Hepatitis C and CKD: News from KDIGO

Ali K. Abu-Alfa, MD, FASN, FASH
Professor of Medicine
Head, Division of Nephrology & Hypertension
Director, Human Research Protection Program
Director for Research Affairs
American University of Beirut

Adjunct Faculty
Section of Nephrology
Yale School of Medicine

Novosibirsksk | September 23rd, 2017
Acknowledgement

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It is based on a set of slides kindly shared by Dr Michel Jadoul.
First global comprehensive guidelines on Hepatitis C Virus in nephrology
Global HCV Genotype Distribution

Messina JP et al. HEPATOLOGY 2015; 61:77-87
Evolution in HCV Therapy: SVRs

Figure 1: Changes in standard of care for HCV, and improvements in numbers of sustained virological responses

SVR in HCV and Long-Term Outcomes

31 studies (n = 33,360) included
Median follow-up 5.4 years
WORK GROUP MEMBERSHIP

Work Group Co-Chairs

Michel Jadoul, MD
Cliniques Universitaires Saint Luc
Université Catholique de Louvain
Brussels, Belgium

Paul Martin, MD, FRCP, FRCPI
Miller School of Medicine
University of Miami
Miami, USA

Work Group

Marina C. Berenguer, MD
La Fe University Hospital
Valencia, Spain

Wahid Doss, MD
National Hepatology and Tropical Medicine Research
Cairo, Egypt

Fabrizio Fabrizi, MD
Maggiore Policlinico Hospital
Milan, Italy

Jacques Izopet, PharmD, PhD
Centre de Physiopathologie de Toulouse Purpan
Toulouse, France

Vivekanand Jha, MBBS, MD, DM, PhD, FRCP
George Institute
New Delhi, India

Nassim Kamar, MD, PhD
CHU Rangueil,
Toulouse, France

Bertram Kasiske, MD
Hennepin County Medical Center
Minneapolis, MN, USA

Ching-Lung Lai, MD
University of Hong Kong
Hong Kong, China

José M. Morales, MD
Hospital Universitario 12 de Octubre
Madrid, Spain

Priti R. Patel, MD, MPH
Centers for Disease Control and Prevention
Atlanta, USA

Stanislas Pol, MD, PhD
Hôpital Cochin
Paris, France

Marcelo O. Silva, MD
Hospital Universitario Austral
Pilar, Argentina
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<td>Treatment of HCV Infection in Patients with CKD</td>
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<td>5</td>
<td>Diagnosis and Management of Kidney Diseases Associated with HCV Infection</td>
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</table>
Chapter 1: Detection and Evaluation of HCV in CKD

HCV Screening of Patients with CKD

1.1.1 We recommend screening all patients for HCV infection at the time of initial evaluation of CKD. (1C)

1.1.1.1 We recommend using immunoassay followed by nucleic acid testing (NAT). (1A)

1.1.2 We recommend screening all patients upon initiation of in-center hemodialysis or upon transferring to another dialysis facility or modality for HCV infection. (1A)

1.1.2.1 We recommend using NAT, or immunoassay followed by NAT. (1A)

1.1.3 We suggest screening all patients upon initiation of peritoneal dialysis or home hemodialysis for HCV infection. (2D)

1.1.4 We recommend screening all patients for HCV infection at the time of evaluation for kidney transplantation. (1A)
Chapter 1: Detection and Evaluation of HCV in CKD
Follow-up HCV Screening of in-Center HD Patients

1.2.1  We recommend screening in-center hemodialysis patients for HCV every 6 months. (1B)

1.2.1.1  Report any new HCV infection identified in a hemodialysis patient to the appropriate public health authority. (Not Graded)

1.2.1.2  If a new HCV infection is identified in a hemodialysis facility, we recommend all patients within the facility who were NAT negative be tested for HCV infection and the frequency of subsequent HCV testing for these patients be increased. (1A)

1.2.1.3  We recommend hemodialysis patients with resolved HCV infection undergo repeat testing every 6 months using NAT. (1B)

1.2.2  We suggest patients have serum alanine aminotransferase (ALT) level checked upon initiation of in-center hemodialysis or upon transfer to another facility or modality.

We suggest NAT-negative hemodialysis patients have serum alanine aminotransferase (ALT) level checked monthly. (2B)
1.3.1 We recommend HCV-infected patients with CKD be assessed for liver fibrosis. (1A)

1.3.2 We recommend an initial non-invasive evaluation of liver fibrosis. (1B)

1.3.3 When the cause of liver disease is uncertain or non-invasive testing results are discordant, consider liver biopsy. (Not Graded)

1.3.4 We recommend assessment of portal hypertension in CKD patients with suspected advanced fibrosis (F3-4). (1A)
Chapter 1: Detection and Evaluation of HCV in CKD
Liver Testing in Patients with CKD and HCV Infection

1.3.1 We recommend HCV-infected patients with CKD be assessed for liver fibrosis. (1A)

1.3.2 We recommend an initial non-invasive evaluation of liver fibrosis. (1B)

1.3.3 When the cause of liver disease is uncertain or non-invasive testing results are discordant, consider liver biopsy. (Not Graded)

1.3.4 We recommend assessment of portal hypertension in CKD patients with suspected advanced fibrosis (F3-4). (1A)
Chapter 1: Detection and Evaluation of HCV in CKD

Other Testing of Patients with HCV Infection

1.4.1 We recommend that all patients be assessed for kidney disease at the time of HCV diagnosis. (1A)

1.4.1.1 Screen for kidney disease with urinalysis and estimated glomerular filtration rate (eGFR). (Not Graded)

1.4.2 If there is no evidence of kidney disease at initial evaluation, patients who remain NAT positive should undergo repeat screening for kidney disease. (Not Graded)

1.4.3 We recommend that all CKD patients with a history of HCV infection, whether NAT positive or not, be followed regularly to assess for progression of kidney disease. (1A)

1.4.4 We recommend that all CKD patients with a history of HCV infection, whether NAT positive or not, be screened and, if appropriate, vaccinated for HAV and HBV, and screened for HIV. (1A)
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</table>
DAA for HCV: Site of Action

NS5A: nonstructural protein 5A; NS5B: nonstructural protein 5B; NNPI: non-nucleoside polymerase inhibitor

DAA for HCV: Molecular Targets

Replication complex

Structural proteins

C  E1  E2  p7

NS2  NS3  NS4A  NS4B  NS5A  NS5B

Non-structural proteins

NS3/4A Protease Inhibitors

Telaprevir
Boceprevir
Simeprevir
Paritaprevir/r
Asunaprevir
Grazoprevir (MK-5172)

NS5A Inhibitors

Daclastavir
Ledipasvir
Ombitasvir
GS-5816
Elbasvir (MK-8742)
ACH-3102

NS5B Polymerase Inhibitors

Nucleos(t)ide

Sofosbuvir
ACH-3422
GS-5816

Non-nucleotide

Dasabuvir
Beclabuvir

Majumdar A et al. Drugs 2015: 75:823–834
**DAA for HCV: Summary by Class**

<table>
<thead>
<tr>
<th></th>
<th>- PREVIR</th>
<th>-ASVIR</th>
<th>-BUVIR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Site of Action</strong></td>
<td>NS3 Protease inhibitors</td>
<td>NS5A inhibitors</td>
<td>Nucleos(t)ide NS5B Polymerase inhibitors</td>
</tr>
<tr>
<td><strong>Potency</strong></td>
<td>High</td>
<td>High</td>
<td>Moderate-High</td>
</tr>
<tr>
<td></td>
<td>1&lt;sup&gt;st&lt;/sup&gt; generation</td>
<td>Increasingly pangenotypic</td>
<td>Increasingly pangenotypic</td>
</tr>
<tr>
<td></td>
<td>variable genotypes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; generation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increasingly pangenotypic</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Barriers to resistance</strong></td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>1a &lt; 1b</td>
<td>1a &lt; 1b</td>
<td>1a = 1b</td>
</tr>
<tr>
<td><strong>Drug interaction potential</strong></td>
<td>High</td>
<td>Low to moderate</td>
<td>Minimal</td>
</tr>
</tbody>
</table>

NS5A: nonstructural protein 5A; NS5B: nonstructural protein 5B; NNPI: non-nucleoside polymerase inhibitor
# Use of DAAs in CKD and ESRD

<table>
<thead>
<tr>
<th>Stage of CKD</th>
<th>SOF</th>
<th>SOF/LDV</th>
<th>SIM</th>
<th>PTV/OMB DSB</th>
<th>DAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 GFR &gt; 90 ml/min</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Stage 2 (mild) GFR 60–89 ml/min</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Stage 3 (moderate) GFR 30–59 ml/min</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Stage 4 (severe) GFR 15–29 ml/min</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Stage 5 (renal failure) GFR &lt; 15 ml/min or dialysis</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
</tbody>
</table>

CKD, chronic kidney disease; LDV, ledipasvir; SOF, sofosbuvir.
Chapter 2: Treatment of HCV Infection in CKD

2.1 We recommend that all CKD patients infected with HCV be evaluated for antiviral therapy. (1A)

2.1.1 We recommend an interferon-free regimen. (1A)

2.1.2 We recommend choice of specific regimen be based on HCV genotype (and subtype), viral load, drug-drug interactions, eGFR category, stage of hepatic fibrosis, kidney and liver transplant candidacy, and comorbidities. (1A)

2.1.3 Treat kidney transplant candidates in collaboration with the transplant center to optimize timing of therapy. (Not Graded)
2.2 We recommend that patients with eGFR > 30 ml/min/1.73 m² be treated with any licensed DAA-based regimen. (1A)
### Recommended Dosage Adjustments for Patients with Mild to Moderate Renal Impairment

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients with mild to moderate renal impairment (eGFR 30 mL/min-80 mL/min), no dosage adjustment is required when using daclatasvir (60 mg*), fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg), fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg), or fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with (or without for HCV genotype 4 infection) twice-daily dosed dasabuvir (250 mg), simeprevir (150 mg), or sofosbuvir (400 mg) to treat or retreat HCV infection in patients with appropriate genotypes.</td>
<td>I, A</td>
</tr>
</tbody>
</table>

Chapter 2: Treatment of HCV Infection in CKD

2.3 We recommend that patients with eGFR < 30 ml/min/1.73 m² be treated with DAA based regimens, preferentially ribavirin-free (1B), as follows:

2.3.1 We recommend for HCV genotype 1 subtype A the use of grazoprevir/elbasvir (1A) and for HCV genotype 1 subtype B, grazoprevir/elbasvir (1A) or the “PROD” regimen (the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir) (1B) for 12 weeks.

2.3.2 We suggest for HCV genotype 4 the use of grazoprevir/elbasvir or the “2D” regimen (the combination of ritonavir-boosted paritaprevir, ombitasvir regimen) for 12 weeks. (2D)

2.3.3 Treat patients with HCV genotypes 2, 3, 5, and 6 on a case-by-case basis. (Not Graded)

Grz/Elb and PROD regimens not active on these genotypes
### Recommended Regimens by evidence level and alphabetically for:

**Patients with Severe Renal Impairment, Including Severe Renal Impairment (eGFR <30 mL/min) or End-Stage Renal Disease (ESRD)**

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>DURATION</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients with genotype 1a, or 1b, or 4 infection and eGFR below 30 mL/min, for whom treatment has been elected, daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)</td>
<td>12 weeks</td>
<td>I, B</td>
</tr>
<tr>
<td><em>(C-SURFER regimen, LANCET 2015)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For patients with genotype 1b infection and eGFR below 30 mL/min, for whom treatment has been elected, daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg)</td>
<td>12 weeks</td>
<td>IIb, B</td>
</tr>
<tr>
<td><em>(PROD regimen, J Virology 2017)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For patients with HCV genotype 2, 3, 5, or 6 infection and eGFR below 30 mL/min, for whom the urgency to treat is high, PEG-IFN and dose-adjusted ribavirin** (200 mg daily)</td>
<td>-</td>
<td>IIb, B</td>
</tr>
</tbody>
</table>

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

** Caution is recommended in this group, owing to the potential for hemolytic anemia due to impaired renal clearance in this population, and ribavirin should be restricted to those with a baseline hemoglobin concentration above 10 g/dL.

C-SURFER in CKD 4-5/ESRD

GZR: Grazoprevir  EBR: Elbasvir

- **Primary efficacy outcome** was a comparison of sustained virological response at 12 weeks (SVR12) after the end of therapy
- HCV Genotype 1 infection (52% 1a, 48% 1b). No Liver biopsy required.
- Treatment-naive and treatment-experienced patients:
  - CKD stage 4/5
  - Hemodialysis-Dependent (76%)
- All HBV and HIV negative.

C-SURFER in CKD 4-5/ESRD: Virologic Response on Treatment

Roth D et al. Lancet 2015; 386: 1537–45
C-SURFER in CKD 4-5/ESRD: Cure Rates

C-SURFER in CKD 4-5/ESRD: Adverse Event Rates

<table>
<thead>
<tr>
<th></th>
<th>GZR/EBR (ITG) (n = 111)</th>
<th>GZR/EBR (DTG) (n = 102)</th>
<th>Placebo (DTG) (n = 113)</th>
<th>Difference in % Estimate ITG vs placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs, a n (%)</td>
<td>84 (75.7)</td>
<td>61 (59.8)</td>
<td>95 (84.1)</td>
<td>-8.3 (--18.9, 2.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>19 (17.1)</td>
<td>7 (6.9)</td>
<td>19 (16.8)</td>
<td>0.3 (-9.6, 10.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>17 (15.3)</td>
<td>10 (9.8)</td>
<td>18 (15.9)</td>
<td>-0.6 (-10.3, 9.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (9.9)</td>
<td>9 (8.8)</td>
<td>17 (15.0)</td>
<td>-5.1 (-14.1, 3.7)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>7 (6.3)</td>
<td>2 (2.0)</td>
<td>12 (10.6)</td>
<td>-4.3 (-12.2, 3.2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6 (5.4)</td>
<td>5 (4.9)</td>
<td>18 (15.9)</td>
<td>-10.5 (-19.1, -2.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (5.4)</td>
<td>5 (4.9)</td>
<td>15 (13.3)</td>
<td>-7.8 (-16.1, -0.2)</td>
</tr>
<tr>
<td>Serious AEs, n (%)</td>
<td>16b (14.4)</td>
<td>13c (12.7)</td>
<td>19 (16.8)</td>
<td>-2.4 (-12.1, 7.3)</td>
</tr>
<tr>
<td>Discontinued due to AE, n (%)</td>
<td>0 (0)</td>
<td>3 (2.9)</td>
<td>5 (4.4)</td>
<td>-4.4 (10.0, -1.0)</td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>1 (0.9)</td>
<td>0 (0)</td>
<td>3 (2.7)</td>
<td>-1.8 (-6.7, 2.5)</td>
</tr>
</tbody>
</table>

Roth D et al. Lancet 2015; 386: 1537–45
2.4 We recommend that all kidney transplant recipients infected with HCV be evaluated for treatment. (1B)

2.4.1 We recommend treatment with a DAA-based regimen. (1A)

2.4.2 We recommend the choice of regimen be based on HCV genotype (and subtype), viral load, drug-drug interactions, eGFR category, stage of hepatic fibrosis, liver transplant candidacy, and comorbidities. (1A)

2.4.3 We recommend that treatment with interferon be avoided. (1A)
RCT: Ledipasvir-Sofosbuvir in Transplant Response Rates


#### Table 2. Response During and After Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ledipasvir-Sofosbuvir</th>
<th>Total (n = 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 wk (n = 57)</td>
<td>24 wk (n = 57)</td>
</tr>
<tr>
<td>HCV RNA level less than the LLOQ during treatment, n/N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0/57 (0)</td>
<td>0/57 (0)</td>
</tr>
<tr>
<td>Week 1</td>
<td>9/57 (16)</td>
<td>7/57 (12)</td>
</tr>
<tr>
<td>Week 2</td>
<td>31/57 (54)</td>
<td>33/57 (58)</td>
</tr>
<tr>
<td>Week 4</td>
<td>50/57 (88)</td>
<td>52/57 (91)</td>
</tr>
<tr>
<td>Week 8</td>
<td>56/56 (100)*</td>
<td>57/57 (100)</td>
</tr>
<tr>
<td>Week 12</td>
<td>56/56 (100)*</td>
<td>57/57 (100)</td>
</tr>
<tr>
<td>Week 16</td>
<td>NA</td>
<td>57/57 (100)</td>
</tr>
<tr>
<td>Week 20</td>
<td>NA</td>
<td>57/57 (100)</td>
</tr>
<tr>
<td>Week 24</td>
<td>NA</td>
<td>57/57 (100)</td>
</tr>
<tr>
<td>HCV RNA level less than the LLOQ after end of treatment, n/N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVR4</td>
<td>57/57 (100 [94-100])</td>
<td>57/57 (100 [94-100])</td>
</tr>
<tr>
<td>SVR12</td>
<td>57/57 (100 [94-100])</td>
<td>57/57 (100 [94-100])</td>
</tr>
<tr>
<td>Overall virologic failure (relapse), n/N (%)</td>
<td>0/0 (0)</td>
<td>0/0 (0)</td>
</tr>
</tbody>
</table>

HCV = hepatitis C virus; LLOQ = lower limit of quantification; NA = not available; SVR4 = sustained virologic response at 4 wk; SVR12 = sustained virologic response at 12 wk.

* Excluding 1 patient in the 12-wk group who discontinued study treatment early at week 4 because of a serious adverse event. This patient achieved SVR12.

- HCV Genotype 1 or 4 infection
- Median of 10 years after kidney transplantation, Cirrhosis 15%
- Median creatinine clearance by CG: 56 ml/min
- Regimens: Tacrolimus 47%, Cyclosporin A 39%, MMF 61%, Steroids 98%

RCT: Ledipasvir–Sofosbuvir in Transplant Changes in GFR

**Figure 1.** Median change in eGFR by Cockcroft-Gault equation.

The horizontal line is the median value, the box is interquartile range, and the whiskers show overall range. BL = baseline; eGFR = estimated glomerular filtration rate; PT = posttreatment.

**KIDIGO**

Chapter 2: Treatment of HCV Infection in CKD Transplantation

2.5 We recommend pre-treatment assessment for drug-drug interactions between the DAA-based regimen and other concomitant medications including immunosuppressive drugs in kidney transplant recipients. (1A)

2.5.1 We recommend that calcineurin inhibitor levels be monitored during and after DAA treatment. (1B)
Drug-Drug Interactions: Imunosuppressive Medications

Table 1. Drug interactions with currently available direct acting antiviral agent

<table>
<thead>
<tr>
<th></th>
<th>SOF</th>
<th>SOF/LDV</th>
<th>SIM</th>
<th>PTV/OMB DSV</th>
<th>DCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>I, reduce TAC to 0.5 1–2 weeks</td>
<td>NI</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>NI</td>
<td>NI</td>
<td>L, C</td>
<td>I, reduce CYA to 20%</td>
<td>NI</td>
</tr>
<tr>
<td>Sirolimus/everolimus</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>I, no data</td>
<td>NI</td>
</tr>
<tr>
<td>Mycophenolate/mycophenolic acid</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>I, reduce MMF by 50%</td>
<td>NI</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
</tr>
</tbody>
</table>

C, contraindicated; CYA, cyclosporin; I, interaction; NI, no interaction demonstrated or expected; LDV, ledipasvir; MMF, mycophenolate mofetil; PTV/OMB DSB, paritaprevir/ombitasvir, Dasabuvir; SIM, simeprevir; SOF, sofosbuvir; TAC, tacrolimus.
## Drug-Drug Interactions: Immunosuppressive Medications

### Table 1. Drug-drug interactions between HCV DAAs and immunosuppressants

<table>
<thead>
<tr>
<th>Drug</th>
<th>SOF</th>
<th>SOF/ LDV</th>
<th>SOF/ VEL</th>
<th>3D</th>
<th>GZR/ EBR</th>
<th>DCV</th>
<th>SIM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>❄️</td>
<td>❄️</td>
<td>❄️</td>
<td>❄️</td>
<td>❄️</td>
<td>❄️</td>
<td>❄️</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>❄️</td>
<td>❄️</td>
<td>❄️</td>
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**Colour legend**

- ❄️: No clinically significant interaction expected.
- ❄️: Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring.
- ❄️: These drugs should not be co-administered.

**Notes:**
- SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; SOF/VEL, sofosbuvir plus velpatasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir; GZR/EBR, grazoprevir plus elbasvir; DCV, daclatasvir; SIM, simeprevir.
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Chapter 3: Preventing HCV Transmission in HD Units

3.1  We recommend that hemodialysis facilities adhere to standard infection-control procedures including hygienic precautions that effectively prevent transfer of blood and blood-contaminated fluids between patients to prevent transmission of blood-borne pathogens (1A) 3.1.1

We recommend regular observational audits of infection control procedures in hemodialysis units. (1C)

3.1.2  We recommend not using dedicated dialysis machines for HCV-infected patients. (1D)

3.1.3  We suggest not isolating HCV-infected hemodialysis patients. (2C)

3.1.4  We suggest that the dialyzers of HCV-infected patients can be reused if there is adherence to standard infection-control procedures. (2D)
3.2 We recommend hemodialysis centers examine and track all HCV test results to identify new cases of HCV infections in their patients. (1B)

3.2.1 We recommend aggressive measures be taken to improve hand hygiene (and proper glove use), injection safety, and environmental cleaning and disinfection when a new case of HCV is identified that is likely to be dialysis-related. (1A)

3.3 Strategies to prevent HCV transmission within hemodialysis units should prioritize adherence to standard infection control practices and should not primarily rely upon the treatment of HCV-infected patients. (Not Graded)
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Chapter 4: Management of HCV Infected Patients Before and After Kidney Transplantation

4.1 We recommend kidney transplantation as the best therapeutic option for patients with end-stage renal disease (ESRD) irrespective of presence of HCV infection. (1A)

4.2 We suggest that all HCV-infected kidney-transplant candidates be evaluated for severity of liver disease and, if indicated, portal hypertension prior to acceptance for an isolated kidney or combined kidney-liver transplantation. (2D)

4.2.1 We recommend that HCV-infected patients with compensated cirrhosis (without portal hypertension) undergo isolated kidney transplantation. (1B)

4.2.2 We recommend to refer HCV-infected patients with decompensated cirrhosis for combined liver-kidney transplantation (1B) and to defer HCV treatment until after transplantation. (1D)
Chapter 4: Management of HCV Infected Patients Before and After Kidney Transplantation

4.3 Timing of HCV treatment in relation to kidney transplantation (before vs. after) should be based on donor type (living vs. deceased donor), waitlist times by donor type, center-specific policies for using or not kidneys from HCV-infected deceased donors, HCV genotype, and severity of liver fibrosis. *(Not Graded)*

4.3.1 For all HCV-infected patients who are candidates for kidney transplantation, we recommend they be considered for antiviral therapy, either before or after transplantation. *(1A)*

4.3.2 For HCV-infected kidney-transplant candidates with a living kidney donor, we suggest they can be considered for treatment before or after transplantation according to HCV genotype and anticipated timing of transplantation. *(2D)*

4.3.3 We suggest that, if receiving a kidney from a HCV-positive donor improves the chances for transplantation, the HCV RNA-positive patient can undergo transplantation with a HCV-positive kidney and be treated for HCV infection after transplantation. *(2D)*
4.4.1 We recommend all kidney donors be screened for HCV infection with both immunoassay and NAT (if NAT is available). (1A)

4.4.2 We recommend that transplantation of kidneys from HCV RNA-positive donors be directed to recipients with positive NAT. (1A)

4.4.3 After the assessment of liver fibrosis, potential HCV-positive living kidney donors who do not have cirrhosis should undergo HCV treatment before donation; they can be accepted for donation if they achieve SVR and remain otherwise eligible to be a donor. (Not Graded)

4.5 We suggest that all conventional current induction and maintenance immunosuppressive regimens can be considered for use in HCV-infected kidney transplant recipients. (2C)

4.6 Management of HCV-related complications in kidney transplant recipients (not shown)
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Chapter 5: Diagnosis and Management of Kidney Diseases Associated with HCV Infection

5.1 We recommend that a kidney biopsy be performed in HCV-infected patients with clinical evidence of glomerular disease. (1B)

5.2 We recommend that patients with HCV-associated glomerular disease be treated for HCV. (1A)

5.2.1 We recommend that patients with HCV-related glomerular disease showing stable kidney function and/or non-nephrotic proteinuria be treated initially with DAA. (1B)

5.2.2 We recommend that patients with cryoglobulinemic flare, nephrotic syndrome, or progressive kidney failure be treated with both DAA and immunosuppressive agents and/or plasma-exchange. (1B)

5.2.3 We recommend immunosuppressive therapy in patients with histologically active HCV-associated glomerular disease who do not respond to antiviral therapy, particularly those with cryoglobulinemic kidney disease. (1A)

5.2.3.1 We recommend rituximab as the first-line immunosuppressive treatment. (1B)
Summary

- Therapy for Hepatitis C Virus infection in CKD/ESRD patients and transplant recipients has been revolutionized towards a cure with newer agents and regimens.
- Many regimens are well tolerated but caution should be exercised given:
  - Need to verify genotype for appropriate regimen
  - Need to avoid certain drugs in CKD 4-5/ESRD (e.g. Sofosbuvir)
  - Need to check for drug-drug interactions, especially in transplant patients
- Transplantation in context of Hepatitis C infection, donor and/or recipient, requires deliberation and careful considerations.
- Coordination with hepatologists and infectious disease specialists is critical for successful and safe therapy.
- Upcoming KDIGO guidelines offer a comprehensive up-to-date summary and reference on Hepatitis C infection in renal patients.