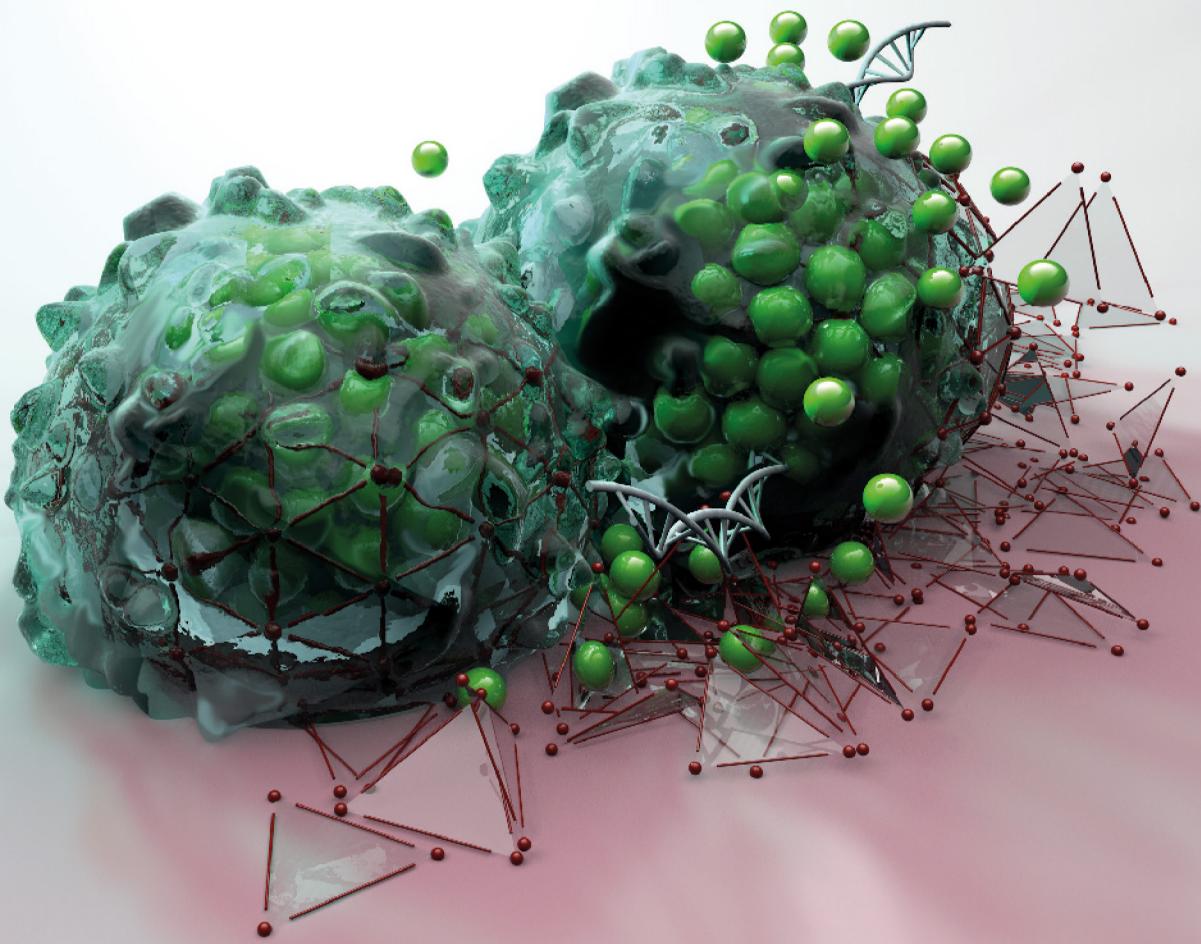


APRIL 2014

EASL Recommendations on Treatment of Hepatitis C

2014



EASL

European Association
for the Study of the Liver

Coordinator: Jean-Michel Pawlotsky
Panel members: Alessio Aghemo (EASL Governing Board)
Geoffrey Dusheiko
Xavier Forns
Massimo Puoti
Christophe Sarrazin

EASL Recommendations on Treatment of Hepatitis C 2014

SUMMARY

Contents

	<i>Page</i>
1. Diagnosis of acute and chronic hepatitis C	1
2. Goals and endpoints of HCV therapy	1
3. Pre-therapeutic assessment	1
4. Contraindications to therapy	1
5. Available drugs (approved by EMA before the end of 2014)	1
6. Treatment of HCV infection	2
Treatment of HCV genotype 1 infection	
Treatment of HCV genotype 2 infection	
Treatment of HCV genotype 3 infection	
Treatment of HCV genotype 4 infection	
Treatment of HCV genotype 5 or 6 infection	
7. Treatment monitoring	6
Monitoring of treatment efficacy	
Stopping (futility) rules	
Virological response-guided triple therapy	
Monitoring treatment safety	
8. Measures to improve treatment adherence	7
9. Post-treatment follow-up of patients who achieve an SVR	7
10. Retreatment of non-sustained virological responders	7
11. Treatment of patients with severe liver disease	7
Compensated cirrhosis	
Patients with an indication for liver transplantation	
Post-liver transplantation recurrence	
12. Treatment of special groups	8
HBV co-infection	
Treatment of patients with co-morbidities	
13. Follow-up of untreated patients and of patients with treatment failure	10
14. Treatment of acute hepatitis C	10

EASL Office

7 rue Daubin, 1203 Geneva, Switzerland
 Tel: (+41) 22 807 03 67
 Fax: (+41) 22 510 24 00
 e-mail: easloffice@easloffice.eu

Coordinator: Jean-Michel Pawlotsky
 Panel members: Alessio Aghemo (EASL Governing Board)
 Geoffrey Dusheiko
 Xavier Forns
 Massimo Puoti
 Christophe Sarrazin

Introduction

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide. The long-term impact of HCV infection is highly variable, ranging from minimal histological changes to extensive fibrosis and cirrhosis with or without hepatocellular carcinoma (HCC). The number of chronically infected persons worldwide is estimated to be about 160 million, but most are unaware of their infection. The implementation of extended criteria for screening for HCV, such as targeting birth cohorts, is a subject of major debate among different stakeholders. Clinical care for patients with HCV-related liver disease has advanced considerably during the last two decades, thanks to an enhanced understanding of the pathophysiology of the disease, and because of developments in diagnostic procedures and improvements in therapy and prevention.

These EASL Recommendations on Treatment of Hepatitis C are intended to assist physicians and other healthcare providers, as well as patients and other interested individuals, in the clinical decision-making process by describing the optimal management of patients with acute and chronic HCV infections. These guidelines apply to therapies that will be approved within less than 6 months at the time of their publication.

1. Diagnosis of acute and chronic hepatitis C

Recommendations

- Anti-HCV antibodies are the first line diagnostic test for HCV infection (**Recommendation A1**)
- In the case of suspected acute hepatitis C or in immunocompromised patients, HCV RNA testing should be part of the initial evaluation (**Recommendation A1**)
- If anti-HCV antibodies are detected, HCV RNA should be determined by a sensitive molecular method (**Recommendation A1**)
- Anti-HCV positive, HCV-RNA negative individuals should be retested for HCV RNA 3 months later to confirm true convalescence (**Recommendation A1**)

2. Goals and endpoints of HCV therapy

Recommendations

- The goal of therapy is to eradicate HCV infection to prevent hepatic cirrhosis, decompensation of cirrhosis, HCC, and death. The endpoint of therapy is undetectable HCV RNA in a sensitive assay (<15 IU/ml) 12 and 24 weeks after the end of treatment (i.e. an SVR) (**Recommendation A1**)
- In patients with cirrhosis, HCV eradication reduces the rate of decompensation and will reduce, albeit not abolish, the risk of HCC. In these patients surveillance for HCC should be continued (**Recommendation A1**)

3. Pre-therapeutic assessment

Recommendations

- The causal relationship between HCV infection and liver disease should be established (**Recommendation A1**)
- The contribution of co-morbid conditions to the progression of liver disease must be evaluated and appropriate corrective measures implemented (**Recommendation A1**)
- Liver disease severity should be assessed prior to therapy. Identifying patients with cirrhosis is of particular importance, as their prognosis is altered and their treatment regimen may be adapted (**Recommendation A1**)
- Fibrosis stage can be assessed by non-invasive methods initially, with liver biopsy reserved for cases where there is uncertainty or potential additional aetiologies (**Recommendation A1**)
- HCV RNA detection and quantification should be made by a sensitive assay (lower limit of detection of <15 IU/ml) (**Recommendation A1**)
- The HCV genotype and genotype 1 subtype (1a/1b) must be assessed prior to treatment initiation and will determine the choice of therapy (**Recommendation A1**)
- *IL28B* genotyping has no role in the indication for treating hepatitis C with the new DAAs (**Recommendation A1**)

4. Contraindications to therapy

Recommendations

- 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**)

5. Available drugs (approved by EMA before the end of 2014)

Pegylated IFN- α 2a should be used at the dose of 180 µg/week, whereas **pegylated IFN- α 2b** should be used at the weight-based dose of 1.5 µg/kg/week. **Ribavirin** dose should be 1000 or 1200 mg/day, based on body weight (<75 kg or ≥75 kg, respectively). **Sofosbuvir** should be administered at the dose of 400 mg (one tablet)

once per day. Currently, no dose recommendation can be given for patients with severe renal impairment (estimated glomerular filtration rate <30 ml/min/1.73m²) or with end-stage renal disease due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite.

Sofosbuvir is well tolerated over 12 to 24 weeks of administration. The most common adverse events ($\geq 20\%$) observed in combination with ribavirin were fatigue and headache. The most common adverse events ($\geq 20\%$) observed in combination with pegylated IFN- α and ribavirin were fatigue, headache, nausea, insomnia, and anaemia.

Drugs that are potent P-gp inducers significantly decrease sofosbuvir plasma concentrations and may lead to a reduced therapeutic effect. Thus sofosbuvir should not be administered with other known inducers of P-gp, such as rifampin, carbamazepine, phenytoin or St. John's wort. No other significant drug-drug interactions have been reported, in particular with all of the antiretroviral agents tested, including emtricitabine, tenofovir, raltegravir, efavirenz, darunavir/ritonavir, and raltegravir, and there are no potential drug-drug interactions with the remaining antiretrovirals. Sofosbuvir AUC is not significantly changed in patients with mild liver impairment, but it is increased 2.3 fold in those with moderate liver impairment.

Simeprevir should be administered at the dose of 150 mg (one capsule) once per day. No dose recommendation can be given for patients with Child-Pugh Class B or C cirrhosis, due to higher simeprevir exposures (particularly in Child-Pugh C patients) that may be associated with increased frequency of adverse reactions.

Simeprevir is well tolerated. Adverse reactions with at least 3% higher frequency in patients receiving simeprevir in combination with pegylated IFN- α and ribavirin were rash (including photosensitivity), pruritus and nausea. Because simeprevir is an inhibitor of the transporters OATP1B1 and MRP2, mild, transient hyperbilirubinaemia not accompanied by changes in other liver parameters was observed in approximately 10% of cases.

Co-administration of simeprevir with substances that are moderate or strong inducers or inhibitors of cytochrome P450 3A (CYP3A) is not recommended as this may lead to significantly lower or higher exposure of simeprevir, respectively. A number of compounds are contra-indicated in patients receiving simeprevir, including anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin), antibiotics (erythromycin, clarithromycin, telithromycin, rifampin, rifabutin, rifapentine), systemically administered antifungals (itraconazole, ketoconazole, posaconazole, fluconazole, voriconazole), systemically administered dexamethasone, cisapride, herbal products (milk thistle, St John's wort) and a number of antiretroviral drugs, including cobicistat-based regimens, efavirenz, delavirdine, etravirine, nevirapine, ritonavir, and any HIV protease inhibitor, boosted or not by ritonavir. Raltegravir, maraviroc, rilpivirine, tenofovir, emtricitabine, lamivudine, and abacavir have no interactions with simeprevir and can thus be safely used in patients receiving this drug. Dose adjustments are needed with some antiarrhythmics, warfarin, calcium channel blockers, HMG Co-A reductase inhibitors and sedative/anxiolytics. No dose changes are required when used in combination with immunosuppressants, such as cyclosporine and tacrolimus, based on studies in healthy volunteers.

Daclatasvir should be administered at the dose of 60 mg (one tablet) once per day. It is overall well tolerated. Dose adjustments are not needed in patients with Child B or C disease. The most frequently reported side effects with daclatasvir were fatigue, headache, and nausea.

Little information has been released on daclatasvir drug-drug interactions. Daclatasvir is a substrate of CYP34A and a substrate and inhibitor of P-gp. The daclatasvir dose should be adjusted to 30 mg daily in HIV-infected patients receiving atazanavir/ritonavir and to 90 mg daily in those receiving efavirenz. No dose adjustment is needed with tenofovir. No information on other antiretroviral drugs is available yet. No dose adjustments are required with cyclosporine or tacrolimus. Total daclatasvir AUC is decreased by 40% and 43% in patients with mild or moderate liver impairment, respectively. However, the unbound pharmacologically active fraction is unchanged, thus dose adjustment is not needed in patients with liver impairment.

6. Treatment of chronic hepatitis C

Recommendations

- Indications for HCV treatment in HCV/HIV co-infected persons are identical to those in patients with HCV mono-infection (**Recommendation A1**)
- The same treatment regimens can be used in HIV-co-infected patients as in patients without HIV infection, as the virological results of therapy are identical (**Recommendation A1**)
- The use of cobicistat-based regimens, efavirenz, delavirdine, etravirine, nevirapine, ritonavir, and any HIV protease inhibitor, boosted or not by ritonavir, is not recommended in HIV-infected patients receiving simeprevir (**Recommendation A1**)
- The daily daclatasvir dose should be adjusted to 30 mg daily in HIV-infected patients receiving atazanavir/ritonavir and to 90 mg daily in those receiving efavirenz (**Recommendation B2**)
- No drug-drug interaction has been reported between sofosbuvir and antiretroviral drugs (**Recommendation A2**)

Treatment of HCV genotype 1 infection

Six treatment options are available for patients infected with HCV genotype 1, including IFN/ribavirin-containing and IFN-free ones. Regardless of the respective costs of these options, the triple combination of pegylated IFN- α , ribavirin and sofosbuvir (Option 1) appears as the most efficacious and the easiest to use IFN-containing option, without the risk of selecting resistant viruses in case of treatment failure. The combination of sofosbuvir and simeprevir with or without ribavirin (Option 5) and the combination of sofosbuvir and daclatasvir with or without ribavirin (Option 6) appear as the most attractive IFN-free combinations in April 2014. The combination of sofosbuvir and ribavirin (Option 4) is suboptimal in patients infected with HCV genotype 1 and should be reserved to cases for which no other option is available. In settings where none of these options is available, the triple combination of pegylated IFN- α , ribavirin and either telaprevir or boceprevir remains acceptable.

Genotype 1, Option 1

Recommendation

- Patients infected with HCV genotype 1 can be treated with a combination of weekly pegylated IFN- α , daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥ 75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks (**Recommendation A1**)

Genotype 1, Option 2

Recommendations

- Patients infected with HCV genotype 1 can be treated with a combination of weekly pegylated IFN- α , daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or \geq 75 kg, respectively), and daily simeprevir (150 mg) (**Recommendation A1**)
- This combination is not recommended in patients infected with subtype 1a who have a detectable Q80K substitution in the NS3 protease sequence at baseline, as assessed by population sequencing (direct sequence analysis) (**Recommendation A2**)
- Simeprevir should be administered 12 weeks in combination with pegylated IFN- α and ribavirin. PEGylated IFN- α and ribavirin should then be administered alone for an additional 12 weeks (total treatment duration 24 weeks) in treatment-naïve and prior relapsing patients, including cirrhotics, and for an additional 36 weeks (total treatment duration 48 weeks) in prior partial and null responders, including cirrhotics (**Recommendation B1**)
- HCV RNA levels should be monitored on treatment. Treatment should be stopped if HCV RNA level is \geq 25 IU/ml at treatment week 4, week 12 or week 24 (**Recommendation A2**)

Genotype 1, Option 3

Recommendations

- Patients infected with HCV genotype 1, subtype 1b can be treated with a combination of weekly pegylated IFN- α , daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or \geq 75 kg, respectively), and daily daclatasvir (60 mg) 24 weeks (**Recommendation B1**)
- This combination should not be proposed to patients infected with HCV genotype 1, subtype 1a, given the preliminary data available, pending results of on-going large-scale studies (**Recommendation B1**)
- Daclatasvir should be administered 12 weeks in combination with pegylated IFN- α and ribavirin. Daclatasvir should be continued in combination with pegylated IFN- α and ribavirin an additional 12 weeks (total duration 24 weeks) in patients who do not achieve an HCV RNA level <25 IU/ml at week 4 and undetectable at week 10. Pegylated IFN- α and ribavirin should be continued alone between week 12 and 24 (total duration 24 weeks) in patients who achieve an HCV RNA level <25 IU/ml at week 4 and undetectable at week 10 (**Recommendation B2**)

Genotype 1, Option 4

Recommendations

- Patients infected with HCV genotype 1 who are IFN-intolerant or -ineligible can be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or \geq 75 kg, respectively), and daily sofosbuvir (400 mg) 24 weeks (**Recommendation B2**)
- This combination should be proposed to these patients exclusively when no other IFN-free option is available (**Recommendation B2**)

Genotype 1, Option 5

Recommendations

- Patients infected with HCV genotype 1 can be treated with an interferon-free combination of daily sofosbuvir (400 mg) and daily simeprevir (150 mg) for 12 weeks (**Recommendation B1**)
- Preliminary results do not indicate a major advantage of adding ribavirin to this regimen. However, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or \geq 75 kg, respectively) should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis (**Recommendation B1**)

Genotype 1, Option 6

Recommendations

- Patients infected with HCV genotype 1 can be treated with an interferon-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) 12 weeks in treatment-naïve patients or 24 weeks in treatment-experienced patients, including those who failed on a triple combination of pegylated IFN- α , ribavirin and either telaprevir or boceprevir (pending data with 12 weeks of therapy in treatment-experienced patients) (**Recommendation B1**)
- Preliminary results do not indicate a major advantage to adding ribavirin to this regimen. However, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or \geq 75 kg, respectively) should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis (**Recommendation B1**)

Treatment of HCV genotype 2 infection

The best treatment option for patients infected with HCV genotype 2 is the combination of sofosbuvir and ribavirin. In settings where this option is not available, the combination of pegylated IFN- α and ribavirin remains acceptable.

Genotype 2, Option 1

Recommendations

- Patients infected with HCV genotype 2 must be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks (**Recommendation A1**)
- Therapy should be prolonged to 16 or 20 weeks in patients with cirrhosis, especially if they are treatment-experienced (**Recommendation B1**)

Genotype 2, Option 2

Recommendation

- Alternatively, cirrhotic and/or treatment-experienced patients could be treated with weekly pegylated IFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks (**Recommendation B1**)

Treatment of HCV genotype 3 infection

Three treatment options are available for patients infected with HCV genotype 3. Based on data with other genotypes and preliminary results in a small group of genotype 3-infected patients, the triple combination of pegylated IFN-α, ribavirin, and sofosbuvir (Option 1) appears to be more efficacious with a shorter duration than the combination of sofosbuvir and ribavirin (Option 2), which is suboptimal in patients with cirrhosis and who have previously failed IFN and ribavirin. Although few data are available, the combination of sofosbuvir and daclatasvir, with or without ribavirin, is an attractive IFN-free option for patients infected with HCV genotype 3. In settings where none of these options is available, the combination of pegylated IFN-α and ribavirin remains acceptable.

Genotype 3, Option 1

Recommendation

- Patients infected with HCV genotype 3 can be treated with a combination of weekly pegylated IFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks (**Recommendation A2**)

Genotype 3, Option 2

Recommendations

- Patients infected with HCV genotype 3 can be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 24 weeks (**Recommendation A2**)
- This therapy is suboptimal in treatment-experienced cirrhotics, who should be proposed an alternative treatment option (**Recommendation A2**)

Genotype 3, Option 3

Recommendations

- Patients infected with HCV genotype 3 can be treated with an interferon-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) 12 weeks in treatment-naïve patients or 24 weeks in treatment-experienced patients (pending data with 12 weeks of therapy in treatment-experienced patients) (**Recommendation B1**)
- Preliminary results do not indicate a major impact of adding ribavirin to this regimen. However, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis (**Recommendation B1**)

Treatment of HCV genotype 4 infection

Six treatment options are available for patients infected with HCV genotype 4, including IFN/ribavirin-containing and IFN-free ones. Regardless of the respective costs of these options, the triple combination of pegylated IFN-α, ribavirin, and sofosbuvir (Option 1) appears as the most efficacious and the easiest to use IFN-containing option, without the risk of selecting resistant viruses in case of treatment failure. The combination of sofosbuvir and simeprevir with or without ribavirin (Option 5) and the combination of sofosbuvir and daclatasvir with or without ribavirin (Option 6) appear as attractive, but data with these combinations is lacking in patients infected with HCV genotype 4. In settings where none of these options is available, the combination of pegylated IFN-α and ribavirin remains acceptable.

Genotype 4, Option 1

Recommendation

- Patients infected with HCV genotype 4 can be treated with a combination of weekly pegylated IFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks (**Recommendation B1**)

Genotype 4, Option 2

Recommendations

- Patients infected with HCV genotype 4 can be treated with a combination of weekly pegylated IFN- α , daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or \geq 75 kg, respectively), and daily simeprevir (150 mg) (**Recommendation B1**)
- Simeprevir should be administered 12 weeks in combination with pegylated IFN- α and ribavirin. Pegylated IFN- α and ribavirin should then be administered alone an additional 12 weeks (total treatment duration 24 weeks) in treatment-naïve and prior relaper patients, including cirrhotics, an additional 36 weeks (total treatment duration 48 weeks) in prior partial and null responders, including cirrhotics (**Recommendation B1**)
- HCV RNA levels should be monitored on treatment. Treatment should be stopped if HCV RNA level is \geq 25 IU/ml at treatment week 4, week 12 or week 24 (**Recommendation A2**)

Genotype 4, Option 3

Recommendations

- Patients infected with HCV genotype 4 can be treated with a combination of weekly pegylated IFN- α , daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or \geq 75 kg, respectively), and daily daclatasvir (60 mg) 24 weeks (**Recommendation B1**)
- Daclatasvir should be administered 12 weeks in combination with pegylated IFN- α and ribavirin. Daclatasvir should be continued in combination with pegylated IFN- α and ribavirin an additional 12 weeks (total duration 24 weeks) in patients who do not achieve an HCV RNA level <25 IU/ml at week 4 and undetectable at week 10. Pegylated IFN- α and ribavirin should be continued alone between week 12 and 24 (total duration 24 weeks) in patients who achieve an HCV RNA level <25 IU/ml at week 4 and undetectable at week 10 (**Recommendation B1**)

Genotype 4, Option 4

Recommendation

- Patients infected with HCV genotype 4 who are IFN-intolerant or -ineligible can be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or \geq 75 kg, respectively), and daily sofosbuvir (400 mg) 24 weeks (**Recommendation C2**)

Genotype 4, Option 5

Recommendations

- Patients infected with HCV genotype 4 can be treated with an interferon-free combination of daily sofosbuvir (400 mg) and daily simeprevir (150 mg) 12 weeks (**Recommendation B2**)
- There is no data on the impact of adding ribavirin to this regimen. However, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or \geq 75 kg, respectively) should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis (**Recommendation B2**)

Genotype 4, Option 6

Recommendations

- Patients infected with HCV genotype 4 can be treated with an interferon-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) 12 weeks in treatment-naïve patients or 24 weeks in treatment-experienced patients (pending data with 12 weeks of therapy in treatment-experienced patients) (**Recommendation B2**)
- There is no data on the impact of adding ribavirin to this regimen. However, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or \geq 75 kg, respectively) should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis (**Recommendation B2**)

Treatment of HCV genotype 5 or 6 infection

The only treatment option for patients infected with HCV genotypes 5 or 6 is the triple combination of pegylated IFN- α , ribavirin and sofosbuvir. Patients who are intolerant or ineligible to IFN-based therapy should receive the combination of sofosbuvir and ribavirin. In settings where none of these options is available, the combination of pegylated IFN- α and ribavirin remains acceptable.

Genotype 5 or 6, Option 1

Recommendation

- Patients infected with HCV genotype 5 or 6 must be treated with a combination of weekly pegylated IFN- α , daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or \geq 75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks (**Recommendation B1**)

Genotype 5 or 6, Option 2

Recommendation

- Patients infected with HCV genotype 5 or 6 who are IFN-intolerant or -ineligible can be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 24 weeks (**Recommendation C2**)

7. Treatment monitoring

Monitoring of treatment efficacy

Recommendations

Recommendations

- A real-time PCR-based assay with a lower limit of detection of <15 IU/ml should be used to monitor HCV RNA levels during and after therapy (**Recommendation A1**)
- In patients treated with the triple combination of pegylated IFN- α , ribavirin and sofosbuvir 12 weeks, HCV RNA should be measured at baseline and at weeks 4, 12 (end of treatment), and 12 or 24 weeks after the end of therapy (**Recommendation A2**)
- In patients treated with the triple combination of pegylated IFN- α , ribavirin and simeprevir (12 weeks plus 12 or 36 weeks of pegylated IFN- α and ribavirin alone), HCV RNA should be measured at baseline, week 4, week 12, week 24 (end of treatment in treatment-naïve and prior relapsers), week 48 (end of treatment in prior partial and null responders), and 12 or 24 weeks after the end of therapy (**Recommendation A2**)
- In patients treated with the triple combination of pegylated IFN- α , ribavirin and daclatasvir 24 weeks (12 weeks plus 12 weeks of pegylated IFN- α and ribavirin alone, or 24 weeks of the triple combination), HCV RNA should be measured at baseline, week 4, week 10, week 24 (end of treatment), and 12 or 24 weeks after the end of therapy (**Recommendation A2**)
- In patients treated with an IFN-free regimen (sofosbuvir plus simeprevir with or without ribavirin 12 weeks, sofosbuvir plus daclatasvir with or without ribavirin 12 or 24 weeks, sofosbuvir plus ribavirin 12 or 24 weeks), HCV RNA should be measured at baseline, week 2 (assessment of adherence), week 4, week 12 or 24 (end of treatment), and 12 or 24 weeks after the end of therapy (**Recommendation A2**)

Stopping (futility) rules

Recommendations

Recommendations

- With the triple combination of pegylated IFN- α , ribavirin and simeprevir, treatment should be stopped if HCV RNA level is ≥25 IU/ml at treatment week 4, week 12 or week 24 (**Recommendation A2**)
- No futility rules have been defined for other treatment regimens (**Recommendation A1**)

Virological response-guided triple therapy

Recommendations

Recommendations

- With the triple combination of pegylated IFN- α , ribavirin and daclatasvir, patients who do not achieve an HCV RNA level <25 IU/ml at week 4 and undetectable at week 10 should receive the 3 drugs 24 weeks. Patients who achieve an HCV RNA level <25 IU/ml at week 4 and undetectable at week 10 should stop daclatasvir at week 12 and continue with pegylated IFN- α and ribavirin alone until week 24 (**Recommendation A2**)
- No response-guided therapy is used in other treatment regimens (**Recommendation A1**)

Monitoring treatment safety

Recommendations

Recommendations

- The patients receiving pegylated IFN- α and ribavirin should be assessed for clinical side effects at each visit, while the haematological side effects should be assessed at weeks 2 and 4 of therapy and at 4 to 8 week intervals thereafter (**Recommendation A1**)
- Renal function should be checked regularly in patients receiving sofosbuvir (**Recommendation B1**)
- Rashes and bilirubin elevations may be seen with simeprevir (**Recommendation A1**)
- The efficacy and toxicity of concurrent drugs given for comorbidities and potential drug-drug interactions should be monitored during treatment (**Recommendation A1**)

8. Measures to improve treatment adherence

Recommendations

Recommendations

- HCV treatment should be delivered within a multidisciplinary team setting, with experience in HCV assessment and therapy (**Recommendation A1**)
- HCV infected patients should be counselled on the importance of adherence for attaining an SVR (**Recommendation A1**)
- In patients with socioeconomic difficulties and in migrants, social support services should be a component of HCV clinical management (**Recommendation B2**)
- In persons who actively inject drugs, access to harm reduction programs is mandatory (**Recommendation A1**)
- Peer-based support should be evaluated as a means to improve HCV clinical management (**Recommendation B2**)
- Patients should be counselled to abstain from alcohol during antiviral therapy. Patients with on-going alcohol consumption during treatment should receive additional support during antiviral therapy (**Recommendation A1**)
- HCV treatment can be considered also for patients actively using drugs, provided they wish to receive treatment and are able and willing to maintain regular appointments. Also, the potential for drug-drug interactions involving prescribed and non-prescribed drugs needs to be considered (**Recommendation A1**)

9. Post-treatment follow-up of patients who achieve an SVR

Recommendations

Recommendations

- 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 (**Recommendation C2**)
- Cirrhotic patients with SVR should undergo surveillance for HCC every 6 months by means of ultrasound (**Recommendation B1**)
- Guidelines for management of portal hypertension and varices should be implemented, though index variceal bleed is seldom seen in low-risk patients after the achievement of SVR (unless additional causes for on-going liver damage are present and persist) (**Recommendation A2**)
- Patients with on-going drug use should not be excluded from HCV treatment on the basis of perceived risk of reinfection (**Recommendation B1**)
- Following SVR, monitoring for HCV reinfection through annual HCV RNA assessment should be undertaken on PWID or MSM with on-going risk behaviour (**Recommendation B2**)

10. Retreatment of non-sustained virological responders

Recommendations

Recommendations

- Patients who failed on a regimen containing sofosbuvir as the only DAA can be retreated with a combination of sofosbuvir and simeprevir (genotypes 1 or 4 only), or a combination of sofosbuvir and daclatasvir (all genotypes) (**Recommendation B1**)
- Patients who failed on a regimen containing simeprevir, telaprevir or boceprevir as the only DAA can be retreated with a combination of sofosbuvir and daclatasvir (**Recommendation B1**)
- Patients who failed on a regimen containing daclatasvir as the only DAA can be retreated with a combination of sofosbuvir and simeprevir (genotypes 1 or 4 only) (**Recommendation B1**)
- Patients who failed on a regimen containing sofosbuvir and simeprevir can be retreated with a combination of sofosbuvir and daclatasvir (**Recommendation B1**)
- Patients who failed on a regimen containing sofosbuvir and daclatasvir can be retreated with a combination of sofosbuvir and simeprevir (genotypes 1 or 4 only) (**Recommendation B1**)
- Alternatively, patients who failed on any of the new treatment regimens including sofosbuvir, simeprevir and/or daclatasvir can wait until new treatment combinations are available if they do not need urgent therapy (**Recommendation B1**)
- The utility of HCV resistance testing (i.e. the determination of the sequence of the DAA target region) prior to retreatment in patients who failed on any of the new treatment regimens including sofosbuvir, simeprevir and/or daclatasvir is unknown (**Recommendation B2**)

11. Treatment of patients with severe liver disease

Compensated cirrhosis

Recommendations

Recommendations

- Patients with compensated cirrhosis should be treated, in the absence of contraindications, in order to prevent short- to mid-term complications (**Recommendation A1**)
- IFN-free combination regimens should be preferred in patients with compensated cirrhosis (**Recommendation B1**)
- If a 12-24 week IFN-based DAA regimen is considered tolerable in patients with compensated cirrhosis and good liver function and without cytopenia, these patients can be treated as recommended above across genotypes (**Recommendation B1**)
- Patients with cirrhosis should undergo regular surveillance for HCC, irrespective of SVR (**Recommendation A1**)

Patients with an indication for liver transplantation

Recommendations

Recommendations

- In patients awaiting liver transplantation, antiviral therapy is indicated, because it prevents graft infection if HCV RNA has been undetectable at least 30 days prior to transplantation (**Recommendation A1**)
- Patients with conserved liver function (Child-Pugh A) in whom the indication for transplantation is HCC should be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) until liver transplantation (**Recommendation A1**)
- Patients with conserved liver function (Child-Pugh A) in whom the indication for transplantation is HCC can also be treated with a combination of weekly pegylated IFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks (**Recommendation B1**)
- In patients with conserved liver function (Child-Pugh A) in whom the indication for transplantation is HCC, the addition of another direct acting antiviral drug is likely to improve the prevention of HCV recurrence post-transplant. Therefore, patients awaiting liver transplantation with genotype 1 to 4 infection can be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), daily sofosbuvir (400 mg), and daily daclatasvir (60 mg) 12 weeks prior to transplantation (**Recommendation B1**)
- Patients with decompensated cirrhosis awaiting liver transplantation (Child-Pugh B and C) can be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) until liver transplantation in experienced centres under close monitoring. IFN is contra-indicated in these patients (**Recommendation B1**)
- The addition of another direct acting antiviral drug is likely to improve the prevention of HCV recurrence post-transplant. Therefore, patients with decompensated cirrhosis awaiting liver transplantation (Child-Pugh B and C) with genotype 1 to 4 infection should be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), daily sofosbuvir (400 mg), and daily daclatasvir (60 mg) until liver transplantation in experienced centres under close monitoring (**Recommendation B1**)
- Patients with decompensated cirrhosis not on a transplant waiting list should only be offered an IFN-free regimen within a clinical trial, an expanded access program or within experienced centres, because the efficacy, safety and outcomes have not yet been established for this group (**Recommendation B1**)

Post-liver transplantation recurrence

Recommendations

Recommendations

- Patients with post-transplant recurrence of HCV infection should be considered for therapy. Significant fibrosis or portal hypertension one year after transplantation predict rapid disease progression and graft loss, and indicate more urgent antiviral treatment (**Recommendation B2**)
- Patients with HCV genotype 2 infection must be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg), 12 to 24 weeks, pending more data in this population (**Recommendation B1**)
- Patients with HCV genotype 1, 3, 4, 5 or 6 infection can be treated with daily sofosbuvir (400 mg), and daily daclatasvir (60 mg), 12 to 24 weeks, with or without daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), pending more data in this population (**Recommendation B1**)
- Patients with HCV genotype 1 or 4 infection can be treated with daily sofosbuvir (400 mg), and daily simeprevir (150 mg), 12 to 24 weeks, with or without daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), pending more data in this population (**Recommendation B1**)
- No dose adjustment is required for tacrolimus or cyclosporine with any of these combinations. Careful monitoring is however important in the absence of safety data in this population (**Recommendation B1**)

12. Treatment of special groups

HBV co-infection

Recommendations

Recommendations

- Patients should be treated with the same regimens, following the same rules as HCV mono-infected patients (**Recommendation B1**)
- If HBV replicates at significant levels before, during or after HCV clearance, concurrent HBV nucleoside/nucleotide analogue therapy is indicated (**Recommendation B1**)

Treatment of patients with co-morbidities

Recommendations

Recommendations

- Haemodialysis patients, particularly those who are suitable candidates for renal transplantation, should be considered for antiviral therapy (**Recommendation B1**)
- Haemodialysis patients should receive an IFN-free, if possible ribavirin-free regimen. However, no safety dosing and efficacy data is available in this population, and the need for dose adjustments for sofosbuvir, simeprevir and daclatasvir is unknown. These drugs should thus be used with extreme caution and sofosbuvir should not be administered to patients with an estimated glomerular filtration rate (eGFR) <30ml/min/1.73m² or with end-stage renal disease until more data is available (**Recommendation B2**)

Recommendations

- HCV treatment before kidney transplantation may avoid liver-related mortality in the post-transplant patient, and may prevent HCV-specific causes of renal graft dysfunction. Where possible, antiviral therapy should be given to potential transplant recipients before listing for renal transplantation. These patients should receive an IFN-free, if possible ribavirin-free regimen. However, no safety and efficacy data is available in this population, and the need for dose adjustments for sofosbuvir, simeprevir and daclatasvir is unknown. These drugs should thus be used with extreme caution and sofosbuvir should not be administered to patients with an estimated glomerular filtration rate (eGFR) <30ml/min/1.73m² or with end-stage renal disease until more data is available (**Recommendation A2**)
- In non-hepatic solid organ transplant recipients, patients with an indication for anti-HCV therapy should receive an IFN-free regimen (**Recommendation A2**)
- Patients with HCV genotype 2 infection must be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg), 12 to 24 weeks, pending more data in this population (**Recommendation B1**)
- Patients with HCV genotype 1, 3, 4, 5 or 6 infection can be treated with daily sofosbuvir (400 mg), and daily daclatasvir (60 mg), 12 to 24 weeks, with or without daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), pending more safety data in this population (**Recommendation B1**)
- Patients with HCV genotype 1 or 4 infection can be treated with daily sofosbuvir (400 mg), and daily simeprevir (150 mg), 12 to 24 weeks, with or without daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), pending more data in this population (**Recommendation B1**)
- No dose adjustment is required for tacrolimus or cyclosporine with any of these combinations. Careful monitoring is however important in the absence of safety data in this population (**Recommendation B1**)

Recommendations

Recommendations

- PWIDs should be routinely and voluntarily tested for HCV antibodies and if negative, every 6-12 months (**Recommendation B1**)
- PWIDs should be provided with clean drug injecting equipment and access to opioid substitution therapy as part of widespread comprehensive harm reduction programs, including in prisons (**Recommendation B1**)
- Pre-therapeutic education should include discussions of HCV transmission, risk factors for fibrosis progression, treatment, reinfection risk and harm reduction strategies (**Recommendation B1**)
- PWIDs should be counselled to moderate alcohol intake, or to abstain if there is evidence of advanced liver disease (**Recommendation A1**)
- PWIDs should be counselled to moderate cannabis use, or to abstain if there is evidence of advanced liver disease (**Recommendation B2**)
- HCV treatment for PWIDs should be considered on an individualized basis and delivered within a multidisciplinary team setting (**Recommendation A1**)
- Pre-therapeutic assessment should include an evaluation of housing, education, cultural issues, social functioning and support, finances, nutrition and drug and alcohol use. PWID should be linked into social support services and peer support, if available (**Recommendation A1**)
- A history of IDU and recent drug use at treatment initiation are not associated with reduced SVR and decisions to treat must be made on a case-by-case basis (**Recommendation B1**)
- Drug and alcohol users or any other patients with ongoing social issues and/or history of psychiatric disease, and those with more frequent drug use during therapy, are at risk of lower adherence and reduced likelihood of achieving SVR. They need to be monitored more closely during therapy and need more intensive multidisciplinary support (**Recommendation B1**)
- Evaluation of safety and efficacy of new IFN-containing and IFN-free regimens in PWIDs is needed (**Recommendation C1**)
- Sofosbuvir and simeprevir can be used in PWIDs on opioid substitution therapy. They do not require specific methadone and buprenorphine dose adjustment, but monitoring for signs of opioid toxicity or withdrawal should be undertaken. More data is needed with daclatasvir (**Recommendation B2**)
- Consideration of IFN-containing or IFN-free therapy in PWIDs should be undertaken on an individualized basis, but those with early liver disease can be advised to await further data and/or potential development of improved therapies (**Recommendation B2**)

Recommendations (continued)

- The anti-HCV regimens that can be used in PWIDs are the same as in non-PWIDs (**Recommendation B1**)
- Awareness should be raised that liver transplantation is a therapeutic option in those with a history of IDU (**Recommendation B1**)
- Opioid substitution therapy is not a contraindication for liver transplantation and individuals on opioid substitution should not be advised to reduce or stop therapy (**Recommendation B1**)

Recommendations

- The indications for HCV therapy are the same in patients with and without haemoglobinopathies (**Recommendation A1**)
- Given that both drugs cause anaemia, the use of pegylated IFN- α and ribavirin should be avoided in patients with haemoglobinopathies, when possible. When the use of ribavirin is needed, careful monitoring is recommended, and blood transfusions may be required (**Recommendation A2**)
- Patients with haemoglobinopathies with HCV genotype 2 infection must be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or \geq 75 kg, respectively), and daily sofosbuvir (400 mg), 12 to 24 weeks (pending more data in this population) (**Recommendation B2**)
- Patients with haemoglobinopathies with HCV genotype 1, 3, 4, 5 or 6 infection can be treated with an interferon-free combination of daily sofosbuvir (400 mg), and daily daclatasvir (60 mg) 12 weeks in treatment-naïve patients or 24 weeks in treatment-experienced patients (**Recommendation B2**)
- Patients with haemoglobinopathies with HCV genotype 1 or 4 infection can be treated with an interferon-free combination of daily sofosbuvir (400 mg), and daily simeprevir (150 mg) 12 weeks (**Recommendation B2**)

Recommendations

- The indications for HCV therapy are the same in patients with and without bleeding disorders (**Recommendation A1**)
- Potential drug-drug interactions in HCV-HIV coinfected patients receiving antiretroviral agents requires careful selection of agents (**Recommendation A1**)

13. Follow-up of untreated patients and of patients with treatment failure

Recommendations

- Untreated patients with chronic hepatitis C and those who failed prior treatment should be regularly followed (**Recommendation A1**)
- Non-invasive methods for staging fibrosis are best suited for follow-up assessment at intervals (**Recommendation A2**)
- HCC surveillance must be continued indefinitely in patients with cirrhosis (**Recommendation A1**)

14. Treatment of acute hepatitis C

Recommendations

Recommendations

- Pegylated IFN- α monotherapy (pegylated IFN- α 2a, 180 μ g/week or pegylated IFN- α 2b, 1.5 μ g/kg/week) for 24 weeks can be used in patients with acute hepatitis C, who will achieve SVR in as many as 90% of cases (**Recommendation A1**)
- Pegylated IFN- α (pegylated IFN- α 2a, 180 μ g/week or pegylated IFN- α 2b, 1.5 μ g/kg/week) should be combined with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or \geq 75 kg, respectively) for 24 weeks in patients with acute hepatitis C who are HIV-coinfected (**Recommendation B1**)
- Although no data is available yet, IFN-free regimens can theoretically be used in these patients and are expected to achieve high SVR rates. The same doses and durations as for patients with chronic hepatitis C must be used, until new data indicate whether shorter and/or less intensive treatment is sufficient to achieve high infection cure rates (**Recommendation B1**)

Conflict of interest

Jean-Michel Pawlotsky

Grant and research support: Gilead.

Advisory Boards: Abbott, Abbvie, Achillion, Boehringer-Ingelheim, Bristol-Myers

Squibb, Gilead, Idenix, Janssen, Merck, Novartis, and Roche.

Speaking and teaching: Abbvie, Boehringer-Ingelheim, Bristol-Myers Squibb,

Gilead, Janssen, Merck, Novartis, and Roche.

Alessio Agemo

Grant and research support: Roche and Gilead.

Advisory Boards: Abbvie, Gilead, and Janssen.

Speaking and teaching: Abbvie, Gilead, Janssen, Merck, and Roche.

Geoffrey Dusheiko

Grant and research support: Abbvie, Boehringer-Ingelheim, Bristol-Myers

Squibb, Gilead, GlaxoSmithKline, Janssen, Merck, Novartis, and Vertex.

Advisory Boards: Abbvie, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead,

GlaxoSmithKline, Janssen, Merck, Novartis, and Vertex.

Speaking and teaching: Abbvie, Boehringer-Ingelheim, Bristol-Myers Squibb,

Gilead, GlaxoSmithKline, Janssen, Merck, Novartis, and Vertex.

Xavier Forns:

Grant and research support: Janssen, Merck, and Roche.

Advisory Boards: Abbvie, Gilead, and Janssen.

Speaking and teaching: Abbvie, Gilead, and Janssen.

Massimo Puoti:

Grant and research support: Gilead and Novartis.

Advisory Boards: Abbvie, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead,

Janssen, Merck, Roche, and Vertex.

Speaking and teaching: Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead,

Janssen, Merck, and Roche

Christoph Sarrazin:

Grant and research support: Abbott, Abbvie, Gilead, Janssen, Qiagen, Roche,

Siemens, and Vertex.

Advisory Boards: Abbott, Abbvie, Achillion, Bristol-Myers Squibb, Boehringer-

Ingelheim, Gilead, Janssen, Merck, Novartis, Roche, and Vertex.

Speaking and teaching: Abbot, Abbvie, Bristol-Myers Squibb, Boehringer-

Ingelheim, Gilead, Janssen, Merck, Novartis, Qiagen, Roche, and Siemens.