

# Treatment of HCV in Persons with Renal Impairment

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Module 6: [Treatment of Key Populations and Unique Situations](#)

Lesson 2: [Treatment of HCV in Persons with Renal Impairment](#)

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## Background

### Epidemiology of Hepatitis C Infection and Renal Disease

The prevalence of chronic hepatitis C virus (HCV) is higher in persons with chronic kidney disease compared with those in the general adult population, particularly among individuals who are on hemodialysis.[1] Kidney disease among persons with HCV infection can be due to an extrahepatic manifestation of HCV (e.g., mixed cryoglobulinemia or membranoproliferative glomerulonephritis), or due to an independent disease process (secondary amyloidosis due to injection drug use). Historically, hemodialysis was a risk factor for acquiring HCV infection, with reports of outbreaks and iatrogenic exposures in hemodialysis units.[2,3,4,5] Earlier studies conducted in Western countries showed an HCV prevalence in hemodialysis patients that ranged from 2.6 to 23%, with a higher prevalence that correlated with longer duration of hemodialysis.[6,7,8] The risk of HCV transmission in hemodialysis units has declined in a number of countries due to improved testing and infection control practices.[9,10,11]

### Interaction of Hepatitis C Infection and Renal Disease

Several studies have shown that patients on long-term hemodialysis have an increased overall mortality risk if they have chronic HCV infection (when compared with those on dialysis who do not have HCV).[12] There also are some data showing that chronic HCV may be a risk factor for developing renal cell carcinoma.[13] Chronic HCV infection has also been associated with an accelerated course of renal disease, including in persons with HIV coinfection.[14,15,16]

### Definitions and Classification

As part of evaluating and treating patients with HCV and renal disease, it is important to first determine the stage of the patient's renal disease, a process that utilizes some of the following information and definitions.

- **Glomerular Filtration rate (GFR):** GFR is generally considered to be the best index of overall kidney function. The normal value for GFR is approximately 130 and 120 mL/min/1.73 m<sup>2</sup> for men and women, respectively. The widely accepted threshold defining a decreased GFR is less than 60 mL/min per 1.73 m<sup>2</sup>; kidney failure is defined as a GFR less than 15 mL/min/1.73 m<sup>2</sup> or treatment by dialysis (Figure 1).[17,18,19,20]
- **Creatinine Clearance (CrCl):** Creatinine clearance is a widely used test to estimate the glomerular filtration rate (eGFR). The creatinine clearance, however, overestimates the GFR since creatinine is both filtered by the glomeruli and secreted in the renal tubules. The Cockcroft-Gault formula is commonly used in clinical practice to estimate creatinine clearance based on serum creatinine,

patient age, body mass in kilograms, and sex ([Figure 2](#)).<sup>[21]</sup> Normal values are 95 to 145 mL/min in men and 75 to 115 mL/min in women.

## **Evaluation of Persons with Chronic HCV and CKD**

Serum creatinine should be measured and creatinine clearance or GFR should be estimated as part of a pretreatment assessment for HCV patients. The chronic kidney disease (CKD) stage should be determined if renal function is abnormal. A complete blood count should be obtained as well, to assess for pre-treatment anemia.

## HCV Treatment Studies in Persons with CKD

Direct-acting antiviral agents (DAAs) have transformed the HCV treatment landscape for persons with chronic renal impairment, since many of these individuals were historically not eligible for treatment in the pre-DAA era due to toxicities associated with interferon and ribavirin-based therapies.[22] The following summarizes key studies involving the use of new DAA-based therapy in persons with chronic renal insufficiency. Older studies that used peginterferon-based regimens or sofosbuvir plus ribavirin are not reviewed since these agents are no longer recommended for the treatment of HCV infection.

- **Glecaprevir-Pibrentasvir (EXPEDITION-4)**: This phase 3, single-arm, open-label trial evaluated the safety and efficacy of 12 weeks of glecaprevir-pibrentasvir in 104 adults with HCV genotype 1, 2, 3, 4, 5, or 6 infection and advanced renal insufficiency (estimated glomerular filtration rate less than 30 mL/min/1.73m<sup>2</sup>); 88% had chronic kidney disease stage 5 and 82% were on hemodialysis.[23] Fifty-two percent of participants had HCV genotype 1 infection, 19% had compensated cirrhosis, and 42% were treatment experienced (all but two with prior interferon-based therapy). The overall SVR rate was 98% by intent-to-treat analysis.[23] The rate of adverse events (pruritus 20%, fatigue 14%, nausea 12%) attributable to glecaprevir-pibrentasvir were comparable to those observed in other glecaprevir-pibrentasvir trials.[23]
- **Glecaprevir-Pibrentasvir (EXPEDITION-5)**: In this open-label, single-arm, phase 3 trial, investigators evaluated the safety and efficacy of the fixed-dose combination of glecaprevir-pibrentasvir for 8, 12, or 16 weeks in treatment-naïve and treatment-experienced participants with chronic HCV genotypes 1, 2, 3, 4, 5, or 6 and advanced renal insufficiency.[24] The renal insufficiency was defined as eGFR less than 45 mL/min/1.73 m<sup>2</sup> (CKD stage 3b, 4, or 5). Most of the participants enrolled received glecaprevir-pibrentasvir for 8 weeks.[24] Overall, 97% (97 of 101) of the participants treated with glecaprevir-pibrentasvir achieved an SRV12.[24]
- **Sofosbuvir-Velpatasvir (Sofosbuvir-Velpatasvir in Patients with ESRD on Dialysis)**: In this phase 2, single-arm study, 59 adults with HCV genotype 1, 2, 3, 4, 5, or 6 infection and ESRD undergoing hemodialysis or peritoneal dialysis received open-label sofosbuvir-velpatasvir (400 mg/100 mg) once daily for 12 weeks.[25] The participants included treatment-naïve or treatment-experienced (not NS5A-experienced) individuals, with and without compensated cirrhosis.[25] Overall, 95% (56 of 59) of the participants achieved an SVR12.[25] Serious adverse events occurred in 11 persons, but the adverse effects were thought to be unrelated to the HCV treatment medications.[25]
- **Elbasvir-Grazoprevir (C-SURFER)**: In this phase 3, randomized study, investigators enrolled 224 adults with HCV genotype 1 and chronic renal disease, including individuals on hemodialysis, to receive immediate treatment with 12 weeks of therapy with elbasvir plus grazoprevir, or deferred therapy.[26] Subjects in the deferred group received placebo during the first 12 weeks; use of placebo was considered important as a comparator for safety purposes, particularly due to safety concerns in this population with advanced renal disease.[26] Overall, 80% of the participants enrolled in the trial were treatment naive, and 76% were receiving hemodialysis. Among all the participants who completed therapy, 99% (115 of 116) achieved an SVR12. Six individuals were excluded from the modified full analysis, but all 6 had HCV RNA levels less than 15 IU/mL at the time of study discontinuation.[26] The safety profile observed in participants who received elbasvir plus grazoprevir was comparable to that seen in the placebo group.
- **Ledipasvir-Sofosbuvir (ERCHIVES-Renal)**: In an observational cohort study conducted in the Veterans Administration system, investigators used the Electronically Retrieved Cohort of HCV-Infected Persons (ERCHIVES) to analyze HCV treatment responses for 13,663 persons who received ledipasvir-sofosbuvir, with or without ribavirin.[27] This cohort included a total of 1,607 with CKD stage 3, 4, or 5 who completed HCV treatment.[27] The SVR12 rates for individuals with stage 3 CDK who completed treatment were 97% (1080 of 1113) in those who received ledipasvir-sofosbuvir and 97% (375 of 386) with ledipasvir-sofosbuvir plus ribavirin.[27] For those with stage 4 or 5 CKD, the

SVR12 rates were 94% (78 of 83) with ledipasvir-sofosbuvir and 100% (25 of 25) with ledipasvir-sofosbuvir plus ribavirin.

## HCV Treatment in Persons with CKD

### AASLD-IDSA Recommended HCV Treatment in Persons with CKD

The AASLD-IDSA HCV Guidance now recommends that no dose adjustment is required for HCV treatment in persons with renal impairment when the treatment regimen is a recommended regimen.[28] The one exception is that if ribavirin is added to a regimen, dose adjustment of the ribavirin is required.[28]

### Dosing of DAA Medications in Persons with CKD

The following (in alphabetical order) summarizes recommended dosing information for oral DAA medications (and ribavirin) used to treat HCV in persons with renal impairment. The information provided is based on specific drug prescribing information for persons with renal impairment. As noted above, the following medications do not require dosage adjustment with mild, moderate, or severe renal impairment, including for individuals receiving hemodialysis.

- Elbasvir-Grazoprevir
- Glecaprevir-Pibrentasvir
- Ledipasvir-Sofosbuvir
- Sofosbuvir-Velpatasvir
- Sofosbuvir-Velpatasvir-Voxilaprevir

### Dosing of Ribavirin in Persons with CKD

Ribavirin may occasionally be used as an adjunct to DAA therapy, but in most cases of treatment-naïve individuals (including those with CKD), ribavirin is not necessary. Dosing of ribavirin in persons with CKD requires special consideration given their heightened risk for symptomatic or severe hemolytic anemia, one of the more serious adverse effects of this drug. In the current era of HCV treatment, ribavirin is recommended for use only in these select situations for treatment-naïve individuals:

- In combination with ledipasvir-sofosbuvir or sofosbuvir-velpatasvir in persons who have decompensated cirrhosis
- In persons with HCV genotype 1a who are receiving treatment with elbasvir-grazoprevir and who have baseline NS5A resistance-associated substitutions (RASs) for elbasvir
- In combination with sofosbuvir-velpatasvir in persons with genotype 3 compensated cirrhosis and a baseline NS5A RAS Y93H mutation

Ribavirin is manufactured by multiple companies and is available as a generic preparation. Concern exists with the use of ribavirin in patients with renal impairment due to reduced drug clearance as renal function decreases. Several ribavirin company package inserts, including *Rebetol* and *Ribasphere*, recommend not using ribavirin in patients with an estimated glomerular filtration rate of less than 50 mL/min. The package insert for *Copegus* permits the use of ribavirin in patients with an estimated glomerular filtration rate of less than 50 mL/min if the dose is reduced and careful monitoring occurs. The AASLD-IDSA HCV Guidance recommends that adults with a creatinine clearance of 30 to 50 mL/min have the ribavirin dose reduced to alternating doses of 200 and 400 mg every other day (for example, 200 mg on Monday, 400 mg on Tuesday, 200 mg on Wednesday, etc.). In addition, these guidelines recommend reducing the dose of ribavirin to 200 mg once daily in adults with severe renal disease (creatinine clearance less than 30 mL/min), end-stage renal disease, or who are receiving hemodialysis.

# Treatment of HCV in Setting of Renal Transplantation

## Hepatitis C Treatment Prior to Renal Transplantation

Most experts recommend that persons with chronic HCV infection who are renal transplantation candidates receive HCV treatment prior to renal transplantation, if possible.[29,30,31] In some circumstances, however, it may not be possible to treat HCV prior to renal transplantation. Historically, HCV treatment was recommended pre-transplant, given the potential for graft dysfunction in patients who received interferon-based therapy post-transplant and the improved clinical outcomes in those who underwent HCV clearance prior to transplantation.[32,33,34] Data from the DAA era also suggests improved clinical outcomes in patients treated in the pre-transplant or early post-transplant period when feasible.[31,35] When treating HCV in a person waiting for renal transplant, the recommended DAA regimens are the same as those for persons with chronic severe renal impairment.[28]

## HCV Treatment Studies in Renal Transplant Recipients

A variety of treatment studies have been conducted using DAAs in renal transplant recipients. Most of these studies have been smaller and observational in nature.[36,37,38,39] Overall, DAA therapy was found to be safe and highly effective. A few larger studies and one systematic review of 16 studies also support the efficacy of HCV treatment in renal transplant recipients.[40,41,42] In a phase 2, open-label trial, investigators in Europe enrolled 114 treatment-naïve or treatment-experienced kidney transplant recipients with chronic HCV genotype 1 or 4 infection to receive either a 12- or 24-week course of ledipasvir-sofosbuvir.[40] All 114 (100%) of the study participants achieved an SVR12.[40] In the observational HCV-TARGET study, 55 renal transplant recipients had treatment of HCV with DAA therapy, most often ledipasvir-sofosbuvir, with or without ribavirin.[41] Overall, 94.5% (52 of 55) renal transplant recipients achieved an SVR12 with DAA therapy for chronic HCV infection.[41] Increasingly, transplant programs have offered the option of post-transplant DAA treatment for kidney transplant recipients of HCV-viremic organs to shorten the wait time.[43] A growing body of evidence supports this approach for increasing the probability of kidney transplants and improving outcomes.[42]

## AASLD-IDSA Guidance for HCV Treatment after Renal Transplant

The following summarizes the AASLD-IDSA HCV Guidance for the treatment of renal transplant recipients, stratified by HCV treatment experience.[35] Note that consideration of drug interactions is extremely important in the post-transplantation period, particularly with regard to the calcineurin inhibitors, particularly cyclosporine and tacrolimus. Further details on potential drug interactions in this setting can be found in the AASLD-IDSA HCV Guidance on Kidney Transplant Patients, which has a table specifically on [Drug-Drug Interactions Between DAAs and Calcineurin Inhibitors](#). [35]

- **Treatment-Naïve and Non-DAA-Experienced; All Genotypes (1, 2, 3, 4, 5, or 6) with or without Compensated Cirrhosis:** The recommended regimens are a 12-week course of glecaprevir-pibrentasvir, ledipasvir-sofosbuvir, or sofosbuvir-velpatasvir.[35] For persons with HCV genotype 1 or 4, elbasvir-grazoprevir is an option if they do not have any baseline NS5A resistance-associated substitutions for elbasvir.[35]
- **DAA-Experienced; All Genotypes (1, 2, 3, 4, 5, or 6) with or without Compensated Cirrhosis:** The recommended regimen is a 12-week course of sofosbuvir-velpatasvir-voxilaprevir, with or without ribavirin.[35]

## Summary Points

- Chronic kidney disease is a major potential comorbidity in people living with chronic HCV infection.
- Renal function, including an estimation of CrCl or GFR, should be assessed before initiating any HCV treatment. Based on the estimated CrCl or GFR value, individuals with renal impairment are classified as having mild (50 to 80 mL/min), moderate (30 to 50 mL/min), or severe (less than 30 mL/min) disease.
- Current DAAs are highly effective and well tolerated for patients with chronic HCV across all stages of CKD. The recommended regimens for individuals with CKD (pre-transplant) are the same as for those without CKD.
- For persons with any stage of renal impairment, from mild to severe (CKD stages 1, 2, 3, 4, or 5), no dose adjustments are needed for DAA medications.
- Ribavirin is required in limited situations in persons with chronic renal failure. Careful dose adjustment of this drug is necessary based on CrCl or GFR to minimize drug toxicity.
- For individuals with severe renal impairment who require ribavirin, the recommended ribavirin dose is 200 mg/day (typically starting at 200 mg three times weekly and titrating up to 200 mg/day as tolerated). Caution should be exerted when using ribavirin in persons with renal failure because of the risk of severe hemolysis.
- Persons with chronic HCV infection who require renal transplantation should undergo prompt evaluation for HCV treatment. Careful review of potential drug interactions is indicated with DAAs and immunosuppressive therapy.

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## Figures

**Figure 1 Glomerular Filtration Rate Categories in Chronic Renal Disease and Definition of Renal Failure**

Source: Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int.*, 2013;Suppl 3: 1-150.

| GFR Category | GFR (mL/min/1.73 m <sup>2</sup> ) | Description                      |
|--------------|-----------------------------------|----------------------------------|
| G1           | ≥90                               | Normal or High                   |
| G2           | 60-89                             | Mildly decreased                 |
| G3a          | 45-59                             | Mildly to moderately decreased   |
| G3b          | 30-44                             | Moderately to severely decreased |
| G4           | 15-29                             | Severely decreased               |
| G5           | <15                               | Kidney failure                   |

## Figure 2 Cockcroft-Gault Formula for Estimating Creatinine Clearance

Note: this is the original Cockcroft-Gault formula for estimating creatinine clearance and should be used only in patients with stable renal function.

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31-41.

### Cockcroft-Gault Formula for Estimating Creatinine Clearance

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times \text{Lean Body Weight (kg)}}{\text{Serum Creatinine (mg/dL)} \times 72} \quad (\times 0.85 \text{ if female})$$