Executive Summary of the KDIGO 2022 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease

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Infection with the hepatitis C virus (HCV) has adverse liver, kidney, and cardiovascular consequences in patients with chronic kidney disease (CKD), including those on dialysis therapy or with a kidney transplant. Since the publication of the Kidney Disease: Improving Global Outcomes (KDIGO) HCV Guideline in 2018, advances in HCV management, particularly in the field of antiviral therapy and treatment of HCV-associated glomerular diseases, coupled with increased usage of HCV-positive kidney grafts, have prompted a reexamination of the 2018 guideline. As a result, the Work Group performed a comprehensive review and revised the 2018 guidance. This Executive Summary highlights key aspects of the updated guideline recommendations for 3 chapters: Chapter 2: Treatment of HCV infection in patients with CKD; Chapter 4: Management of HCV-infected patients before and after kidney transplantation; and Chapter 5: Diagnosis and management of kidney diseases associated with HCV infection.

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Hepatitis C virus (HCV) infection in the chronic kidney disease (CKD) population has presented some unique challenges. These include its high prevalence among dialysis patients, transmission within dialysis units and by infected grafts, and the resultant increased risk of progressive liver disease in chronically infected patients who remain on dialysis, as well as in kidney transplant recipients. Additional challenges in these populations previously included potentially reduced tolerance of antiviral therapy and choice of appropriate regimen. In 2008, Kidney Disease: Improving Global Outcomes (KDIGO) published a guideline[1] addressing

HCV management in CKD, and in 2018, a complete update of the guideline was produced that encompassed the major advances in HCV management that had occurred in the preceding decade,[2] such as noninvasive methods for evaluating liver-disease severity and the availability of oral direct-acting antiviral (DAA) therapies. Since the 2018 guideline was published, additional DAA regimens are being used in the CKD population and kidney transplant recipients. In addition, the increasing experience with the use of organs from HCV-infected donors has expanded allograft access in kidney transplantation. The role of antiviral therapy in treating glomerulonephritis due to HCV infection has also been more clearly defined. As a result of these advances, we undertook an update on portions of the 2018 guideline focusing on these evolving areas in Chapters 2, 4, and 5. Chapters 1 and 3, addressing detection and evaluation of HCV in CKD, and prevention of its transmission in hemodialysis units, respectively, remain current and did not warrant any substantive revision; thus, they remain unchanged from the 2018 guideline. This Executive Summary presents the revised recommendations and highlights the rationale for the revisions to Chapters 2, 4, and 5.[3] These recommendations fully replace all recommendations from the equivalent chapters in the 2018 guideline.[2]

Chapter 2: Treatment of HCV infection in patients with CKD

DAA therapy is highly effective and well-tolerated (with rare serious adverse events) in patients across all stages of CKD, including in patients undergoing dialysis and following kidney transplantation. Sustained virologic response rates 12 weeks after treatment (SVR12) range from 92%–100% in all stages of CKD and across a variety of DAA regimens. Serious adverse event rates attributed to DAA generally are reported in fewer than 1% of treated patients. As a result, interferon-based therapy is no longer used in HCV. With the introduction of several DAA regimens active against all HCV genotypes (pangenotypic), awareness of HCV genotype is less of a concern in antiviral therapy. However, in some countries, genotype-specific DAA regimens are more readily accessible, and use of these regimens thus requires ascertainment of HCV genotype prior to treatment.

Multiple pangenotypic and genotype-specific DAA regimens have been investigated in CKD G4–G5ND (ND, non-dialysis), G5D (D, dialysis), and in kidney transplant recipients, and they are consistently highly effective and well-tolerated. Since the publication of the KDIGO 2018 HCV guideline, evidence has mounted that sofosbuvir, a key component of several regimens, is safe for all stages of CKD, including for individuals with low glomerular filtration rate (GFR) or undergoing dialysis. This development is important because in many nations, the only available DAA regimens are those that are sofosbuvir-based. Additionally, protease inhibitors ("-previrs" such as simeprevir, paritaprevir, and grazoprevir) are contraindicated in patients with Child-Pugh B and C cirrhosis.

In patients with normal kidney function, DAA therapy arrests progression of liver disease and reduces its complications, while improving patient survival with acceptable toxicity. Additionally, evidence exists for improvement in cardiovascular disease following anti-HCV therapy in the general population. These benefits of DAA therapy potentially translate to patients with CKD as well. The KDIGO HCV Work Group agreed with other specialty guidelines, including the American Association for the Study of Liver Diseases/Infectious Diseases Society of America Guideline [AASLD/IDSA]), that HCV treatment should be withheld in patients with a very limited life expectancy (https://www.hcvguidelines.org/evaluate/when-whom).

CKD G1–G5ND. As shown in Figure 1, a number of pangenotypic regimens can be used, irrespective of GFR. If a non-pangenotypic regimen is contemplated, identification of specific genotype is necessary to determine its efficacy. Dose adjustment of DAA is not required in CKD G1–G5ND. Treatment duration varies by regimen (but currently is typically 12 weeks), presence of cirrhosis, and prior DAA therapy. The most recent recommendations should be confirmed by consulting the latest AASLD/IDSA guidelines (https://www.hcvguidelines.org) or the European Association for the Study of the Liver (EASL) guidelines (http://www.easl.eu/research/our-contributions/clinical-practice-guidelines) on HCV therapy.

CKD G5D. Similar to CKD G1–G5ND, multiple pangenotypic as well as genotype-specific regimens are available for patients with CKD G5D (Figure 1), with treatment durations varying based on DAA regimen as well as the presence or absence of cirrhosis and/or prior HCV treatment. DAA dose adjustment is also not required for patients with CKD G5D. The most recent recommendations should be confirmed by consulting the latest AASLD/IDSA or EASL guidelines on HCV therapy. The majority of data on DAA therapy in CKD G5D derives from patients undergoing hemodialysis with limited information on the safety and efficacy of DAA in patients undergoing peritoneal dialysis.

Kidney transplant recipients. Pangenotypic regimens, as well as genotype-specific regimens, are safe and effective in kidney transplant recipients. Most of the data for DAA use in kidney transplant recipients derive from individuals with GFR $\geq$30 ml/min per 1.73 m^2 (CKD G1T–G3T; Figure 1). Limited information on high efficacy and safety of DAA can be extrapolated from DAA use in the highly selected population of HCV-uninfected recipients of kidneys from HCV-infected donors who at least initially have low GFR. The major concern about DAA use in kidney transplantation is the potential for drug–drug interactions that could occur with concomitant use of immunosuppressive agents such as calcineurin and mTOR inhibitors. The most recent recommendations should be confirmed by consulting the latest AASLD/IDSA or EASL guidelines on HCV therapy as well as the University of Liverpool Hepatitis Drug Interactions website (http://www.hep-druginteractions.org).

Reactivation of hepatitis B virus infection with DAA therapy. With suppression of HCV replication, reactivation of HBV replication may occur in patients with current or prior

CHAPTER 2: TREATMENT OF HCV INFECTION IN PATIENTS WITH CKD

2.1: We recommend that all patients with CKD (G1-G5), on dialysis (G5D), and kidney transplant recipients (G1T-G5T) with HCV be evaluated for direct-acting antiviral (DAA)-based therapy as outlined in Figure 1 (*1A*).

2.1.1: We recommend that the choice of specific regimen be based on prior treatment history, drug–drug interactions, glomerular filtration rate (GFR), stage of hepatic fibrosis, kidney and liver transplant candidacy, and comorbidities (*1A*). If pangenotypic regimens are not available, HCV genotype (and subtype) should guide the choice of treatment (Figure 1).

CKD populations	Direct acting antiviral (DAA) regimens[a]	HCV genotypes	Quality of evidence (total N)[b]
G1–G3b,[c] not KTR	Any licensed DAA regimen	All	Not evaluated
G4–G5ND,[d] including KTR[e,f]	Sofosbuvir / Daclatasvir, 12 or 24 wk Glecaprevir / Pibrentasvir, 8 wk Grazoprevir / Elbasvir, 12 wk Sofosbuvir / Velpatasvir, 12 wk Sofosbuvir / Ledipasvir, 12 wk	All All 1a, 1b, 4 All All	High (571) High (132) High (857) Low (99) Very low (43)
G5D[g]	Sofosbuvir / Velpatasvir, 12 wk Glecaprevir / Pibrentasvir, 8 wk Sofosbuvir / Daclatasvir, 12 or 24 wk Sofosbuvir / Ledipasvir, 12 wk Grazoprevir / Elbasvir, 12 wk PrO ± D, 12 wk Daclatasvir / Asunaprevir, 24 wk	All All All All 1a, 1b, 4 1a, 1b, 4 1b	High (405) Moderate (529) Moderate (278) Moderate (220) Moderate (962) Moderate (582) Low (341)
KTR,[e] G1–G3b[c]	Sofosbuvir / Ledipasvir, 12 or 24 wk Sofosbuvir / Daclatasvir, 12 or 24 wk PrO ± D, 12 wk Grazoprevir / Elbasvir, 12 wk	All All 1a, 1b, 4 1a, 1b, 4	High (300) High (290) Very low (33) Very low (21)

Figure 1 | Direct-acting antiviral (DAA) regimens with evidence of effectiveness for various chronic kidney disease (CKD) populations. [a]The table includes only regimens that were evaluated by *at least 2 studies* in the specific CKD population and for which summary sustained virologic response at 12 weeks [wks] (SVR12) was >92%. Sofosbuvir monotherapy is excluded since current DAA regimens incorporate at least 2 agents. Other regimens may be appropriate for the above populations. Readers are encouraged to consult the Association for the Study of Liver Diseases (AASLD) or European Association for the Study of the Liver (EASL) guidelines for the latest information on various regimens. The suggested durations of treatment are those most commonly employed by the relevant studies. Studies commonly extended treatment for patients with cirrhosis, prior DAA failure, or for some genotypes. Readers should consult the AASLD or EASL guidelines, as needed, to determine optimal treatment duration. [b]The order of hepatitis C virus (HCV) regimens does not indicate a ranking or preferential order of selection. The regimens are presented in order of the quality of evidence, then by HCV genotype, then alphabetically. The differences in quality of evidence primarily relate to the numbers of evaluated patients and small differences in methodological quality of the underlying studies (see Guideline Supplementary Tables S5–S7). [c]Estimated glomerular filtration rate (eGFR) ≥30 ml/min per 1.73 m^2. [d]eGFR <30 ml/min per 1.73 m^2, not dialysis-dependent. [e] Regimens in kidney transplant recipients (KTRs) should be selected to avoid drug–drug interactions, particularly with calcineurin inhibitors. [f] Strength of evidence for CKD G4T-G5T is very low for all regimens. [g]Evidence primarily for patients on hemodialysis. Very few patients were on peritoneal dialysis. G, refers to the GFR category with suffix D denoting patients on dialysis and ND denoting patients not on dialysis; PrO±D, ritonavir-boosted paritaprevir and ombitasvir with or without dasabuvir.

2.1.2: Treat kidney transplant candidates in collaboration with the transplant center to optimize timing of therapy (*Not Graded*).

2.1.3: 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*).

2.1.4: We recommend that calcineurin inhibitor levels be monitored during and after DAA treatment in kidney transplant recipients (*1B*).

2.2: All patients with CKD (G1-G5), on dialysis (G5D), and kidney transplant recipients (G1T-G5T) with HCV should undergo testing for hepatitis B virus (HBV) infection prior to DAA therapy (*Not Graded*).

2.2.1: If hepatitis B surface antigen [HBsAg] is present, the patient should undergo assessment for HBV therapy (*Not Graded*).

2.2.2: If HBsAg is absent but markers of prior HBV infection (HBcAb-positive with or without HBsAb) are detected, exclude HBV reactivation with HBV DNA testing if levels of liver function tests rise during DAA therapy (*Not Graded*).

HBV infection. Testing for markers of HBV infection including hepatitis B surface antigen (HBsAg), total core antibody (anti-HBc antibody), and antibody to hepatitis B surface antigen (anti-HBs antibody) is indicated prior to DAA therapy. HBV antiviral therapy should be administered prior to DAA therapy if criteria for HBV treatment in accordance with AASLD or EASL are met.[4,5] If HBsAg is absent but markers of prior HBV infection (HBcAb-positive with or without HBsAb) are detected, HBV antiviral therapy is not required prior to DAA therapy, but aminotransferase levels should be checked regularly and HBV DNA testing should be performed if levels of liver function tests rise during DAA therapy. If HBV viremia is present, confirming reactivation as the reason for the rise in aminotransferases, therapy for HBV should be started.

Chapter 4: Management of HCV-infected patients before and after kidney transplantation

If left untreated, HCV infection decreases patient survival and allograft survival following kidney transplantation. However, for patients with CKD G5 or G5D and HCV infection, survival is still improved by kidney transplantation compared to remaining on chronic dialysis. DAA therapy has also been shown to be effective and well-tolerated in kidney transplant recipients.

4.1: Evaluation and management of kidney transplant candidates regarding HCV infection

4.1.1: We recommend kidney transplantation as the best therapeutic option for patients with CKD G5 irrespective of presence of HCV infection (*1A*).

4.1.2: We suggest that all kidney transplant candidates with HCV be evaluated for severity of liver disease and presence of portal hypertension prior to acceptance for kidney transplantation (*2D*).

4.1.2.1: We recommend that patients with HCV, compensated cirrhosis, and no portal hypertension undergo isolated kidney transplantation and that patients with decompensated cirrhosis or clinically significant portal hypertension (i.e., hepatic venous pressure gradient ≥10 mm Hg or evidence of portal hypertension on imaging or exam) undergo a simultaneous liver–kidney transplantation (*1B*). Treatment of those with mild-to-moderate portal hypertension should be determined on a case-by-case basis.

4.1.2.2: We recommend referring patients with HCV and decompensated cirrhosis for combined liver–kidney transplantation (*1B*).

4.1.3: Timing of HCV treatment in relation to kidney transplantation (before vs. after) should be based on donor type (living vs. deceased donor), wait-list times by donor type, center-specific policies governing the use of kidneys from HCV-infected deceased donors, and severity of liver fibrosis (*Not Graded*).

4.1.3.1: We recommend that all kidney transplant candidates with HCV be considered for DAA therapy, either before or after transplantation (*1A*).

4.1.3.2: We suggest that HCV-infected kidney transplant candidates with a living kidney donor be considered for treatment before or shortly after transplantation depending on the anticipated timing of transplantation (*2B*).

Management of HCV-infected kidney transplant candidates. An approach to the evaluation and management of HCV-infected kidney transplant candidates is presented in Figure 2. First, patients who are anti-HCV antibody–positive require confirmation of viremia (HCV RNA), and evaluation of the severity of liver disease and extent of fibrosis, typically by noninvasive means, is also needed as outlined in Chapter 1. If cirrhosis is suspected based on clinical findings or after assessment of liver fibrosis, additional evaluation is needed to determine if clinically significant portal hypertension is present. A wedged hepatic venous pressure gradient ≥10 mm Hg is consistent with significant portal hypertension. Patients with clinical evidence of decompensated cirrhosis (esophageal varices or other clinical findings, such as ascites or hepatic encephalopathy, among others) or significant portal hypertension should be evaluated for simultaneous liver–kidney transplant even if they have achieved SVR (Figure 2). In HCV-infected patients with compensated cirrhosis without portal hypertension or in those without evidence of cirrhosis, kidney transplantation alone is recommended as DAA therapy can prevent progression of liver disease (Figure 2). DAA therapy should be administered to all HCV-infected kidney transplant candidates, either before or after transplantation.

Timing of antiviral therapy. Factors guiding timing of HCV treatment (before vs. after kidney transplantation) include donor type (living vs. deceased donor), anticipated waiting-list time by donor type, severity of hepatic fibrosis, and

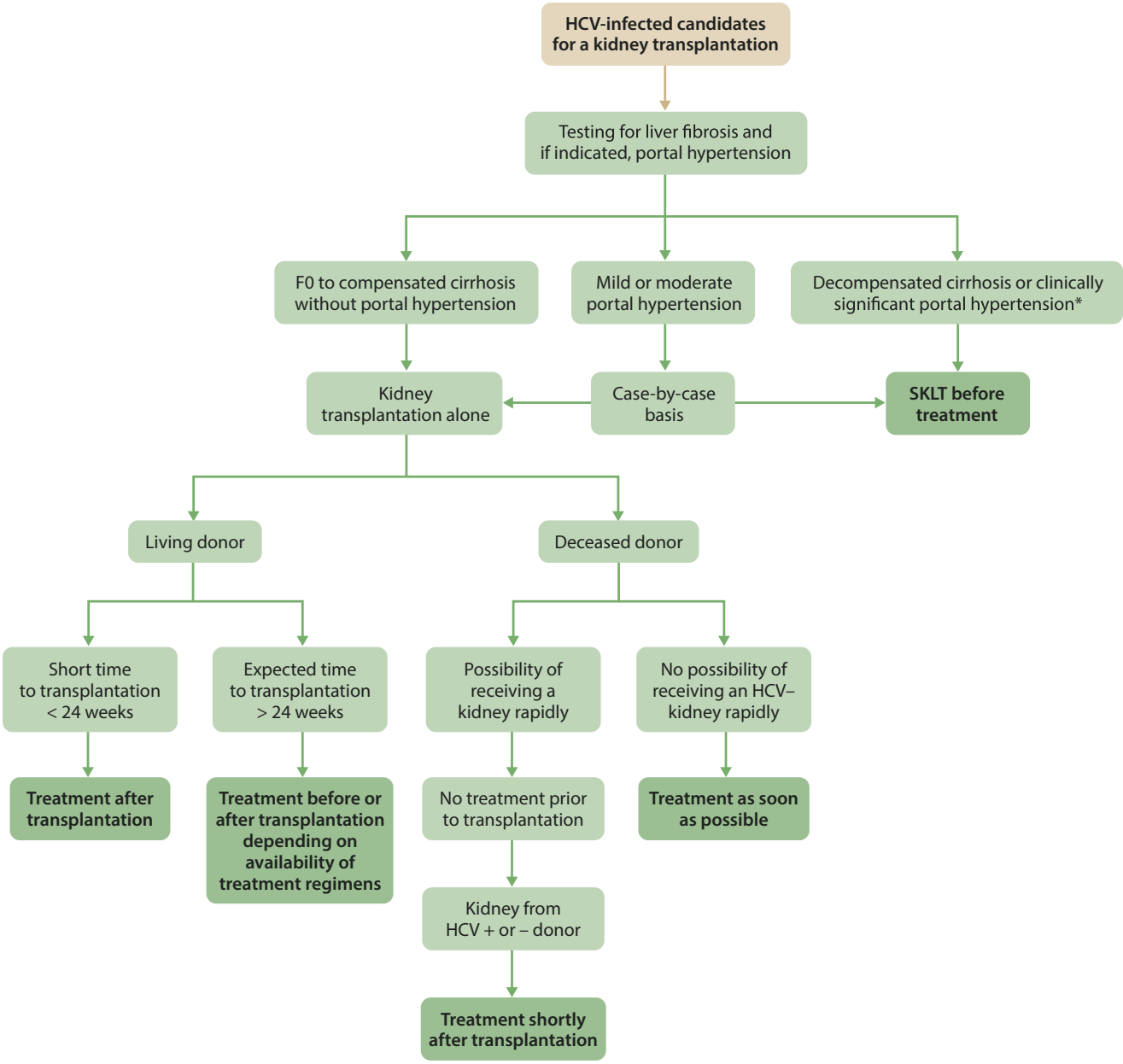

Figure 2 | Proposed management strategy in a hepatitis C virus (HCV)-infected kidney transplant candidate. *Clinically significant portal hypertension is defined as hepatic venous pressure gradient ≥10 mm Hg or evidence of portal hypertension on imaging or exam, e.g., ascites, esophageal varices, collaterals on imaging. F0, no scarring or fibrosis; SKLT, simultaneous kidney–liver transplantation.

willingness of the patient and program to accept an organ from an HCV-infected donor. In a patient with compensated cirrhosis or no cirrhosis whose waiting period for transplant is likely to be greater than 24 weeks, DAA therapy can be administered prior to transplant to allow treatment of 12 weeks duration with confirmation of SVR 12 weeks after its completion (Figure 2). HCV-infected kidney transplant candidates with an identified living kidney donor can be treated for HCV before or shortly after transplantation depending on the anticipated timing of transplantation.

4.2: Use of kidneys from HCV-infected donors

4.2.1: We recommend that all kidney donors be screened for HCV infection with both immunoassay and nucleic acid testing (NAT) (if NAT is available) (*1A*).

4.2.2: After assessment of liver fibrosis, HCV-infected potential living kidney donors who do not have cirrhosis should undergo HCV treatment before donation if the recipient is HCV-uninfected; they can be accepted for donation if they achieve sustained virologic response (SVR) and remain otherwise eligible to be a donor (*Not Graded*).

4.2.3: We recommend that kidneys from HCV-infected donors be considered regardless of HCV status of potential kidney transplant recipients (*1C*).

4.2.4: When transplanting kidneys from HCV-infected donors into HCV-uninfected recipients, transplant centers must ensure that patients receive education and are engaged in discussion with sufficient information to provide informed consent. Patients should be informed of the risks and benefits of transplantation with an HCV-infected kidney, including the need for DAA treatment (*Not Graded*).

4.2.5: When transplanting kidneys from HCV-infected donors into HCV-uninfected recipients, transplant centers should confirm availability of DAAs for initiation in the early post-transplant period (*Not Graded*).

Use of kidneys from HCV-infected living and deceased donors expands the donor pool, and their use should be encouraged. Previously, kidneys from HCV-infected deceased donors were offered only to HCV-infected recipients, which reduced waiting times for transplantation without a negative impact on patient survival. In this setting, DAA therapy should be administered post-transplant to prevent progression of liver disease and other extrahepatic complications of HCV.

Deceased donor transplantation from HCV-infected donors to uninfected recipients. More recently, kidneys from HCV-infected donors have been transplanted into HCV-uninfected recipients. For these patients, DAA therapy administered at the time of transplant or early thereafter is safe and effective to prevent complications of HCV infection in the recipient. Despite differing DAA regimens and timing of initiation, DAA treatment for 4–8 weeks has been associated with excellent rates of viral clearance (SVR12) as well as excellent allograft function and survival, with excellent patient survival rates at 1 year following transplant. Very short treatment duration (<8 days) have been more frequently associated with viral relapse; thus, a full 12-week treatment course is often required. Therapy should be started promptly post-transplant to avoid severe acute HCV infection.

HCV and living kidney donation. Potential living kidney donors should undergo HCV testing using immunoassay as well as nucleic acid testing (NAT). If a potential living kidney donor is HCV-NAT–positive, an evaluation for severity of liver disease and fibrosis should be undertaken and donation should be deferred until after successful DAA therapy in the donor and SVR are confirmed. Living donation can then proceed if evaluation of the donor excludes extensive hepatic fibrosis.

4.3: Use of maintenance immunosuppressive regimens

4.3.1: We recommend that kidney transplant recipients being treated with DAAs be evaluated for the need for dose adjustments of concomitant immunosuppressants (*1C*).

HCV viral load increases following kidney transplantation due to therapeutic immunosuppression, although this does not prevent successful DAA therapy. Drug–drug interactions are an important issue to consider when DAA regimens are used in kidney transplant recipients due to shared cytochrome P450 metabolism leading to substrate competition. This issue is particularly relevant in kidney transplant recipients treated with calcineurin and mTOR inhibitors. The Hepatitis Drug Interactions website is a useful resource for potential drug–drug interactions (http://www.hep-druginteractions.org).

4.4: Management of HCV-related complications in kidney transplant recipients

4.4.1: We suggest that patients previously infected with HCV who achieved SVR before transplantation undergo testing by NAT 3 months after transplantation or if liver dysfunction occurs (*2D*).

4.4.2: Kidney transplant recipients with cirrhosis should have the same liver disease follow-up as non-transplant patients, as outlined in the American Association for the Study of Liver Diseases (AASLD) guidelines (*Not Graded*).

4.4.3: HCV-infected kidney transplant recipients should be tested at least every 6 months for proteinuria (*Not Graded*).

4.4.3.1: We suggest that patients who develop new-onset proteinuria (either urine protein-creatinine ratio > 1 g/g or 24-hour urine protein > 1 g on 2 or more occasions) have an allograft biopsy with immunofluorescence and electron microscopy included in the analysis (*2D*).

4.4.4: We recommend treatment with a DAA regimen in patients with post-transplant HCV-associated glomerulonephritis (*1D*).

Successful antiviral therapy prevents progression of liver disease and allograft injury due to HCV infection. SVR is durable but if there is evidence of hepatic dysfunction, HCV reinfection and HBV reactivation or acquisition should be excluded. As in any cirrhotic patient, regular surveillance for hepatocellular carcinoma and other complications of HCV and liver disease is recommended following kidney transplantation of HCV-infected patients, as outlined in the AASLD and EASL guidelines. Following transplantation, patients with prior HCV infection should be monitored for proteinuria, microscopic hematuria, and decreased GFR. HCV-related allograft injury is suggested by abnormalities in these parameters in HCV viremic recipients and should prompt allograft biopsy including immunofluorescence and electron microscopy. Evidence of post-transplant HCV-associated glomerulonephritis is an additional indication for DAA therapy.

CHAPTER 5: DIAGNOSIS AND MANAGEMENT OF KIDNEY DISEASES ASSOCIATED WITH HCV INFECTION

5.1: HCV-infected patients with a typical presentation of immune-complex proliferative glomerulonephritis can be managed without a confirmatory kidney biopsy. However, a biopsy may be indicated in certain clinical circumstances (Figure 3) (*Not Graded*).

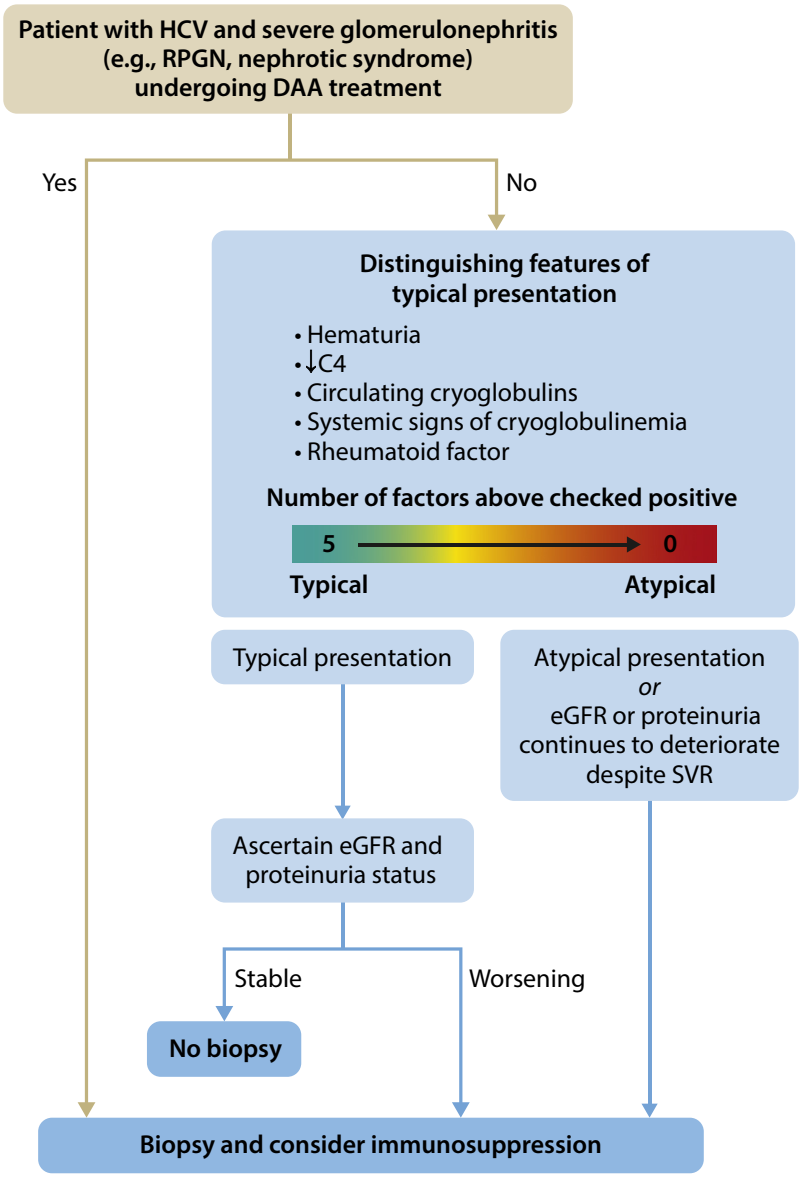

Figure 3 | Indications for biopsy in patients with hepatitis C virus (HCV) and severe glomerulonephritis. Algorithm above assumes that patient with HCV and chronic kidney disease is already receiving direct-acting antiviral (DAA) treatment. Systemic signs of cryoglobulinemia include skin lesions such as purpura, arthralgias, and weakness. eGFR, estimated glomerular filtration rate; RPGN, rapidly progressive GN; SVR, sustained virologic response.

5.2: We recommend that patients with HCV-associated glomerulonephritis receive antiviral therapy (*1A*).

5.2.1: We recommend that patients with HCV-associated glomerulonephritis, stable kidney function, and without nephrotic syndrome be treated with DAAs prior to other treatments *(1C)*.

5.2.2: We recommend that patients with cryoglobulinemic flare or rapidly progressive glomerulonephritis be treated with both DAAs and immunosuppressive agents with or without plasma exchange (*1C*).

5.2.2.1: The decision whether to use immunosuppressive agents in patients with nephrotic syndrome should be individualized (*Not Graded*).

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

5.2.3.1: We recommend rituximab as the first-line immunosuppressive treatment (*1C*).

Chapter 5: Diagnosis and management of kidney diseases associated with HCV infection

Immune-complex glomerulonephritis is a common extrahepatic manifestation of HCV infection. This can occur with or without evidence of mixed cryoglobulinemic vasculitis.

In an HCV-infected patient with a typical presentation of immune-complex glomerulonephritis (Figure 3) and stable GFR, DAA therapy can be initiated without performing kidney biopsy. In the event that GFR or proteinuria worsens following treatment, or if immunosuppressive therapy is being considered, kidney biopsy should be performed. Patients with atypical presentations, and those with evidence of rapidly progressive glomerulonephritis or severe nephrotic syndrome, should undergo kidney biopsy.

In patients with progressive decline in GFR due to active glomerulonephritis or a cryoglobulinemic flare, concomitant immunosuppressive therapy should be administered. If successful treatment with DAA does not result in an improvement in glomerulonephritis, immunosuppressive therapy is recommended. If nephrotic syndrome is present, treatment should be individualized based on various factors, including severity of kidney dysfunction and degree of nephrotic syndrome. When immunosuppressive treatment is indicated, rituximab is generally used as the first-line agent.

Table 1 | Summary of key messages from KDIGO 2022 HCV Guideline Update

- DAAs are highly effective and well-tolerated for treatment of HCV in patients across all CKD stages, including those undergoing dialysis therapy and kidney transplant recipients, with no need for dose adjustment

  Pangenotypic DAA regimens, including sofosbuvir-based regimens, and genotype-specific regimens are safe and effective for advanced CKD (CKD G4-G5ND or G5D) and for kidney transplant recipients, and can be selected based on local practices and availability of specific DAAs

- If pangenotypic regimens are not available, genotypes should be ascertained prior to DAA treatment
- Protease inhibitors ("-previrs" such as simeprevir, paritaprevir, and grazoprevir) are contraindicated in patients with Child-Pugh B and C cirrhosis
- Particular care with DAA agents should be exercised in kidney transplant recipients given the potential drug–drug interactions with immunosuppressive agents such as calcineurin and mTOR inhibitors. Readers should consult http://www.hep-druginteractions.org
- Because of concerns about HBV reactivation during/after DAA treatment, testing for HBV serological markers (i.e., hepatitis B surface antigen [HBsAg], total core antibody [anti-HBc] and antibody to HBV surface antigen [anti-HBs]) should be performed prior to HCV treatment with DAA therapy

  If HBsAg is present, the patient should undergo assessment for HBV therapy. If HBsAg is absent but markers of prior HBV infection (HBcAb-positive with or without HBsAb) are detected, HBV reactivation should be excluded with HBV DNA testing if levels of liver function tests rise during DAA therapy

- Kidney transplant candidates with HCV should be evaluated for severity of liver disease and presence of portal hypertension prior to acceptance for kidney transplantation. Results from this assessment will help guide the decision of kidney transplantation alone versus simultaneous kidney–liver transplantation
- DAA therapy should be administered to all HCV-infected kidney transplant candidates, either before or after transplantation
- Timing of DAA treatment for kidney transplantation candidates (before vs. after transplantation) should be based on donor type (living vs. deceased donor), wait-list times by donor type, center-specific policies governing the use of kidneys from HCV-positive deceased donors, and severity of liver fibrosis
- All living kidney donors should be screened for HCV infection with immunoassay and NAT if seropositive
- Kidneys from HCV-infected donors can be offered to potential recipients regardless of HCV status, provided that national or regional laws and regulations allow this practice

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Table 1 | (Continued) **Summary of key messages from KDIGO 2022 HCV Guideline Update**

- Kidney transplantation from HCV-infected donors to uninfected recipients with immediate or early DAA treatment is associated with excellent viral, allograft, and patient outcomes
- When transplanting kidneys from HCV-infected donors into HCV-uninfected recipients, transplant centers must ensure that recipients receive education and are engaged in discussion with sufficient information to provide informed consent. Patients should be informed of the risks and benefits of transplantation with an HCV-positive kidney, including the need for DAA treatment. Transplant centers should confirm availability of DAAs to be administered to recipients in the early post-transplant period
- HCV-infected patients with a typical presentation of immune-complex glomerulonephritis can be managed without a confirmatory kidney biopsy. However, a biopsy should be considered if there is worsening of GFR or proteinuria, or if immunosuppressive therapy is considered
- All patients with chronic HCV and glomerulonephritis should be treated with DAAs just as those without glomerulonephritis
- Patients with cryoglobulinemic flare or rapidly progressive glomerulonephritis can be treated with both DAAs and immunosuppressive agents, with or without plasma exchange. Rituximab is generally used as the first-line immunosuppressive treatment, although steroids should also be considered in rapidly progressive glomerulonephritis

CKD, chronic kidney disease; DAA, direct-acting antiviral; GFR, glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; mTOR, mammalian target of rapamycin; NAT, nucleic acid testing.

Conclusion

The efficacy and safety of DAA has profoundly changed the landscape of HCV management in patients with CKD and necessitated an update to the KDIGO 2018 guideline on HCV in CKD. The key messages related to HCV in CKD are outlined in Table 1. The most significant new developments are reviewed below. First, the finding of safety and efficacy of sofosbuvir in patients with CKD G4-G5 and G5D adds an additional pangenotypic agent to the DAA armamentarium and one that can be utilized in patients with cirrhosis. Second, the field of deceased donor kidney transplantation from HCV-viremic individuals to uninfected recipients has made major advances since the publication of the 2018 guideline, with future studies expected to refine the timing and duration of treatment and provide additional information on long-term clinical outcomes associated with this practice. Finally, the role of DAAs and immunosuppressive agents for HCV-associated immune-complex glomerulonephritis continues to evolve with an increasingly clear message about which patients require kidney biopsy before therapy, which can be treated with DAA alone, and which require immunosuppressive treatment, primarily with rituximab.

DISCLOSURE

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REFERENCES

1. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and

treatment of hepatitis C in chronic kidney disease. *Kidney Int Suppl*. 2008;73:S1–S99.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Hepatitis C Work Group. KDIGO 2018 clinical practice guideline for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. *Kidney Int Suppl*. 2018;8:91–165.
3. Kidney Disease: Improving Global Outcomes (KDIGO) Hepatitis C Work Group. KDIGO 2022 clinical practice guideline for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. *Kidney Int*. 2022;102(6S):S129–S205.
4. European Association for the Study of the Liver (EASL). EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. *J Hepatol*. 2017;67:370–398.
5. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology*. 2018;67:1560–1599.