

# Treatment of Hepatitis C in Patients with Renal Impairment

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

Lesson 3: [Treatment of Hepatitis C in Patients with Renal Impairment](#)

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## Background and Definitions

**Interaction of Hepatitis C Infection and Renal Disease:** Persons infected with hepatitis C virus (HCV) can develop kidney disease as a result of extrahepatic manifestation of HCV or as a disease process independent of the HCV infection. In addition, hemodialysis has been a risk factor for acquiring HCV infection, with 8.4% of hemodialysis patients in the United States having chronic HCV in the year 2000. Several studies have shown that patients on chronic hemodialysis have an increased overall mortality risk if they have chronic hepatitis C infection (when compared with those on dialysis who do not have hepatitis C infection). There are also some data showing that chronic hepatitis C may be a risk factor for developing renal cell carcinoma. Chronic hepatitis C infection has also been associated with an accelerated course of renal disease in HIV-infected persons. Extrahepatic manifestations related to HCV, including immune complex-related renal disease, can require urgent HCV treatment to resolve or prevent further organ damage.

**Definitions and Classification:** As part of evaluating and treating patients with hepatitis C 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 definitions.

- **Chronic Kidney Disease (CKD):** Chronic kidney disease is defined based on the presence of either kidney damage or decreased kidney function for three or more months, irrespective of cause.
- **Glomerular Filtration rate (GFR):** GFR is generally considered to be the best index of overall kidney function. The GFR varies in normal individuals by age and sex, dietary protein intake, and possibly by race-ethnicity. 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](#)). The GFR is equal to the sum of the filtration rates in all of the functioning nephrons, but since the GFR cannot be measured directly, it is usually estimated from serum markers. The gold standard for assessment of GFR is the renal inulin clearance test, but this method is highly complex and not practical for routine clinical purposes. Accordingly, several methods, including the Cockcroft-Gault formula and the Modification of Diet in Renal Disease (MDRD), have been utilized in clinical practice to estimate GFR.
- **Creatinine Clearance (CrCl):** The 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 the creatinine clearance based on the serum creatinine, patient age, body mass in kilograms, and sex ([Figure 2](#)). Normal values are 95 to 145 mL/min in men and 75 to 115 mL/min in women. This

formula is less accurate in weight extremes. A more accurate, but less practical, determination of creatinine clearance can be made with a 24-hour urine collection. The creatinine clearance is then calculated by dividing the 24-hour urine creatinine by the serum creatinine; the 24-hour urine creatinine is equal to the urine creatinine concentration multiplied by urine volume. There are several limitations to the 24-hour urine creatinine clearance that can cause inaccuracies, such as an incomplete urine collection.

- **Staging of Kidney Disease:** Guidelines such as the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines state that among patients who are diagnosed using the criteria described above, staging of CKD should be done according to the cause of disease, category of eGFR and category of albuminuria. The KDIGO classifies kidney disease based on the cause, patient's GFR and albuminuria categories ([Figure 3](#)), with an overall prognosis generated based on the both of these categories ([Figure 4](#)).

**Evaluation of Patients with Chronic HCV and Renal Insufficiency:** Serum creatinine should be measured and creatinine clearance or GFR should be estimated as part of a pre-treatment assessment for HCV patients. The CKD stage should be determined if renal function is abnormal. Complete blood count should be obtained as well, to assess for pre-treatment anemia.

## Hepatitis C Treatment Experience with Chronic Renal Disease

**Peginterferon and Ribavirin-Based Therapy in Patients with Renal Disease:** Renal insufficiency, regardless of the cause, has created problems with the use of peginterferon and ribavirin therapy for HCV, since the kidney plays a role in the catabolism and filtration of both interferon and ribavirin. With renal insufficiency, the clearance of interferon and peginterferon is reduced and overall exposure increased in proportion to the degree of renal dysfunction. Because of the very large molecular weight of interferon and peginterferon, hemodialysis does not remove significant amounts of interferon or peginterferon and thus has negligible effect on the clearance of interferon or peginterferon. In patients with chronic renal insufficiency, including those on hemodialysis, the reduced clearance of interferon, peginterferon, and ribavirin can accentuate treatment-related toxicity. In addition, since patients with kidney disease frequently have baseline anemia, ribavirin-induced hemolytic anemia can put these patients at greater risk of developing severe treatment-related anemia. Therefore, limited treatment of HCV in patients with renal disease has occurred with a regimen consisting of peginterferon and ribavirin, due to potential enhanced medication toxicity and the potential need to significantly reduce medication doses. The use of boceprevir is problematic since it requires peginterferon and ribavirin. Because of the high rates of hepatitis C treatment-related toxicity that occur in patients with advanced renal disease, most major randomized clinical trials have excluded patients with renal disease. The following summarizes major studies with the use of interferon-based therapies in patients with renal insufficiency.

- **Interferon Monotherapy:** In 2003, Russo and colleagues published a meta-analysis of 11 studies and 213 patients on chronic hemodialysis who receive interferon alfa monotherapy for treatment of hepatitis C infection. Analysis of the 8 studies in which a total of 153 patients received interferon alfa-2b (*Intron A*) 3 million units three times per week for 6 to 12 months revealed a pooled SVR rate of 33% (range 19 to 68%), with a subanalysis showing a pooled SVR rate of 26% in the 123 patients with genotype 1 infection. Overall, 45 (30%) of the 152 patients discontinued therapy because of side effects, but no treatment-related deaths were reported. Three studies in this meta-analysis utilized interferon doses greater than 3 million units three times per week and showed lower SVR rates due to high rates of discontinuation related to side effects. A subsequent meta-analysis published in 2008 by Gordon included 20 studies with interferon treatment and the overall SVR rate was 41%, with 26% of the patients discontinuing treatment due to adverse effects.
- **Peginterferon Monotherapy:** In a 2010 meta-analysis of clinical trials using peginterferon monotherapy for hepatitis C treatment in patients on chronic hemodialysis, Fabrizi and coworkers reported a pooled SVR rate of 33% and a dropout rate of 23%. The meta-analysis included 16 clinical trials, with a total of 254 patients.
- **Peginterferon plus Ribavirin:** In 2014, Fabrizi and colleagues published a meta-analysis of 11 studies involving 287 patients on chronic hemodialysis who received treatment with peginterferon alfa (2a or 2b) plus ribavirin; the summary SVR rate was 60% and summary dropout rate was 18%. The SVR results were similar with peginterferon alfa-2a and peginterferon alfa-2b. In a recent large randomized controlled study (HELPER-1), 205 treatment-naïve patients with genotype 1 HCV on chronic hemodialysis were randomized to receive a 48-week course with peginterferon alfa-2a 135 mcg weekly monotherapy or peginterferon alfa-2a with ribavirin 200 mg daily; the SVR 24 rates were significantly higher in the group receiving dual therapy (64% versus 33%) ([Figure 5](#)). In a similar study (HELPER-2) patients with genotype 2 HCV on chronic hemodialysis were randomized to receive a 24-week course with peginterferon alfa-2a 135 mcg weekly with or without or ribavirin 200 mg daily. The patients receiving peginterferon plus ribavirin had an SVR 24 rate of 74% compared with only 44% in those receiving peginterferon alone ([Figure 6](#)).
- **Peginterferon plus Ribavirin plus First-Generation Protease Inhibitor:** Very limited data exist with the use of peginterferon plus ribavirin plus either boceprevir or telaprevir in patients with chronic renal insufficiency. The potential use of telaprevir in patients with renal insufficiency is now irrelevant since telaprevir is no longer manufactured in the United States. There are no published studies in hemodialysis patients with chronic hepatitis C treated with

a boceprevir-containing regimen.

**Use of New Direct-Acting Agents in Patients with Renal Disease:** The availability of new direct-acting antiviral agents (DAAs) has sparked major enthusiasm for treating HCV-infected patients with renal impairment. The following summarizes key studies involving use of new DAA-based therapy in patients with chronic renal insufficiency.

- **Daclatasvir:** In a recent study (AI444-063), investigators compared the pharmacokinetics and safety of a single 60 mg dose of daclatasvir in patients with renal failure (moderate, severe, and hemodialysis) with healthy controls. None of the patients in the study had hepatitis C infection. The increases in daclatasvir levels in patients with renal failure were within the normal range of variability and patients tolerated the dose well.
- **Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir:** In the RUBY-1 trial, investigators treated HCV-infected patients with stage 4 or 5 renal disease, including patients on hemodialysis, with a 12-week regimen of ombitasvir-paritaprevir-ribavirin and dasabuvir, with or without ribavirin. All patients enrolled in the initial phase had genotype 1 chronic HCV infection, were treatment-naïve, and had noncirrhotic liver disease. In the preliminary analysis, 10 (100%) of 10 treated patients achieved a sustained virologic response 4 weeks after completion of therapy (SVR4) and no treatment related serious adverse events occurred.
- **Sofosbuvir-Based Therapy:** In the HCV TARGET trial, investigators reported findings from a longitudinal cohort study of 1893 patients using one of four sofosbuvir-containing regimens: (1) sofosbuvir plus peginterferon plus ribavirin, (2) sofosbuvir plus ribavirin, (3) sofosbuvir plus simeprevir, and (4) sofosbuvir plus simeprevir plus ribavirin. Overall, the SVR12 rates were high (81 to 89%) across different levels of baseline renal insufficiency ([Figure 7](#)), with the one exception that cirrhotic patients with estimated GFR less than 30 ml/min/1.73m<sup>2</sup> had lower SVR12 rates. Rates of treatment-related anemia were higher in patients with more advanced renal disease. A phase 2 trial is underway using a 24-week course of sofosbuvir plus ribavirin for patients with hepatitis C genotype 1 or 3 and renal insufficiency (CrCl less than 30 ml/min and not on dialysis); in this trial sofosbuvir will be given at a dose of either 200 mg or 400 mg once daily and ribavirin at a reduced dose of 200 mg once daily.
- **Sofosbuvir (low dose) plus Simeprevir:** In a small study involving 15 patients with renal insufficiency, including 12 on dialysis, Kalyan and coworkers treated patients with genotype 1 HCV and chronic renal insufficiency with standard-dose simeprevir and low-dose sofosbuvir (200 mg daily or 400 mg every other day); the treatment duration was 12 weeks in 14 of the patients and 24 weeks in 1 patient with cirrhosis. Overall, 13 (87%) of the 15 patients achieved an SVR12. In another small study, 12 patients with advanced renal disease (CrCl less than 30 ml/min) received standard-dose simeprevir and sofosbuvir and all 12 achieved an SVR12. A phase 2a, single arm trial is planned to examine the safety, efficacy, tolerability, and pharmacokinetics of a 12-week course of simeprevir plus daclatasvir in patients with HCV genotype 1b or 4 and renal disease (either severe renal impairment or end-stage renal disease on hemodialysis).
- **Grazoprevir and Elbasvir (Investigational):** In C-SURFER, a phase 2/3 trial involving patients with chronic HCV genotype 1 and advanced renal disease (stage 4 or 5), investigators reported findings using a 12-week course of the investigational agents grazoprevir and elbasvir. Enrollment included treatment-naïve patients (83%) and treatment-experienced patients (17%) who had failed a peginterferon-based regimen. Overall, 115 (99%) of 116 patients treated achieved an SVR12.

## Dosing of HCV Medications in Patients with Renal Impairment

**Overview of AASLD/IDSA Recommended Dosing Adjustment for Patients with Renal Impairment:** Very limited data exist regarding the use of newer direct-acting antiviral agents in patients with severe renal impairment, including those on hemodialysis. The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America (AASLD/IDSA) guidance for hepatitis C provides recommendations for dosage of medications in patients with renal insufficiency, including those with severe renal impairment or end-stage renal disease, in the section [Unique Patient Populations: Patients with Renal Impairment](#). For a summary of the recommendations for the treatment of HCV in patients with renal impairment see the [Summary Box](#) for this topic. In addition, the following summary outlines key items from the AASLD/IDSA guidance:

**Patients with Mild Renal Impairment (CrCl 50 to 80 mL/min):** No dosage adjustment needed when using any of the recommended agents or regimens to treat HCV.

**Patients with Moderate Renal Impairment (CrCl 30 to 50 mL/min):** No dosage adjustment needed when using standard dosing of any of the following medications or regimens: (a) daclatasvir, (b) ledipasvir-sofosbuvir, (c) ombitasvir-paritaprevir-ritonavir, (d) ombitasvir-paritaprevir-ritonavir plus dasabuvir, (e) simeprevir, (f) sofosbuvir, or (g) peginterferon alfa-2a. The dose of peginterferon alfa-2b should be reduced by 25% (1.125 mcg/kg once weekly) and the ribavirin dosing should be reduced to a schedule of 200 mg alternating with 400 mg every other day.

**Patients with Severe Renal Impairment (CrCl less than 30 mL/min) or End-Stage Renal Disease:** The following regimens are recommended, based on genotype, when the urgency to treat is high, the patient does not have cirrhosis, and renal transplantation is not an immediate option.

- **Genotype 1a:** The recommended regimen is standard dose ombitasvir-paritaprevir-ritonavir and dasabuvir in combination with reduced-dose ribavirin (200 mg three times weekly to 200 mg once daily). See details below on caution regarding use of ribavirin in this setting.
- **Genotype 1b:** The recommended regimen is standard dose ombitasvir-paritaprevir-ritonavir plus dasabuvir, but note that limited data exist with this regimen in patients with renal failure.
- **Genotype 2:** The recommended regimen is peginterferon plus dose-adjusted ribavirin.
- **Genotype 3:** The recommended regimen is peginterferon plus dose-adjusted ribavirin.
- **Genotype 4:** The recommended regimen is standard dose ombitasvir-paritaprevir-ritonavir, but note that limited data exist with this regimen in patients with renal failure.
- **Genotype 5 or 6:** The recommended regimen is peginterferon plus dose-adjusted ribavirin.
- **Peginterferon Dosing:** In patients with severe renal insufficiency, including those with end-stage renal disease, the dose of peginterferon alfa-2a should be reduced to 135 mcg once weekly and the dose of peginterferon alfa-2b should be reduced by 50% (to 1.0 mcg/kg once weekly).
- **Ribavirin Dosing:** The recommended ribavirin dose with severe renal disease, including end-stage renal disease is 200 mg/day. Most experts recommend starting the dose at 200 mg three times weekly and titrating up to 200 mg/day as tolerated. Caution should be exerted when using ribavirin in patients with renal failure because of the risk of severe hemolysis. In addition, ribavirin use should be restricted to patients who have a baseline hemoglobin greater than 10 g/dL and it should be discontinued if the hemoglobin level decreases by more than 2 g/dL despite the use of erythropoietin.
- **Patients who are Ribavirin Intolerant or Ineligible to Receive Ribavirin:** In this situation, expert consultation is recommended to evaluate for possible use of a sofosbuvir-containing regimen.

**Individual Drug Dosing Recommendations:** The following (in alphabetical order) summarizes recommended dosing information from the drug product information and dosage recommendations in the AASLD/IDSA guidance for FDA-approved medications for treatment of hepatitis C in patients

with renal impairment. Of note, the medication daclatasvir was recently approved by the FDA (after the most recent version of the dosage recommendations in the AASLD/IDSA guidance); daclatasvir does not need to be adjusted in patients with any degree of renal impairment.

- **Boceprevir:** Boceprevir undergoes extensive hepatic metabolism and the route of elimination is via feces with minimal urinary excretion. No dose adjustment of boceprevir is required in patients with renal insufficiency.
- **Daclatasvir:** Daclatasvir is highly plasma bound and primarily undergoes extensive metabolism by the liver. Less than 10% of daclatasvir is renally excreted. There are limited data regarding the use of daclatasvir in patients with a CrCl less than 30 mL/min or in patients on hemodialysis.
- **Ledipasvir-Sofosbuvir:** For patients with mild to moderate renal impairment, no dosage adjustment of ledipasvir-sofosbuvir is recommended. There are insufficient data regarding the safety and efficacy of ledipasvir-sofosbuvir in patients with severe renal impairment (eGFR less than 30 mL/min/1.73m<sup>2</sup>) or end-stage renal disease requiring dialysis.
- **Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir:** The prescribing information for ombitasvir-paritaprevir-ritonavir and dasabuvir states that no dosage adjustment is required for patients with mild, moderate, or severe renal impairment, but notes this regimen has not been studied in patients on hemodialysis. The AASLD/IDSA hepatitis C treatment guidance recommends standard dosing with this regimen in patients with mild or moderate renal impairment, but states data are not available for patients with severe renal disease or hemodialysis.
- **Peginterferon alfa-2a:** With renal insufficiency, the clearance of peginterferon is reduced and overall exposure increased in proportion to the degree of renal dysfunction. Hemodialysis, however, has negligible effect on the clearance of peginterferon alfa-2a. The peginterferon alfa-2a prescribing information recommends that patients with any degree of renal impairment should undergo close monitoring for laboratory abnormalities and adverse reactions, and creatinine clearance. In addition, the prescribing information recommends reducing the dose of peginterferon alfa-2a (from a standard dose of 180 mcg once weekly to 135 mcg once weekly) in patients who have creatinine clearance less than 30 ml/min, including those on hemodialysis; if interferon-related adverse reactions or laboratory abnormalities develop, the dose may be reduced further to 90 mcg once weekly. The AASLD/IDSA hepatitis C treatment guidance also recommends reducing the dose of peginterferon alfa-2a to 135 mcg once weekly in patients with a creatinine clearance less than 30 ml/min and for patients on hemodialysis.
- **Peginterferon alfa-2b:** With renal insufficiency, the clearance of peginterferon is significantly reduced in patients with severe renal disease, but hemodialysis, has negligible effect on the clearance of peginterferon alfa-2b. The prescribing information for peginterferon alfa-2b recommends reducing the dose of peginterferon alpha-2b by 25% for patients with moderate renal dysfunction (creatinine clearance 30 to 50 ml/min) and by 50% for those with severe renal insufficiency (creatinine clearance 10 to 29 ml/min, including those on dialysis). The prescribing information recommends discontinuing peginterferon alfa-2b if renal function decreases during the treatment course. The AASLD/IDSA/IAS-USA hepatitis C guidance recommends the same dose reductions.
- **Ribavirin:** Ribavirin is manufactured by multiple companies and is available as a generic preparation. In general, concern exists with the use of ribavirin in patients with renal impairment since ribavirin levels will increase 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 less than 50 ml/min. The package insert for *CoPegus* permits the use of ribavirin in patients with an estimated glomerular filtration rate less than 50 ml/min if the dose is reduced. The AASLD/IDSA/IAS-USA hepatitis C guidance table recommends that patients with a creatinine clearance of 30 to 50 mL/min have 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 that patients who have severe renal disease (creatinine

clearance less than 30 mL/min), end stage renal disease, or hemodialysis reduce the dose of ribavirin to 200 mg once daily.

- **Simeprevir:** Based on recommendations in the product information, simeprevir does not require dosage adjustment for mild, moderate, or severe renal impairment. No clinically significant differences in pharmacokinetics were observed in HCV-noninfected volunteers with mild, moderate, or severe renal impairment. In addition, because simeprevir is highly protein bound, the levels of simeprevir are unlikely to be significantly altered by hemodialysis. Creatinine clearance was not identified as a significant factor in pharmacokinetics of simeprevir. Simeprevir, however, has not been studied in patients with end-stage renal disease or in patients on hemodialysis. If simeprevir is used in patients with renal insufficiency, no dose adjustment is recommended (it should be given at full dose). The AASLD/IDSA/IAS-USA hepatitis C guidance recommends standard dosing in patients with mild, moderate, or severe renal impairment, but does not have a recommendation for end-stage renal disease or hemodialysis based on the lack of data.
- **Sofosbuvir:** The main sofosbuvir metabolite (GS-331007) is eliminated primarily via renal clearance. No dosage adjustment is required for patients with mild or moderate renal impairment (CrCl greater than or equal to 30 ml/min). Pharmacokinetic studies using a single 400 mg dose of sofosbuvir in HCV-negative patients with renal impairment show a significant increase in serum levels of sofosbuvir and the metabolite GS-3310007, when compared to levels in persons with normal renal function. Nevertheless, the safety and efficacy of sofosbuvir has not been established in patients with severe renal impairment (CrCl less than 30 ml/min). At the time of this writing, inadequate data exist regarding use of sofosbuvir in patients with severe renal impairment (CrCl less than 30 ml/min) or end-stage renal disease requiring dialysis. Thus, based on available data, sofosbuvir may be used in the setting of mild-moderate renal impairment, but should not be used for severe renal impairment (CrCl less than 30 ml/min or in patients on hemodialysis).
- **Telaprevir:** Telaprevir undergoes extensive hepatic metabolism and the route of elimination is via feces with minimal urinary excretion. No dose adjustment of telaprevir is required in patients with renal insufficiency. Telaprevir is no longer manufactured in the United States.

## Treatment of HCV in Setting of Renal Transplantation

**General Approach to Hepatitis C Treatment and Renal Transplantation:** Treatment of hepatitis C in patients prior to and after renal transplantation presents several challenges. For HCV-infected patients who undergo renal transplantation, the hepatitis C infection can have both hepatic and extrahepatic clinical consequences in the post-transplantation period. In addition, the use of interferon or peginterferon in the treatment of hepatitis C in the post-renal transplant setting is problematic because these medications significantly increase the risk of allograft rejection. For these reasons, most experts recommend that all HCV-infected renal transplantation candidates undergo evaluation for potential treatment of hepatitis C prior to renal transplantation. Nevertheless, in some patients, treatment of hepatitis C cannot be given prior to renal transplant; in this situation, chronic hepatitis C infection should not be considered a contraindication for renal transplantation since long-term patient survival is better with renal transplantation than with chronic dialysis.

**Approach Prior to Renal Transplantation:** The general approach to treating hepatitis C prior to renal transplant is similar to the approach of treating patients with chronic renal insufficiency who are not waiting for renal transplantation. If interferon or peginterferon is used in the treatment regimen for the treatment of hepatitis C, the treatment course should be completed at least 4 weeks prior to proceeding to renal transplantation.

**Approach Post Renal Transplantation:** In post-transplantation, despite most patients having excellent recovery of renal function, the use of interferon or peginterferon is usually avoided due to the risk of inducing renal graft rejection, particularly in the first year following transplantation. The 2008 Kidney Disease Outcome Quality Initiative (KDOQI) Clinical Practice Guidelines recommend use of an interferon regimen only when serious HCV-related outcomes are expected after transplantation, such as fibrosing cholestatic hepatitis, rapid cirrhosis, or cryoglobulinemic glomerulonephritis in the transplanted kidney. Use of new and future direct acting antiviral agents in patients with end-stage renal disease, including those on dialysis, has been complicated by sparse clinical efficacy and safety data. In the post-transplantation setting, however, patients typically have good recovery of renal function, and use of new directly acting antiviral agents may provide excellent interferon-free treatment options.

**Treatment Options Post Renal Transplantation:** Consideration for drug-drug interactions is extremely important in the post-transplantation period, particularly with regard to immunosuppressant medications, such as cyclosporine or tacrolimus. Investigators will need to establish that use of all-oral direct-acting agents in this setting does not increase the risk for renal allograft rejection. In a pilot study from France, use of various sofosbuvir-based regimens for HCV treatment in 25 patients after renal transplantation was highly successful (100% SVR12 rate) and very well tolerated. A phase 2 international trial is underway with ledipasvir-sofosbuvir given for 12 or 24 weeks in kidney transplantation recipients with chronic HCV genotype 1 or 4 infection. The use of the regimen ombitasvir-paritaprevir-ritonavir and dasabuvir also has potential for use in the post renal transplant setting, but the ritonavir cytochrome p450 inhibition is potentially significant and may require cyclosporine or tacrolimus dose adjustments. In addition, the combination of daclatasvir and sofosbuvir may provide an option in the post-transplantation setting.

## Summary Points

- Renal function, including an estimation of CrCl or GFR, must be assessed before initiating any hepatitis C treatment. Based on the estimated CrCl or GFR value, patients 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
- For patients with mild renal impairment, no dose adjustments are needed for any of the medications used to treat HCV.
- For patients with moderate renal impairment, standard doses are recommended for the direct-acting antiviral agents and peginterferon alfa-2a. Peginterferon alfa-2b requires a 25% dose reduction and ribavirin doses should be reduced to a schedule of 200 mg alternating with 400 mg every other day.
- For patients with severe renal impairment, including those with end-stage renal disease, the peginterferon alfa-2a dose should be reduced to 135 mcg per week; the peginterferon alfa-2b requires a 50% dose reduction. Adjustments are needed for any of the medications used to treat HCV. 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 patients with renal failure because of the risk of severe hemolysis. Ribavirin should be discontinued if the hemoglobin level decreases by more than 2 g/dL despite the use of erythropoietin.
- Based on the available limited data, the AASLD/IDSA hepatitis C guidance provides genotype-specific recommendation for the treatment of patients with severe renal disease, including those with end-stage renal disease. Several trials are underway for the treatment of HCV in patients with severe renal disease.
- Patients with hepatitis C infection who require renal transplantation should be evaluated for hepatitis C treatment; the treatment of hepatitis C prior to renal transplantation is strongly preferred over treatment of hepatitis C post renal transplantation.
- A phase 2 trial is underway examining a 12- and 24-week course of ledipasvir-sofosbuvir to treat hepatitis C in the post-renal transplant setting.

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## Figures

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

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. This formula should be used only in patients with stable renal function. In addition, the formula performs better when adjusted for body surface area, particularly in patients with diminished 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**

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

**Figure 3 (Image Series) - Glomerular Filtration Rate and Albumin Categories in Chronic Renal Disease (Image Series) - Figure 3 (Image Series) - Glomerular Filtration Rate and Albumin Categories in Chronic Renal Disease**

**Image 3A: Glomerular Filtration Rate Categories**

GFR Categories in Chronic Kidney Disease (CKD)		
GFR Category	GFR (mL/min/1.73 m <sup>2</sup> )	Description
<sup>^</sup> G1	≥90	Normal or High
<sup>^</sup> 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

Abbreviations: GFR = glomerular filtration rate  
<sup>^</sup>In the absence of evidence of kidney disease, neither G1 or G2 fulfill the criteria for CKD  
 \*Relative to young adult level

**Figure 3 (Image Series) - Glomerular Filtration Rate and Albumin Categories in Chronic Renal Disease**  
**Image 3B: Albumin Categories**

Albuminuria Categories in Chronic Kidney Disease (CKD)				
Category	AER (mg/24 hours)	ACR (approximate equivalent)		Terms
		(mg/mL)	(mg/g)	
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased*
A3	>300	>30	>300	Severely increased**

Abbreviations: AER=albumin excretion rate; ACR=albumin-to-creatinine ratio  
 \*Relative to young adult level  
 \*\*Including nephrotic syndrome (albumin excretion usually >2200 mg/24 hours [ACR > 2200 mg/g; > 220 mg/mmol])

**Figure 4 Prognosis of Chronic Kidney Disease based on GFR and Albumin Categories**

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012				Persistent albuminuria categories		
				Description and Range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g	30-300 mg/g	>300 mg/g
GFR Categories (mL/min/1.73 m <sup>2</sup> ) Description and Range	G1	Normal or High	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

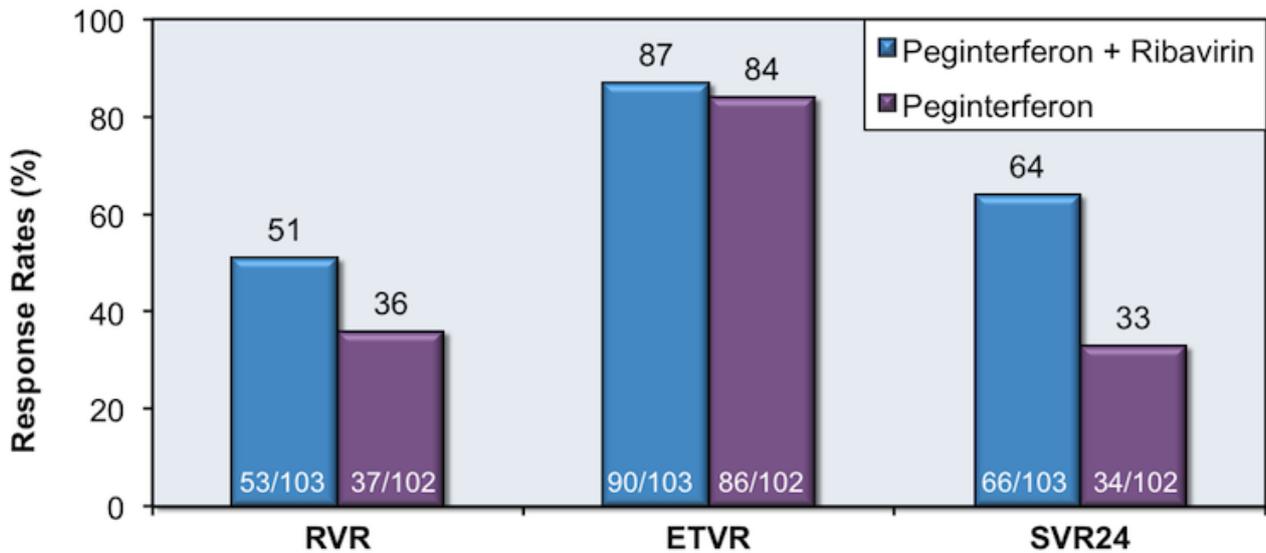
Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

**Figure 5 Treatment of HCV Genotype 1 in Patients Receiving Hemodialysis**

In this trial, patients received a 48-week course of peginterferon alfa-2a (135 mcg 1x/week with or without ribavirin 200 mg once daily).

Source: Liu CH, Huang CF, Liu CJ, et al. Pegylated interferon- $\alpha$ 2a with or without low-dose ribavirin for treatment-naive patients with hepatitis C virus genotype 1 receiving hemodialysis: a randomized trial. *Ann Intern Med.* 2013;159:729-38.

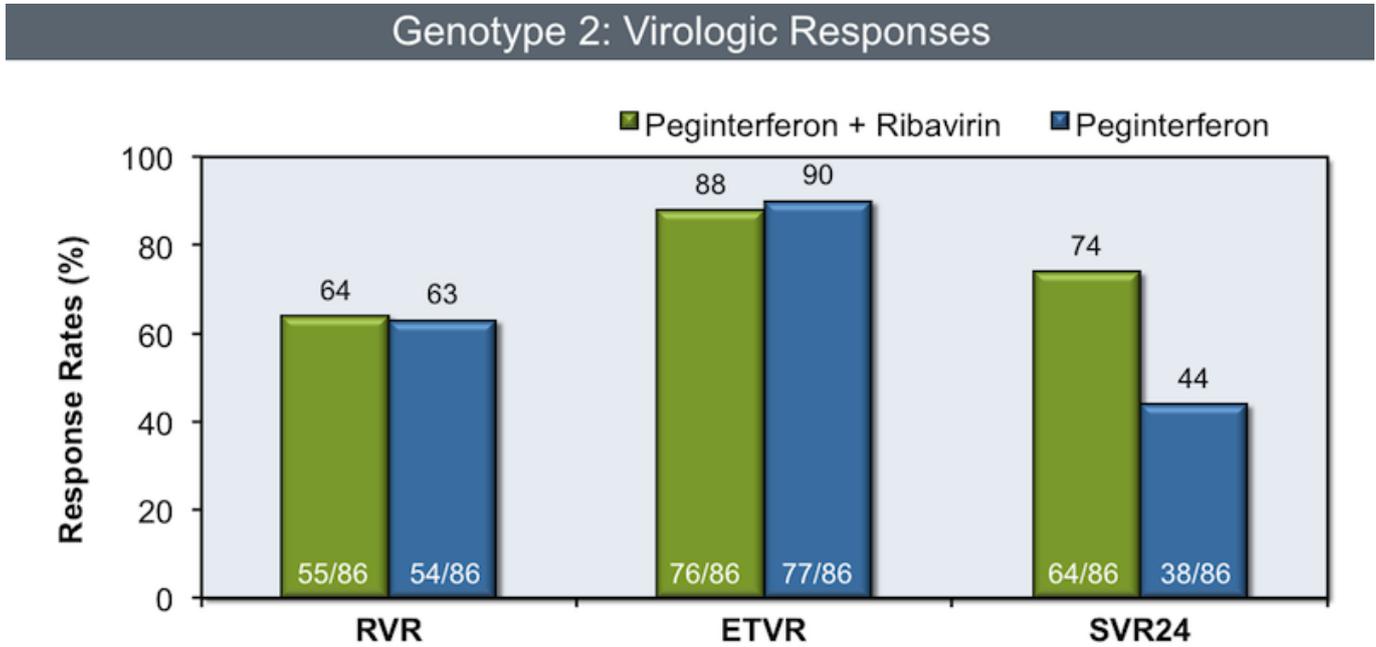
**Genotype 1: Virologic Responses**



**Figure 6 Treatment of HCV Genotype 2 in Patients Receiving Hemodialysis**

In this trial, treatment-naive patients with HCV genotype 2 infection received a 24-week course of peginterferon alfa-2a (135 mcg 1x/week with or without ribavirin 200 mg once daily).

Source: Liu CH, Liu CJ, Huang CF, et al. Peginterferon alfa-2a with or without low-dose ribavirin for treatment-naive patients with hepatitis C virus genotype 2 receiving haemodialysis: a randomised trial. Gut. 2015;64:303-11.



**Figure 7 Sofosbuvir-Containing Regimens in Patients with Renal Disease: HCV TARGET**

This graph shows preliminary findings from patients with renal diseases who received HCV treatment with sofosbuvir-containing regimens.

Source: Saxena V, Korashy FM, Sise M, et al. Safety and efficacy of sofosbuvir-containing regimens in hepatitis C infected patients with reduced renal function: real-world experience from HCV-TARGET. 50th Annual Meeting of the European Association for the Study of the Liver; April 22-26, 2015; Vienna, Austria. Abstract LP08.

