR
Genotype 1a	12 weeks	8-12 weeks	12 weeks if HCVRNA <800.000 IU/MI and no significant RAS in NS5a
Genotype 1b	12 weeks	8-12 weeks	12 weeks
Genotype 2	12 weeks	8-12 weeks	No
Genotype 3	12 weeks	8-12-16 weeks	No
Genotype 4	12 weeks	8-12 weeks	12 weeks if HCV RNA <800.000 IU/MI
Genotype 5	12 weeks	8-12 weeks	No
Genotype 6	12 weeks	8-12 weeks	No

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AIFA Criteria 3,4,7,8,9

Genotype	Pangenotypic regimens		Genotype-specific regimens
	SOF/VEL	GLE/PIB	GZR/EBR
Genotype 1a	12 weeks	8 weeks	12 weeks if HCVRNA <800.000 IU/Ml and no significant RAS in NS5a
Genotype 1b	12 weeks	8 weeks	12 weeks
Genotype 2	12 weeks	8 weeks	No
Genotype 3	12 weeks	8-16 weeks	No
Genotype 4	12 weeks	8 weeks	12 weeks if HCV RNA <800.000 IU/Ml
Genotype 5	12 weeks	8 weeks	No
Genotype 6	12 weeks	8 weeks	No

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Retreatment of patients who failed after a treatment with ≥2 DAA

Genotype	F0-F4:CPT A5	CPT A6-B9
	SOF/VEL/VOX	SOF/VEL
Genotype 1a	12 weeks	24 weeks + RBV
Genotype 1b	12 weeks	24 weeks + RBV
Genotype 2	12 weeks	24 weeks + RBV
Genotype 3	12 weeks	24 weeks + RBV
Genotype 4	12 weeks	24 weeks + RBV
Genotype 5	12 weeks	24 weeks + RBV
Genotype 6	12 weeks	24 weeks + RBV

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Post-treatment follow-up: Patients with advanced fibrosis

- Patients with Metavir F3-F4 or Ishak 4-6 liver fibrosis , or patients with clinical evidence of cirrhosis and/or Fibroscan > 10 KPa at pre-treatment assessment, should be considered advanced fibrotic patients

- Patients with advanced fibrosis who achieve an SVR should be carefully and periodically monitored for clinical assessment in a specialist Center, in cooperation with General Practitioner

- In all patients with cirrhosis and in those with Fibroscan®>20 KPa and / or a platelet value <150,000 elements/mm3 at pre-treatment baseline, it is strongly recommended to perform an esophagogastroduodenoscopy to evaluate the presence of esophageal varices. Treatment and monitoring of varices do not differ from what is suggested for patients with cirrhosis, according to the Baveno VI indications.

- Patients with advanced fibrosis should remain under surveillance for HCC every 6 months by liver ultrasound, with or without alpha-fetoprotein plasma dosage. It is also indicated a monitoring of liver function, through assessment of laboratory tests and clinical evaluation to calculate the Child-Pugh and MELD scores

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Post-treatment follow-up: Patients without fibrosis or with mild or moderate fibrosis

- Patients with no fibrosis or mild-to-moderate fibrosis and without comorbidities at pre-treatment assessment, due to the very low probability of liver disease progression or development of HCC, should be discharged

- Patients with no fibrosis or mild-to-moderate fibrosis and comorbidities (dismetabolic syndrome, obesity, liver steatosis, excessive alcohol intake, autoimmunity, viral coinfections) at pre-treatment assessment, remain at risk of liver disease progression. These patients should be carefully an periodically monitored with non-invasive assessment of liver fibrosis (biochimical tests of liver function, Fibroscan and/or ultrasound)

- Patients with HCV extrahepatic manifestations (such as crioglobulinemia), regardless of the presence of cofactors for liver damage, require periodic assessment

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