

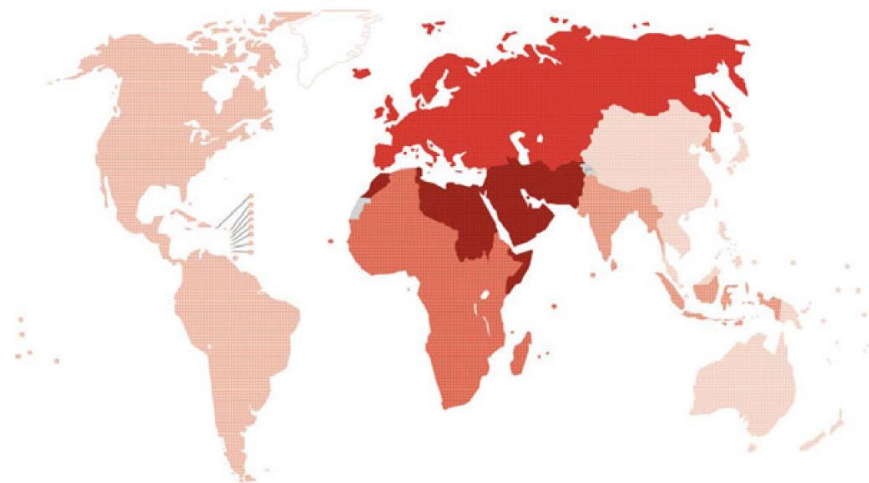
HCV TEDAVİSİ

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9. Hepatoloji Okulu Çeşme izmir 2022



- Estimated global prevalence of HCV in 2015: 1.0% (95% uncertainty interval 0.8–1.1)¹
- Corresponds to **71.1 million** (62.5–79.4) viraemic infections^{1,2}
- ~**399,000** deaths each year, mostly from cirrhosis and HCC²
- GT 1 and 3 are the most common causes of infection (44% and 25%, respectively)¹

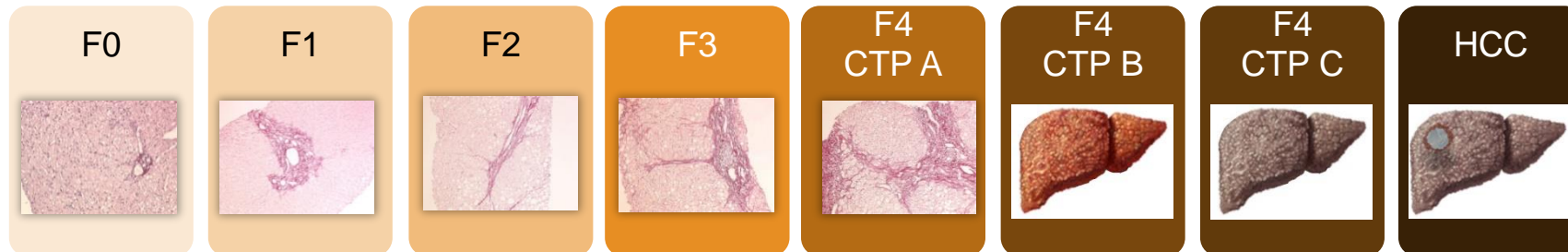
Incidence of HCV infection and new HCV infections in the general population, by WHO region, 2015²



| WHO region | Map key | HCV incidence rate per 100,000: Best estimate (uncertainty level) | New HCV infections (x 1,000): Best estimate (uncertainty level) |
|-----------------------|---------|---|---|
| African | ● | 31.0 (22.5–54.4) | 309 (222–544) |
| Americas | ● | 6.4 (5.9–7.0) | 63 (59–69) |
| Eastern Mediterranean | ● | 62.5 (55.6–65.2) | 409 (363–426) |
| European | ● | 61.8 (50.3–66.0) | 565 (460–603) |
| South-East Asia | ● | 14.8 (12.5–26.9) | 287 (243–524) |
| Western Pacific | ● | 6.0 (5.6–6.6) | 111 (104–124) |
| Global | | 23.7 (21.3–28.7) | 1,751 (1,572–2,120) |



- Long-term natural history of HCV infection is highly variable
- Chronic HCV infection is accompanied by
 - Extrahepatic manifestations reported in up to 75% of patients, including:¹
 - Mixed cryoglobulinaemia vasculitis, renal disease (elevated creatinine), type 2 diabetes, cardiovascular disease (vasculitis, arterial hypertension), porphyria cutanea tarda, lichen planus and lymphoproliferative disorders
 - Non-specific symptoms: fatigue, nausea, abdominal pain, weight loss
 - Rapid development of hepatic fibrosis and accelerated time to cirrhosis²



- Increased risk for liver failure, HCC and liver-related mortality
 - Overall estimated annual risk for liver failure of 2.9%, HCC 3.2% and liver-related death 2.7% in patients with advanced fibrosis^{1,3}



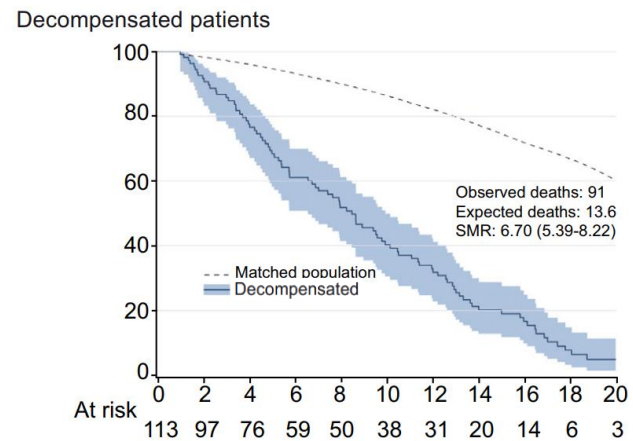
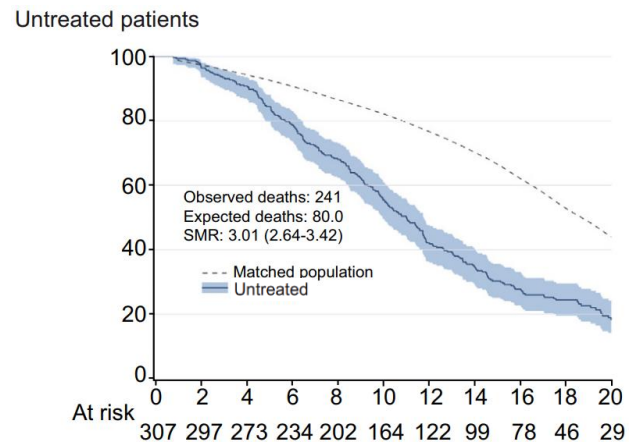
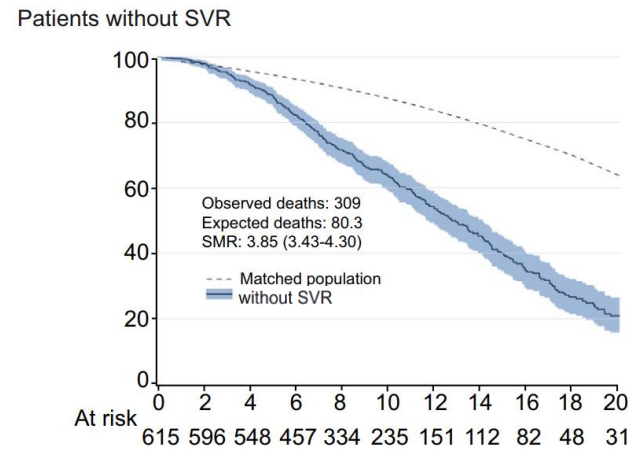
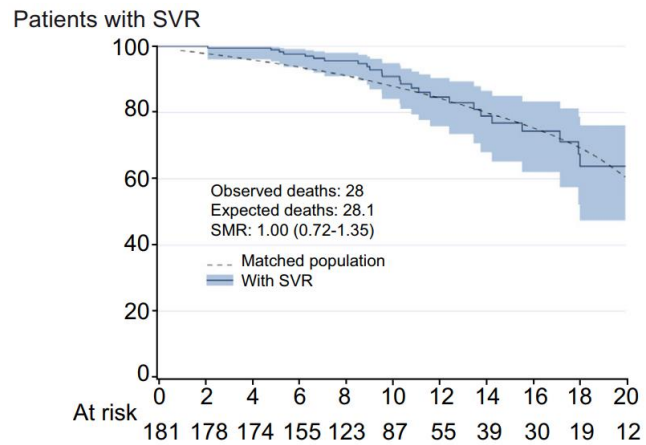
Primary goal of therapy – cure HCV infection (SVR12 or SVR24)

- SVR corresponds to a definitive cure of HCV infection in nearly all cases and is frequently associated with
 - Improvement in extrahepatic manifestations¹
 - Improvement/disappearance of liver necroinflammation and fibrosis¹
 - Regression of advanced hepatic fibrosis (F3) or cirrhosis (F4)²
 - Reduced risk of HCC, hepatic decompensation, non-liver- and liver-related mortality, and liver transplantation^{3–7}
- HCV therapy is one of the interventions necessary to reduce global burden of disease⁸

Overall survival in patients with chronic HCV infection and cirrhosis with and without SVR



Overall survival in patients with chronic HCV infection and cirrhosis compared with an age- and sex-matched general population without infection



Recommendations



1. Goals of therapy
2. Endpoints of therapy
3. Screening for chronic HCV infection
4. Diagnosis of acute and chronic HCV infection
5. Pre-therapeutic assessment
6. Non-invasive assessment of liver disease severity
7. Indications for treatment: who should be treated?
8. Available drugs in Europe in 2018
9. Treatment of patients without cirrhosis or with compensated cirrhosis
 - I. General considerations
 - II. Combination regimens recommended for each genotype
 - III. Treatment recommendations for patients with CHC without cirrhosis
 - IV. Treatment of patients with CHC with compensated cirrhosis



10. Contraindications to therapy
11. Drug–drug interactions
12. Simplified treatment of CHC with pangenotypic drug regimens
13. Retreatment of DAA failure
14. Patients with severe liver disease
15. Treatment of special groups
16. Treatment of acute hepatitis C
17. Post-treatment follow-up
18. Treatment monitoring
19. Measures to improve adherence

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to that section



- **Goal** – to cure HCV infection (**A1**) in order to
 - Prevent the complications of HCV-related liver and extrahepatic diseases, including:
 - Hepatic necroinflammation, fibrosis, cirrhosis, decompensation of cirrhosis, HCC, severe extrahepatic manifestations and death
 - Improve quality of life and remove stigma
 - Prevent onward transmission of HCV



| Recommendations | ■ Grade of evidence | ■ Grade of recommendation |
|---|---------------------|---------------------------|
| <p>Main endpoint</p> <ul style="list-style-type: none"> Undetectable serum or plasma HCV RNA by sensitive assay (LLOD \leq15 IU/mL) 12 weeks (SVR12) or 24 weeks (SVR24) after EOT | A | 1 |
| <p>Alternative endpoint</p> <ul style="list-style-type: none"> Undetectable HCV core antigen in serum or plasma by EIA 24 weeks (SVR24) after EOT <ul style="list-style-type: none"> In patients with detectable HCV core antigen prior to therapy, if HCV RNA assays are not available and/or not affordable | A | 1 |
| <p>Additional endpoint</p> <ul style="list-style-type: none"> Undetectable serum or plasma HCV RNA (SVR24) after EOT by qualitative HCV RNA assay with LLOD \leq1000 IU/mL <ul style="list-style-type: none"> In areas where sensitive assays are not available and/or not affordable | B | 1 |
| <ul style="list-style-type: none"> In patients with advanced fibrosis and cirrhosis, HCC surveillance must be continued: an SVR will reduce, but not abolish, the risk of HCC | A | 1 |

Screening for chronic HCV infection



| Recommendations | Grade of evidence | Grade of recommendation |
|--|-------------------|-------------------------|
| <p>Screening strategies</p> <ul style="list-style-type: none"> • Screening according to local epidemiology and within framework of national plans • May include at-risk populations, birth cohort testing and general population testing in areas of intermediate to high seroprevalence ($\geq 2-5\%$) • Based on detection of serum/plasma anti-HCV Abs using EIA | A | 1 |
| | B | 2 |
| | A | 1 |
| <p>Anti-HCV Ab testing</p> <ul style="list-style-type: none"> • Should be offered with linkage to prevention, care and treatment • Dried blood spots can be used as alternative to serum or plasma* • Use RDTs[†] (as an alternative to classical EIA) at patient's care site to facilitate screening and improve access to care | A | 1 |
| | A | 2 |
| | A | 2 |
| <p>HCV RNA testing</p> <ul style="list-style-type: none"> • If anti-HCV Ab detected, test for serum/plasma HCV RNA (or HCV core antigen)[‡] to identify patients with ongoing infection • Dried blood spots can be used as alternative to serum or plasma* • Reflex testing for HCV RNA in patients who are anti-HCV Ab+ should be applied to increase linkage to care • Anti-HCV Ab screening can be replaced by a point-of-care HCV RNA assay (LLOD: ≤ 1000 IU/mL) or HCV core antigen testing[§] | A | 1 |
| | A | 2 |
| | B | 1 |
| | C | 2 |

*After shipment to a central laboratory where the EIA will be performed; [†]Using serum, plasma, fingerstick whole blood or saliva as matrices;

[‡]If HCV RNA assays are not available and/or not affordable; [§]If available and screening strategy is cost effective

Diagnosis of acute and chronic HCV infection



| Recommendations | ■ Grade of evidence | ■ Grade of recommendation |
|--|---------------------|---------------------------|
| All patients with suspected HCV infection should be tested for anti-HCV Ab in serum or plasma as first-line diagnostic test | A | 1 |
| In cases of suspected acute hepatitis C, in immunocompromised patients and patients on haemodialysis, serum or plasma HCV RNA testing should be part of the initial evaluation | A | 1 |
| If anti-HCV Ab detected, HCV RNA should be determined by a sensitive molecular method (LLOD: ≤ 15 IU/mL) | A | 1 |
| Anti-HCV Ab+, HCV RNA– individuals should be retested for HCV RNA 12 and 24 weeks later to confirm definitive clearance | A | 1 |
| In low- and middle-income countries, and specific high-income country settings, a qualitative HCV RNA assay (LLOD: ≤ 1000 IU/mL) can be used to provide broad affordable access to HCV diagnosis and care | B | 2 |
| Serum or plasma HCV core antigen (a marker of HCV replication) can be used instead of HCV RNA to diagnose acute or chronic HCV infection when HCV RNA assays are not available and/or not affordable | A | 1 |



- Other causes of chronic liver disease, i.e. other blood-borne viruses, particularly HBV and HIV, should be investigated and ruled out

| Recommendations | ■ Grade of evidence | ■ Grade of recommendation |
|--|---------------------|---------------------------|
| Evaluate contribution of comorbidities to progression of liver disease and implement corrective measures | A | 1 |
| Liver disease severity must be assessed prior to therapy | A | 1 |
| Identify patients with cirrhosis (F4): adjust treatment accordingly; mandatory post-treatment surveillance for HCC | A | 1 |
| Post-treatment surveillance for HCC must also be performed in patients with advanced fibrosis (METAVIR score F3) | B | 1 |
| Initially, assess fibrosis stage by non-invasive methods; reserve liver biopsy for when there is uncertainty or potential additional aetiologies | A | 1 |
| Renal function (creatinine/eGFR) should be ascertained | A | 1 |
| Identify extrahepatic manifestations of HCV infection in case of symptoms* | A | 1 |
| HBV and HAV vaccination should be proposed to patients who are not protected | A | 1 |

*Alcoholism, cardiac disease, renal impairment, autoimmunity, genetic or metabolic liver diseases (e.g. genetic haemochromatosis, diabetes mellitus or obesity) and the possibility of drug-induced hepatotoxicity
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Non-invasive assessment of liver disease severity



| Test | Stage of fibrosis | Number of patients | Cut-off(s) | AUROC | Sensitivity | Specificity | PPV | NPV |
|-------------|-------------------|-----------------------|--|----------------------------------|-------------------|------------------|--------|--------|
| FibroScan® | F3 | 560 HCV+ | 10 kPa* | 0.83 | 72% | 80% | 62% | 89% |
| | F4 | 1,855 HCV+ | 13 kPa* | 0.90–0.93 | 72–77% | 85–90% | 42–56% | 95–98% |
| ARFI (VTQ®) | F3 | 2,691 (1,428 HCV+) | 1.60–2.17 m/sec | 0.94 (0.91–0.95)‡ | 84% (80–88%)‡ | 90% (86–92%)‡ | NA | NA |
| | F4 | 2,691 (1,428 HCV+) | 2.19–2.67 m/sec | 0.91 (0.89–0.94)‡ | 86% (80–91%)‡ | 84% (80–88%)‡ | NA | NA |
| Aixplorer® | F3 | 379 HCV+ | 9 kPa* | 0.91 | 90% (72–100%)‡ | 77% (78–92%)‡ | NA | NA |
| | F4 | 379 HCV+ | 13 kPa* | 0.93 | 86% (74–95%)‡ | 88% (72–98%)‡ | NA | NA |
| FibroTest® | F4 | 1,579 (1,295 HCV+) | 0.74 | 0.82–0.87 | 63–71% | 81–84% | 39–40 | 93–94 |
| FIB-4 | F4 | 2,297 HCV+ | 1–45 [†] 3.25 [†] | 0.87 [§] (0.83–0.92) | 90% 55% | 58% 92% | NA | NA |
| APRI | F4 | 16,694 HCV+ | 1.0 [†] 2.0 [†] | 0.84 [§] (0.54–0.97) | 77% 48% | 75% 94% | NA | NA |

*Scales for liver stiffness cut-offs (in kPa) are different between FibroScan® and Aixplorer®;

†Two cut-offs are provided for FIB-4 and for APRI, respectively, with their own sensitivities and specificities;

‡95%CI; §Median (range)

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Indications for treatment: who should be treated?



| Recommendations | Grade of evidence | Grade of recommendation |
|---|-------------------|-------------------------|
| All patients with HCV infection must be considered for therapy, including treatment-naïve and treatment-experienced* patients | A | 1 |
| Patients who should be treated without delay <ul style="list-style-type: none"> • Significant fibrosis or cirrhosis (METAVIR score \geqF2): including compensated (Child–Pugh A) and decompensated (Child–Pugh B or C) cirrhosis • Clinically significant extra-hepatic manifestations[†] • HCV recurrence after liver transplantation • Patients at risk of rapid evolution of liver disease due to concurrent comorbidities[‡] • Individuals at risk of transmitting HCV <ul style="list-style-type: none"> – PWID – MSM with high-risk sexual practices – Women of child-bearing age who wish to get pregnant – Haemodialysis patients – Incarcerated individuals | A | 1 |
| <ul style="list-style-type: none"> • In patients with decompensated cirrhosis and an indication for liver transplantation (MELD score \geq18–20), transplant first and treat after transplantation | B | 1 |
| <ul style="list-style-type: none"> • For waiting time >6 months, treat before transplant (clinical benefit not well established) | B | 2 |
| <ul style="list-style-type: none"> • Treatment is generally not recommended in patients with limited life expectancy due to non-liver-related comorbidities | B | 2 |

*Individuals who failed to achieve SVR after prior treatment; [†]Symptomatic vasculitis associated with HCV-related mixed cryoglobulinaemia, HCV immune complex-related nephropathy and non-Hodgkin B-cell lymphoma; [‡]Non-liver solid organ or stem cell transplant recipients, HBV coinfection, diabetes
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HCV DAAs approved in Europe and recommended in this document



| Product | Presentation | Posology |
|---|--|------------------------|
| Pangenotypic drugs or drug combinations | | |
| Sofosbuvir | Tablets containing: 400 mg SOF | 1 tablet QD |
| Sofosbuvir/velpatasvir | Tablets containing: 400 mg SOF, 100 mg VEL | 1 tablet QD |
| Sofosbuvir/velpatasvir/ voxilaprevir | Tablets containing: 400 mg SOF, 100 mg VEL, 100 mg VOX | 1 tablet QD |
| Glecaprevir/pibrentasvir | Tablets containing: 100 mg GLE, 40 mg PIB | 3 tablets QD |
| Genotype-specific drugs or drug combinations | | |
| Sofosbuvir/ledipasvir | Tablets containing: 400 mg SOF, 90 mg LDV | 1 tablet QD |
| Ombitasvir/ paritaprevir/ritonavir | Tablets containing: 75 mg PTV, 12.5 mg OBV, 50 mg RTV | 2 tablets QD |
| Dasabuvir | Tablets containing: 250 mg DSV | 1 tablet BID (am & pm) |
| Grazoprevir/elbasvir | Tablets containing 100 mg GZR, 50 mg EBR | 1 tablet QD |

Treatment of patients without cirrhosis or with compensated cirrhosis: general considerations



- Because of their virological efficacy, ease of use, safety and tolerability, **IFN-free, ribavirin-free, DAA-based regimens** must be used in HCV-infected patients without cirrhosis or with compensated (Child–Pugh A) cirrhosis, including:
 - **Treatment-naïve (TN) patients**: never been treated for their HCV infection
 - **Treatment-experienced (TE) patients**: previously treated with PEG-IFN α + RBV; PEG-IFN α + RBV + SOF; or SOF + RBV
- The same IFN-free treatment regimens should be used in HIV-coinfected patients as in patients without HIV infection

IFN-free, RBV-free combination regimens recommended for each genotype



| Genotype | Pangenotypic regimens | | | Genotype-specific regimens | | |
|----------|-----------------------|---------|-----------------|----------------------------|---------|--------------------|
| | SOF/VEL | GLE/PIB | SOF/VEL/ VOX | SOF/LDV | GZR/EBR | OBV/PTV/r + DSV |
| 1a | Yes | Yes | No* | Yes† | Yes‡ | No |
| 1b | Yes | Yes | No* | Yes | Yes | Yes |
| 2 | Yes | Yes | No* | No | No | No |
| 3 | Yes§ | Yes | Yes | No | No | No |
| 4 | Yes | Yes | No* | Yes† | Yes¶ | No |
| 5 | Yes | Yes | No* | Yes† | No | No |
| 6 | Yes | Yes | No* | Yes† | No | No |

*Triple combination therapy efficacious but not useful due to the efficacy of double combination regimens;

†TN patients without cirrhosis or with compensated (Child–Pugh A) cirrhosis;

‡TN and TE patients without cirrhosis or with compensated (Child–Pugh A) cirrhosis with HCV RNA $\leq 800,000$ IU/mL (5.9 Log₁₀ IU/mL);

§TN and TE patients without cirrhosis;

||TN and TE patients with compensated (Child–Pugh A) cirrhosis;

¶TN patients without cirrhosis or with compensated (Child–Pugh A) cirrhosis with HCV RNA $\leq 800,000$ IU/mL (5.9 Log₁₀ IU/mL)

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Treatment recommendations for TN or TE patients with CHC without cirrhosis



| GT | | SOF/VEL | GLE/PIB | SOF/VEL/VOX | SOF/LDV | GZR/EBR | OBV/PTV/r + DSV |
|----|----|----------|----------|-------------|------------|----------------------------------|----------------------------------|
| 1a | TN | 12 weeks | 8 weeks | No | 8–12 weeks | 12 weeks (HCV RNA ≤800,00 IU/mL) | No |
| | TE | 12 weeks | 8 weeks | No | No | 12 weeks (HCV RNA ≤800,00 IU/mL) | No |
| 1b | TN | 12 weeks | 8 weeks | No | 8–12 weeks | 8 weeks (F0–F2) 12 weeks (F3) | 8 weeks (F0–F2) 12 weeks (F3) |
| | TE | 12 weeks | 8 weeks | No | 12 weeks | 12 weeks | 12 weeks |
| 2 | TN | 12 weeks | 8 weeks | No | No | No | No |
| | TE | 12 weeks | 8 weeks | No | No | No | No |
| 3 | TN | 12 weeks | 8 weeks | No | No | No | No |
| | TE | 12 weeks | 12 weeks | No | No | No | No |
| 4 | TN | 12 weeks | 8 weeks | No | 12 weeks | 12 weeks (HCV RNA ≤800,00 IU/mL) | No |
| | TE | 12 weeks | 8 weeks | No | No | No | No |
| 5 | TN | 12 weeks | 8 weeks | No | 12 weeks | No | No |
| | TE | 12 weeks | 8 weeks | No | No | No | No |
| 6 | TN | 12 weeks | 8 weeks | No | 12 weeks | No | No |
| | TE | 12 weeks | 8 weeks | No | No | No | No |

Treatment recommendations for TN or TE patients with CHC with compensated (Child–Pugh A) cirrhosis



| GT | | SOF/VEL | GLE/PIB | SOF/VEL/VOX | SOF/LDV | GZR/EBR | OBV/PTV/r + DSV |
|----|----|----------|----------|-------------|----------|----------------------------------|-----------------|
| 1a | TN | 12 weeks | 12 weeks | No | 12 weeks | 12 weeks (HCV RNA ≤800,00 IU/mL) | No |
| | TE | 12 weeks | 12 weeks | No | No | 12 weeks (HCV RNA ≤800,00 IU/mL) | No |
| 1b | TN | 12 weeks | 12 weeks | No | 12 weeks | 12 weeks | 12 weeks |
| | TE | 12 weeks | 12 weeks | No | 12 weeks | 12 weeks | 12 weeks |
| 2 | TN | 12 weeks | 12 weeks | No | No | No | No |
| | TE | 12 weeks | 12 weeks | No | No | No | No |
| 4 | TN | 12 weeks | 12 weeks | No | 12 weeks | 12 weeks (HCV RNA ≤800,00 IU/mL) | No |
| | TE | 12 weeks | 12 weeks | No | No | No | No |
| 5 | TN | 12 weeks | 12 weeks | No | 12 weeks | No | No |
| | TE | 12 weeks | 12 weeks | No | No | No | No |
| 6 | TN | 12 weeks | 12 weeks | No | 12 weeks | No | No |
| | TE | 12 weeks | 12 weeks | No | No | No | No |

For GT 3 recommendations, see next slide

Treatment recommendations for TN or TE patients with CHC with HCV genotype 3 and compensated (Child–Pugh A) cirrhosis



| Patients infected with HCV genotype 3 with compensated cirrhosis | | | | |
|---|--|--|---|--|
| Availability/ performance of HCV NS5A resistance testing | Results of HCV NS5A resistance testing* | SOF/VEL-based regimen | | GLE/PIB-based regimen |
| | | SOF/VEL/VOX available and affordable | SOF/VEL/VOX not available or affordable | GLE/PIB available |
| Not available/ not performed | - | SOF/VEL/VOX for 12 weeks | SOF/VEL + RBV for 12 weeks | GLE/PIB for 12 weeks in TN or 16 weeks in TE patients† |
| Available and performed | Presence of Y93H RAS at baseline | SOF/VEL/VOX for 12 weeks | SOF/VEL + RBV for 12 weeks | GLE/PIB for 12 weeks in TN or 16 weeks in TE patients† |
| | No Y93H RAS at baseline | SOF/VEL for 12 weeks | SOF/VEL for 12 weeks | GLE/PIB for 12 weeks in TN or 16 weeks in TE patients† |

*The presence of the NS5A RAS Y93H at baseline is by population sequencing or >15% by deep sequencing;

†Data with 12 weeks of treatment with GLE/PIB in TE patients with cirrhosis are needed

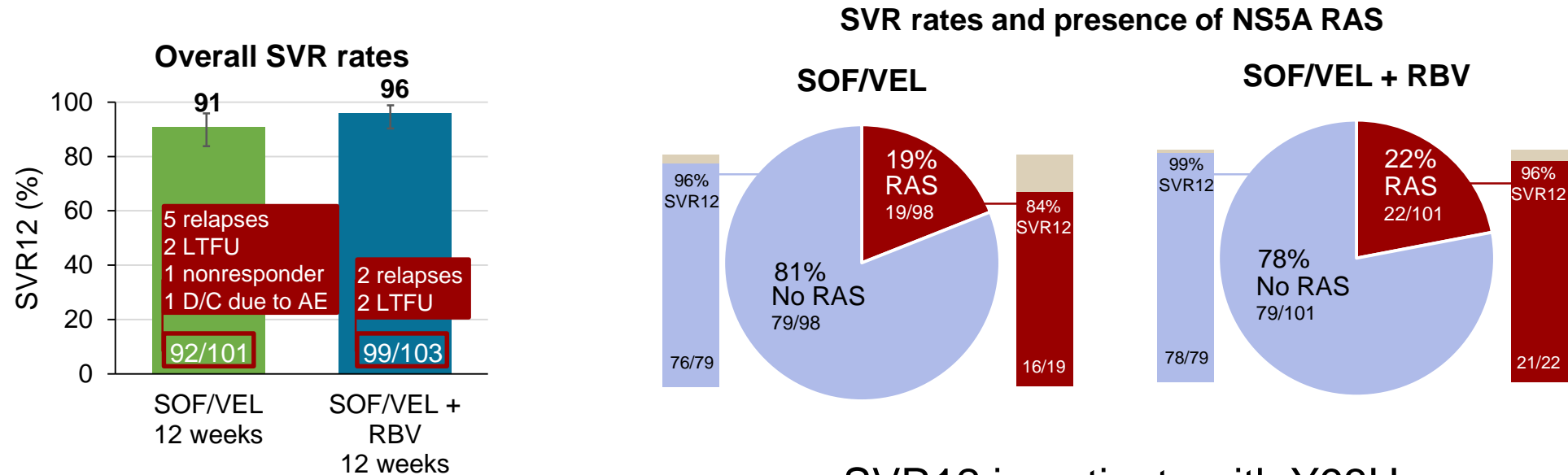
EASL. J Hepatol 2018; doi: 10.1016/j.jhep.2018.11.004;

EASL CPG HCV. J Hepatol 2018;69:461–511.

Sofosbuvir/velpatasvir with and without ribavirin in GT 3 HCV-infected patients with cirrhosis



- 204 patients were randomised to receive SOF/VEL or SOF/VEL + RBV for 12 weeks in an open-label study in GT 3 patients with compensated cirrhosis (TN and TE)



- SVR12 in patients with Y93H
 - SOF/VEL: 50% (2/4)
 - SOF/VEL + RBV: 89% (8/9)

This study was not powered to assess noninferiority of the two treatment arms, and the numeric difference in relapse rate between the two treatment arms does not suggest a clinically meaningful difference in outcome

Contraindications to therapy



- There are few contraindications to treatment with DAAs

| Recommendations | Grade of evidence | Grade of recommendation |
|---|-------------------|-------------------------|
| Certain CYP/P-gp-inducing agents (e.g. carbamazepine, phenytoin) are contraindicated with all regimens; risk of significantly reduced DAA concentrations | A | 1 |
| PIs must not be used in patients with Child–Pugh B or C decompensated cirrhosis or in patients with previous episodes of decompensation | A | 1 |
| In patients with eGFR <30 mL/min/1.73 m² , SOF should only be used if no alternative treatment approved for use in patients with severe renal impairment is available | B | 1 |

Drug–drug interactions



| Recommendations | Grade of evidence | Grade of recommendation |
|--|-------------------|-------------------------|
| <p>Numerous and complex DDIs are possible with HCV DAAs</p> <p>A thorough risk assessment is required in all patients prior to starting DAAs and before starting other medications during treatment*</p> | A | 1 |
| <p>DDIs are a key consideration in treating HIV-HCV coinfecting patients</p> <p>Close attention must be paid to anti-HIV drugs that are contraindicated, not recommended or require dose adjustment with particular DAA regimens</p> | A | 1 |
| <p>Patients should be educated on the importance of:</p> <ul style="list-style-type: none"> • Adherence to therapy • Following dosing recommendations • Reporting the use of: <ul style="list-style-type: none"> – Other prescribed medications – OTC medications – Medications bought via the internet – Use of party or recreational drugs | A | 1 |

- A summary of data on key interactions can be found in **Appendix 1** in this document
- Key internet resource: www.hep-druginteractions.org

*Based on the PI for each DAA
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Simplified treatment of CHC with pangenotypic drug regimens



- Simplified anti-HCV treatment recommendations are now available due to approval of efficacious, well-tolerated pangenotypic anti-HCV regimens (**B1**)

| Recommendations | Grade of evidence | Grade of recommendation |
|---|-------------------|-------------------------|
| Pre-treatment assessment <ul style="list-style-type: none"> Proof of HCV replication (presence of HCV RNA or of HCV core antigen) Assessment of cirrhosis by simple non-invasive markers (e.g. FIB-4 or APRI)* | B | 1 |
| Treatment <ul style="list-style-type: none"> TN and TE patients[†] (without cirrhosis/with compensated cirrhosis) <ul style="list-style-type: none"> Fixed-dose SOF/VEL for 12 weeks Fixed-dose GLE/PIB (8 weeks without cirrhosis;‡ 12 weeks with cirrhosis) Generic drugs can be used, provided quality controls met and guaranteed Check possible DDIs and implement dose modifications when necessary | B B A A | 1 1 1 1 |
| Follow-up <ul style="list-style-type: none"> Checking SVR12 after EOT is dispensable (given high expected SVR12 rates) Test patients with high-risk behaviour/reinfection risk for SVR12 and yearly where possible HCC surveillance (when treatment for HCC is available) in patients with advanced fibrosis (F3) or compensated cirrhosis (F4) | B B A | 1 1 1 |

*Determines whether the patient needs post-treatment follow-up; [†]Without testing genotype;

‡If cirrhosis can be reliably excluded by means of a non-invasive marker in TN patients, fixed-dose combination GLE/PIB can be administered for 8 weeks only (A1)

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Retreatment of DAA failures



- Retreatment strategy depends on initial regimen

| Recommendations | Grade of evidence | Grade of recommendation |
|--|-------------------|-------------------------|
| After failure of PEG-IFN α + RBV, SOF + PEG-IFN α /RBV or SOF + RBV <ul style="list-style-type: none"> Retreat according to recommendations for TE patients, by HCV genotype | A | 1 |
| HCV resistance testing after failure of any DAA-based regimen (excluding regimens with SOF as the only DAA) is a useful guide to retreatment | B | 2 |
| After failure of DAA (PI and/or NS5A inhibitor)-containing regimen <ul style="list-style-type: none"> First-line retreatment <ul style="list-style-type: none"> SOF/VEL/VOX for 12 weeks (without cirrhosis/with compensated cirrhosis) SOF/VEL + RBV* for 24 weeks (decompensated cirrhosis) Patients with predictors of poor response, SOF + GLE/PIB for 12 weeks: <ul style="list-style-type: none"> Advanced liver disease Multiple courses of DAA-based treatment Complex NS5A RAS profile Very difficult-to-cure patients:[†] SOF/VEL/VOX + RBV or SOF + GLE/PIB + RBV for 12 weeks or for 16 or 24 weeks | A B B C | 1 2 2 2 |

*Daily weight-based RBV (1,000 mg or 1,200 mg in patients <75 kg or \geq 75 kg, respectively); start RBV at a dose of 600 mg daily and adjust dose depending on tolerance;

[†]Patients with NS5A RASs who failed twice to achieve SVR after a combination regimen including a PI and/or an NS5A inhibitor

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Patients with severe liver disease (1)



- Due to efficacy, ease of use, safety and tolerability, IFN-free regimens are the only options in patients with decompensated (Child–Pugh B or C) cirrhosis without HCC awaiting liver transplantation (A1)

| Recommendations | ■ Grade of evidence | ■ Grade of recommendation |
|---|---------------------|---------------------------|
| Indications for treatment <ul style="list-style-type: none"> • MELD score <18–20: treat prior to liver transplantation • MELD score ≥18–20: <ul style="list-style-type: none"> – Transplant first without antiviral treatment and treat HCV infection after transplantation – Treat before transplant if waiting time exceeds 6 months (depending on the local situation) | A | 1 |
| | B | 1 |
| | B | 2 |
| Treatment (MELD score <18–20) <ul style="list-style-type: none"> • SOF/LDV (GT 1, 4, 5 and 6) or SOF/VEL (all genotypes) + RBV* for 12 weeks • PI-containing regimens are contraindicated • Contraindications/poor tolerance to RBV: SOF/LDV (GT 1, 4, 5, 6) or SOF/VEL (all genotypes) for 24 weeks | A | 1 |
| | A | 1 |
| | A | 1 |

*Daily weight-based RBV (1,000 mg or 1,200 mg in patients <75 kg or ≥75 kg, respectively); start RBV at a dose of 600 mg daily and adjust dose depending on tolerance
EASL CPG HCV. J Hepatol 2018;69:461–511.

Patients with severe liver disease (2)



| Recommendations | Grade of evidence | Grade of recommendation |
|--|----------------------------|----------------------------|
| <p>Post-liver transplant recurrence</p> <ul style="list-style-type: none"> All patients with post-transplant recurrence should be considered for therapy Treatment should be initiated early after transplantation (≥ 3 months) Treatments include: <ul style="list-style-type: none"> SOF/VEL for 12 weeks (all genotypes) SOF/LDV for 12 weeks (GT 1, 4, 5, 6) GLE/PIB for 12 weeks (eGFR ≤ 30 mL/min/1.73 m²; all genotypes)* SOF/LDV or SOF/LDV + RBV for 24 weeks (decompensated cirrhosis)[†] | A A A A B B | 1 1 1 1 1 1 |
| <p>HCC with an indication for liver transplant</p> <ul style="list-style-type: none"> Liver transplantation must be considered the main therapeutic goal Make treatment decisions on a case by case basis through MDT discussion HCV treatment can be initiated before or delayed until after transplantation, depending on circumstances | A A A | 1 1 1/2 |
| <p>HCC without an indication for liver transplant</p> <ul style="list-style-type: none"> HCV treatment should not be withheld but HCC surveillance should be carried out post-SVR Use the same DAA regimens as for patients with decompensated cirrhosis without HCC awaiting liver transplantation | A | 1 |

*Monitor immunosuppressant drug levels and dose adjust;

[†]Daily weight-based RBV (1,000 mg or 1,200 mg in patients <75 kg or ≥ 75 kg, respectively); start RBV at a dose of 600 mg daily and adjust dose depending on tolerance

EASL CPG HCV. J Hepatol 2018;69:461–511.



- HBV-HCV coinfection
 - Immune-complex mediated manifestations of CHC
 - Patients with renal impairment, including haemodialysis
 - Non-hepatic solid organ transplant recipients
 - Recipients of an HCV+ organ transplant
 - PWID and patients receiving OST
 - Haemoglobinopathies and bleeding disorders
 - Adolescents and children
-
- Details on the management of these special groups can be found in **Appendix 2**

Treatment of acute hepatitis C



- Most patients with acute hepatitis C are asymptomatic
 - Chronicity is expected in 50–90% of cases
- Patients with acute hepatitis C should be considered for antiviral therapy
 - Highly cost-effective compared with deferring treatment until chronicity
 - Ideal time point for starting therapy has not been firmly established

| Recommendations | Grade of evidence | Grade of recommendation |
|---|-------------------|-------------------------|
| <ul style="list-style-type: none"> • Treatment with the same regimens as for CHC for 8 weeks, according to HCV genotype <ul style="list-style-type: none"> – Can treat with: SOF/LDV (GT 1, 4, 5 and 6) or OBV/PTV/r + DSV (GT 1b) – May treat with: SOF/VEL (all genotypes), GLE/PIB (all genotypes), GZR/EBR (GT 1b and 4) pending confirmation in clinical trials | B C | 1 2 |
| <ul style="list-style-type: none"> • SVR12 and SVR24 should be assessed* | B | 2 |
| <ul style="list-style-type: none"> • No indication for antiviral therapy as post-exposure prophylaxis in the absence of documented HCV transmission | B | 1 |



| Recommendations | ■ Grade of evidence | ■ Grade of recommendation |
|---|--|--|
| <p>In patients who achieve SVR</p> <ul style="list-style-type: none"> • Discharge patients with no/moderate fibrosis (F0–F2) and no ongoing risk behaviour or other comorbidities • Monitor for HCC (by US every 6 months) in patients with advanced fibrosis (F3) or cirrhosis (F4) <ul style="list-style-type: none"> – In patients with cirrhosis, perform surveillance for oesophageal varices by endoscopy if varices were present at pre-treatment endoscopy (A1)* • Explain risk of reinfection to positively modify risk behaviour • Bi-annual/annual monitoring in PWID, MSM with ongoing risk behaviour • Make retreatment available if reinfection is identified during post-SVR follow-up | <p>A</p> <p>A</p> <p>B</p> <p>A</p> <p>A</p> | <p>1</p> <p>1</p> <p>1</p> <p>1</p> <p>1</p> |
| <p>Untreated patients or patients with treatment failure</p> <ul style="list-style-type: none"> • Follow untreated patients and those who failed prior treatment at regular intervals • Carry out non-invasive methods for staging fibrosis at intervals of 1 to 2 years • Continue HCC surveillance every 6 months indefinitely in patients with advanced fibrosis and cirrhosis | <p>A</p> <p>A</p> <p>A</p> | <p>1</p> <p>1</p> <p>1</p> |

*Index variceal bleed seldom seen in low-risk patients after SVR (unless additional causes for ongoing liver damage are present and persist)
 EASL CPG HCV. J Hepatol 2018;69:461–511.



| Recommendations | ■ Grade of evidence | ■ Grade of recommendation |
|---|----------------------------------|----------------------------------|
| <p>Monitoring of treatment efficacy</p> <ul style="list-style-type: none"> HCV RNA (serum or plasma): <ul style="list-style-type: none"> Sensitive molecular assay, LLOD ≤ 15 IU/mL Low/middle-income countries: qualitative assay, LLOD $\leq 1,000$ IU/mL* HCV core antigen (serum or plasma) by EIA can be used as an alternative* When treating with IFN-free DAA regimen, monitor at baseline and SVR12/24 Checking SVR12 after EOT is dispensable (given high expected SVR12 rates)† | <p>A B A A B</p> | <p>1 1 1 1 2</p> |
| <p>Monitoring of treatment safety</p> <ul style="list-style-type: none"> Assess for clinical side effects (of DAA regimen) at each visit Assess ALT: baseline, 12/24 weeks post-treatment, or in case of symptoms Monitor for indirect bilirubin increase in patients receiving OBV/PTV/r + DSV Check renal function monthly in patients with reduced eGFR receiving SOF Use of PI-containing regimens is contraindicated with decompensated cirrhosis | <p>A B A A B</p> | <p>1 1 1 1 1</p> |
| <p>Monitoring of DDIs</p> <ul style="list-style-type: none"> Monitor potential DDIs and efficacy/toxicity of drugs given for comorbidities When possible, stop or switch interacting co-medication during HCV treatment | <p>A B</p> | <p>1 1</p> |

*When sensitive molecular HCV RNA assays are not available/affordable to give broad affordable access to diagnosis and care;

†In some parts of the world; exception is patients with high-risk behaviours and risk of reinfection

EASL CPG HCV. J Hepatol 2018;69:461–511.

Measures to improve adherence



| Recommendations | ■ Grade of evidence | ■ Grade of recommendation |
|--|---------------------|---------------------------|
| HCV treatment should be delivered within a MDT setting, with experience in HCV assessment and therapy | A | 1 |
| HCV-infected patients should be counselled on the importance of adherence for attaining an SVR | A | 1 |
| Social support services should be a component of HCV clinical management for patients with socioeconomic disadvantages, migrants | B | 1 |
| Peer-based support and patient activation assessment are recommended to improve HCV clinical management | B | 2 |
| Patients with harmful alcohol consumption should receive additional support during antiviral therapy | B | 1 |

Immune-complex mediated manifestations of CHC



| Recommendations | ■ Grade of evidence | ■ Grade of recommendation |
|---|---------------------|---------------------------|
| Mixed cryoglobulinaemia and renal disease associated with CHC must be treated with IFN-free, RBV-free DAA-based anti-HCV combinations, according to the above recommendations | B | 1 |
| Careful monitoring for adverse events is mandatory | B | 1 |
| The indication for RTX in HCV-related renal disease must be discussed by a MDT | B | 1 |
| HCV-associated lymphoma should be treated with IFN-free, RBV-free DAA regimens according to the above recommendations, in combination with specific chemotherapy, taking into account possible DDIs | B | 1 |

Patients with renal impairment, including haemodialysis



| Recommendations | Grade of evidence | Grade of recommendation |
|---|-----------------------|-------------------------|
| <p>Mild to moderate renal impairment (eGFR \geq30 mL/min/1.73 m²)</p> <ul style="list-style-type: none"> • Treat according to the general recommendations • No dose adjustments are needed • Patients should be carefully monitored | A | 1 |
| <p>Severe renal impairment (eGFR $<$30 mL/min/1.73 m² or ESRD*)</p> <ul style="list-style-type: none"> • Treat in expert centres with close monitoring by a MDT • GLE/PIB for 8 or 12 weeks (all GT) • GZR/EBR for 12 weeks (GT 1a, 1b and 4)[†] • OBV/PTV/r + DSV for 12 weeks (GT 1b) • Use SOF with caution, only if an alternative treatment is not available | B A A A B | 1 1 1 1 1 |
| <ul style="list-style-type: none"> • Risk/benefit of treating patients with ESRD and an indication for kidney transplant before or after renal transplantation require individual assessment | B | 1 |

*ESRD on haemodialysis (CKD stage 4/5) without an indication for liver transplant; [†]With HCV RNA level \leq 800,000 IU/mL (GT 1a/4)
EASL CPG HCV. J Hepatol 2018;69:461–511.

Non-hepatic solid organ transplant recipients*



| Recommendations | Grade of evidence | Grade of recommendation |
|--|-------------------|-------------------------|
| Treat HCV infection before or after transplantation, provided that life expectancy exceeds 1 year | A | 1 |
| Before transplantation, while on waiting list, patients can receive HCV treatment according to general recommendations for GT, liver disease severity and prior anti-HCV treatment | A | 1 |
| After transplantation, <ul style="list-style-type: none">Treat with fixed-dose SOF/LDV (GT 1, 4, 5 and 6) or SOF/VEL (all GT) according to the general recommendations[†]Treat patients with an eGFR <30 mL/min/1.73 m² with GLE/PIB for 12 weeks[‡] | A B | 1 1 |

*Including kidney, heart, lung, pancreas or small bowel recipients;

[†]Without the need for immunosuppressant drug dose adjustments;

[‡]Immunosuppressant drug levels need to be monitored and adjusted as needed during and after EOT

EASL CPG HCV. J Hepatol 2018;69:461–511.

Recipients of an HCV+ organ transplant



| Recommendations | ■ Grade of evidence | ■ Grade of recommendation |
|---|---------------------|---------------------------|
| Organs from anti-HCV Ab+, HCV RNA+ donors can be transplanted to HCV RNA+ recipients | B | 1 |
| Use of anti-HCV Ab+, HCV RNA+ organs for HCV RNA– recipients is possible , provided that: <ul style="list-style-type: none">• It is allowed by local regulations• Rigorous informed consent is obtained• Rapid post-transplant DAA therapy is guaranteed | C | 2 |
| Use of liver grafts with moderate (F2) or advanced (F3) fibrosis is not recommended | B | 2 |

PWID and patients receiving OST



| Recommendations | Grade of evidence | Grade of recommendation |
|---|-------------------|-------------------------|
| Test routinely and voluntarily for anti-HCV Abs and HCV RNA; test HCV RNA annually and following any high-risk injecting episode | A | 1 |
| Provide appropriate access to OST and clean drug injecting equipment as part of widespread comprehensive harm reduction programs, including in prisons | A | 1 |
| All HCV-infected PWIDs have an indication for antiviral therapy ; DAA-based therapies are safe and effective in HCV-infected patients receiving OST, those with a history of IDU and those who recently injected drugs | A | 1 |
| HCV treatment should be offered to HCV-infected patients in prison | B | 1 |
| Pre-therapeutic education: include discussions of HCV transmission, risk factors for fibrosis progression, treatment, reinfection risk, and harm reduction strategies | B | 1 |
| In patients on OST, DAA-based anti-HCV therapy does not require methadone or buprenorphine dose adjustment | A | 1 |
| Provide harm reduction, education and counselling to prevent HCV reinfection following successful treatment | B | 1 |
| Monitor after SVR in PWID with an ongoing risk behaviour* | A | 1 |
| Retreat if reinfection identified during post-SVR follow-up | A | 1 |

*Ideally bi-annual or at least annual HCV RNA assessment
EASL CPG HCV. J Hepatol 2018;69:461–511.

Haemoglobinopathies and bleeding disorders



Recommendations

■ Grade of evidence

■ Grade of recommendation

Indications for HCV therapy are the same in patients with and without haemoglobinopathies or bleeding disorders

A

1

The same IFN-free, RBV-free anti-HCV DAA regimens can be used in patients with and without haemoglobinopathies or bleeding disorders

B

1



Recommendations

■ Grade of evidence

■ Grade of recommendation

Adolescents aged ≥ 12 years

- TN or TE, without cirrhosis or with compensated cirrhosis
- GT 1, 4, 5 or 6: fixed-dose **SOF/LDV for 12 weeks**
- GT 2 or 3: other regimens approved for adults, with caution pending more safety data in this population

B

1

C

2

Children < 12 years

Defer treatment until DAAs, including pangenotypic regimens, are approved for this age group

B

1



Erişkin hastada hcv .tedavisi

■ Grade of evidence

■ Grade of recommendation

Non sirotik hastada

Glik +Bip 8 hafta veya

SOF+Velp+Vox 8 hafta

Kompanse sirozlu (ctp A)

Glik+bip 8 hafta

SOF+Velp+Vox 12 hafta

Dekompanze (CTP B C)

Genotip 1a 1b, 4,5,6) SOF+LED+RIB 12 hafta

Tedavi deneyimli kr HCV li hastada tedavi

Daha önce NS5A olan ilaçlar haricinde bir ilaçla tedavi olanda

Glik+bip ile 8 hafta veya

SOF+VEL+VOX ile 12 hafta

Daha önce NS5A olan ilaçlar haricinde bir ilaçla tedavi alan kompanse siroz olanda

Glik+Bip 12 hafta

SOF +VELP+VOX 12 hafta

Daha önce NS5A inhibitörü veya proteaz inhibitörü ile ted deneyimli nonsirotik veya kompanse sirozda

SOF+Velp+VOX 12 hafta

Glik+Bip +Rib veya Glik+Bip ile 16 hafta

Daha önce NS5A inhibitörü veya proteaz ile ted deneyimli nonsirotik veya dekompanse sirozda



Organ nakli hastasında hcv tedavisi

■ Grade of evidence

■ Grade of recommendation

Organ nakli olmuş hastada tedavi süresi

SOF+LED+RİB 12 hafta

Ombitasvir+Paritaprevir+Ritonavir+Dasabuvir +RIB 24 hafta

Glik +Bip 12 hafta



- Soru
- **Transplant sonrası nüks eden HCV’de tedavi nasıl olmalıdır**
- a) Sof+velp 8 haf b) SOF+VOK 12 haf c)Omb+prt+dsb 24 haf
-
- d)PEGINFalfa+SOF 8haf e)SOF +LED+RİB 12haf



TEŞEKKÜRLER