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

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**KDIGO 2022 CLINICAL PRACTICE GUIDELINE
FOR THE PREVENTION, DIAGNOSIS, EVALUATION,
AND TREATMENT OF HEPATITIS C
IN CHRONIC KIDNEY DISEASE**



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

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Reference keys

NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

Within each recommendation, the strength of recommendation is indicated as **Level 1** or **Level 2**, and the quality of the supporting evidence is shown as **A**, **B**, **C**, or **D**.

Grade	Implications		
	Patients	Clinicians	Policy
Level 1, strong "We recommend"	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2, weak "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.
Grade	Quality of evidence	Meaning	
A	High	We are confident that the true effect is close to the estimate of the effect.	
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	
C	Low	The true effect may be substantially different from the estimate of the effect.	
D	Very low	The estimate of effect is very uncertain, and often it will be far from the true effect.	

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is defined as abnormalities of kidney structure or function, present for > 3 months, with implications for health. CKD is classified based on Cause, GFR category (G1–G5), and Albuminuria category (A1–A3), abbreviated as CGA.

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 <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m ²) 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.

CONVERSION FACTORS OF CONVENTIONAL UNITS TO SI UNITS

	Conventional unit	Conversion factor	SI unit
Creatinine	mg/dl	88.4	μmol/l

Note: Conventional unit x conversion factor = SI unit.

ALBUMINURIA CATEGORIES IN CKD

Category	AER (mg/24 h)	ACR (approximate equivalent)		Terms
		(mg/mmol)	(mg/g)	
A1	<30	<3	<30	Normal to mildly increased
A2	30–300	3–30	30–300	Moderately increased ^a
A3	>300	>30	>300	Severely increased ^b

ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; CKD, chronic kidney disease.

^aRelative to young adult level.

^bIncluding nephrotic syndrome (AER usually >2200 mg/24 h [ACR >2200 mg/g; >220 mg/mmol]).

INTERPRETATION OF HCV ASSAYS

Anti-HCV	HCV-NAT	Interpretation
Positive	Positive	Acute or chronic HCV infection depending on the clinical context
Positive	Negative	Resolution of HCV infection (i.e., successfully treated or spontaneously cleared)
Negative	Positive	Early acute HCV infection; chronic HCV in the setting of immunosuppressed state; false anti-HCV negative or false HCV-NAT positive
Negative	Negative	Absence of HCV infection

Anti-HCV, HCV antibody; HCV, hepatitis C virus; NAT, nucleic acid testing.

Abbreviations and acronyms

AASLD	American Association for the Study of Liver Diseases	GRADE	Grading of Recommendations Assessment, Development and Evaluation
ALT	alanine aminotransferase	GT	genotype
Anti-HCV	HCV antibody	GZR	grazoprevir
APASL	Asian Pacific Association for the Study of the Liver	HAV	hepatitis A virus
APRI	aspartate aminotransferase-to-platelet ratio index	HBcAb	antibody to hepatitis B core antigen
ASN	American Society of Nephrology	HBsAb	antibody to hepatitis B surface antigen
ASV	asunaprevir	HBsAg	hepatitis B surface antigen
AUC	area under the curve	HBV	hepatitis B virus
BSI	bloodstream infection	HCC	hepatocellular carcinoma
CDC	Centers for Disease Control and Prevention	HCV	hepatitis C virus
CI	confidence interval	HIV	human immunodeficiency virus
CKD (ND, D, T)	chronic kidney disease (suffix ND: non-dialysis; D: dialysis; T: transplant recipient)	HR	hazard ratio
CKD G4,	chronic kidney disease GFR category 4;	IDSA	Infectious Diseases Society of America
CKD G5	chronic kidney disease GFR category 5	IFN	interferon
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration	IU	international unit
COGS	Conference on Guideline Standardization	KDIGO	Kidney Disease: Improving Global Outcomes
CNI	calcineurin inhibitor	KTR	kidney transplant recipient
CPG	clinical practice guideline	LDV	ledipasvir
DAA	direct-acting antiviral	MMF	mycophenolate mofetil
DAC	daclatasvir	MPGN	membranoproliferative glomerulonephritis
DOPPS	Dialysis Outcomes and Practice Patterns Study	mTOR	mammalian target of rapamycin
EASL	European Association for the Study of the Liver	NAT	nucleic acid test(ing)
eGFR	estimated glomerular filtration rate	NS5A	nonstructural protein 5A
ELB	elbasvir	NS5B	nonstructural protein 5B
ERA-EDTA	European Renal Association–European Dialysis and Transplant Association	OR	odds ratio
ERT	Evidence Review Team	PrOD (3D regimen)	paritaprevir/ritonavir/ombitasvir and dasabuvir
ESKD	end-stage kidney disease	RBV	ribavirin
FDA	Food and Drug Administration	RCT	randomized controlled trial
GFR	glomerular filtration rate	RR	relative risk
GN	glomerulonephritis	SIM	simeprevir
		SOF	sofosbuvir
		SVR (weeks)	sustained virologic response (at stated weeks)
		US	United States
		VEL	velpatasvir

Notice

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based, in part, upon literature searches last conducted in February 2022, supplemented with additional evidence through April 2022. Chapters 2, 4, and 5 have been updated and revised. Chapters 1 and 3 remain unchanged since the 2018 guideline. It is designed to assist decision making. It is not intended to define a standard of care and should not be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Healthcare professionals using these recommendations should decide how to apply them to their own clinical practice.

SECTION II: DISCLOSURE

Kidney Disease: Improving Global Outcomes (KDIGO) makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise from an outside relationship or a personal, professional, or business interest of a member of the Work Group. All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived as or are actual conflicts of interest. This document is updated annually, and information is adjusted accordingly. All reported information is published in its entirety at the end of this document in the Work Group members' Disclosure section, and is kept on file at KDIGO.

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Foreword



Kidney International (2022) **102** (Suppl 6S), S129–S205 <https://doi.org/10.1016/j.kint.2022.07.013>

Reflecting the growing awareness that chronic kidney disease (CKD) is an international health problem, Kidney Disease: Improving Global Outcomes (KDIGO) was established in 2003. Its stated mission is to “improve the care and outcomes of patients with kidney disease worldwide through the development and implementation of global clinical practice guidelines.”

More than 15 years ago, KDIGO convened an expert group of nephrologists, hepatologists, virologists, and specialists from other relevant disciplines to develop guideline recommendations for the prevention, diagnosis, and management of hepatitis C virus (HCV) in CKD, which resulted in the publication of the very first KDIGO guideline in 2008. Since then, major advances in HCV therapy have made treatment of an increasing number of patients with CKD and HCV feasible irrespective of specific genotype or severity of liver disease. Advances in diagnostic testing in liver disease, most notably non-invasive evaluation of hepatic fibrosis, have further simplified the management of HCV. The KDIGO guideline was first updated in 2018 and incorporated many of these changes and innovations. However, given the rapid evolution of HCV therapies since then as well as the accumulating new information about HCV treatment in transplant recipients and the potential use of HCV-positive donor kidneys, it became evident that another focused update was needed for these guidelines to remain current.

Today, I am thrilled to present to the global kidney community an updated version of the HCV in CKD Clinical Practice Guideline. Just like the previous iteration, this update was led by our colleagues, Paul Martin, MD, and Michel Jadoul, MD, and carried out by a global panel of Work Group members who provided their time and expertise to this endeavor. In addition, this Work Group was ably assisted by colleagues from the independent evidence review team led by Ethan Balk, MD, MPH, Craig Gordon, MD, MS, and Gaelen Adam, MLIS, MPH, whose diligent work made this guideline possible. Finally, I thank our KDIGO colleagues, Michael Cheung, Amy Earley, and Melissa Thompson, for their tireless and detail-oriented management and support of this important effort.

In keeping with KDIGO’s policy for transparency and rigorous public review during the guideline development process, the draft guideline was made available for open commenting. The feedback received from the public review was carefully considered by the Work Group members and the guideline was revised as appropriate for the final publication.

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The 2022 guideline Work Group members thank panel members from the 2018 guideline for their contributions to Chapters 1 and 3 which are reproduced in this current edition without alteration. These prior Work Group members include Drs. Wahid Doss, Jacques Izopet, Vivekanand Jha, Bertram L. Kasiske, Ching-Lung Lai, José M. Morales, Priti R. Patel, and Marcelo O. Silva.

Abstract

The Kidney Disease: Improving Global Outcomes (KDIGO) 2022 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease represents a focused update of the 2018 guideline. This guideline is intended to assist the practitioner caring for patients with hepatitis C virus (HCV) and kidney disease, including those who are on dialysis therapy, and kidney transplant candidates and recipients. Topic areas for which recommendations are updated include: 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. Previous chapters on the detection and evaluation of HCV in CKD (Chapter 1) and prevention of HCV transmission in hemodialysis units (Chapter 3) have been deemed current, and their content has therefore remained unchanged. Development of this guideline followed an explicit process of evidence review and appraisal. Treatment approaches and guideline recommendations are based on systematic reviews of relevant studies, and appraisal of the quality of the evidence and the strength of recommendations followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Limitations of the evidence are discussed, with areas of future research also presented.

Keywords: chronic kidney disease; cryoglobulinemia; dialysis; direct-acting antivirals; glomerular diseases; guideline; hemodialysis; hepatitis C virus; infection control; KDIGO; kidney transplantation; liver testing; nosocomial transmission; screening; systematic review

CITATION

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Summary of recommendation statements

Chapter 1: Detection and evaluation of HCV in CKD

1.1: Screening patients with chronic kidney disease (CKD) for hepatitis C virus (HCV) infection

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 an immunoassay followed by nucleic acid testing (NAT) if immunoassay is positive (1A).

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

1.1.2.1: We recommend using NAT alone or an immunoassay followed by NAT if immunoassay is positive (1A).

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

1.1.4: We recommend screening all patients for HCV infection at the time of evaluation for kidney transplantation (1A).

1.2: Follow-up HCV screening of in-center hemodialysis patients

1.2.1: We recommend screening for HCV infection with immunoassay or NAT in in-center hemodialysis patients 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: In units with a new HCV infection, we recommend that all patients be tested for HCV infection and that the frequency of subsequent HCV testing be increased (1A).

1.2.1.3: We recommend that hemodialysis patients with resolved HCV infection undergo repeat testing every 6 months using NAT to detect possible re-infection (1B).

1.2.2: We suggest that patients have serum alanine aminotransferase (ALT) level checked upon initiation of in-center hemodialysis or upon transfer from another facility (2B).

1.2.2.1: We suggest that hemodialysis patients have ALT level checked monthly (2B).

1.3: Liver testing in patients with CKD and HCV infection

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

1.3.2: We recommend an initial noninvasive evaluation of liver fibrosis (1B).

1.3.3: When the cause of liver disease is uncertain or noninvasive testing results are discordant, consider liver biopsy (*Not Graded*).

1.3.4: We recommend assessment for portal hypertension in CKD patients with suspected advanced fibrosis (F3–4) (1A).

1.4: Other testing of patients with HCV infection

1.4.1: We recommend assessing all patients for kidney disease at the time of HCV infection 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 up 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 against hepatitis A virus (HAV) and hepatitis B virus (HBV), and screened for human immunodeficiency virus (HIV) (1A).

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, 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, ^h 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.

^aThe figure 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. ^bThe 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 [Supplementary Tables S5–S7](#)). ^cEstimated glomerular filtration rate (eGFR) ≥30 ml/min per 1.73 m². ^deGFR <30 ml/min per 1.73 m², not dialysis-dependent. ^eRegimens in kidney transplant recipients (KTRs) should be selected to avoid drug–drug interactions, particularly with calcineurin inhibitors. ^fStrength of evidence for CKD G4T–G5T is very low for all regimens. ^gEvidence 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*).

Chapter 3: Preventing HCV transmission in hemodialysis 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 (see [Table 1](#)) (*1A*).

Table 1 | Infection control practices (“hygienic precautions”) particularly relevant for preventing HCV transmission

- Proper hand hygiene and glove changes, especially between patient contacts, before invasive procedures, and after contact with blood and potentially blood-contaminated surfaces/supplies
- Proper injectable medication preparation practices following aseptic techniques and in an appropriate clean area, and proper injectable medication administration practice
- Thorough cleaning and disinfection of surfaces at the dialysis station, especially high-touch surfaces
- Adequate separation of clean supplies from contaminated materials and equipment

- 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 that 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 that 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*).

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

- 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*).
- 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 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*).
- 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*).
- 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*).

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 4](#)) (*Not Graded*).
- 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*).

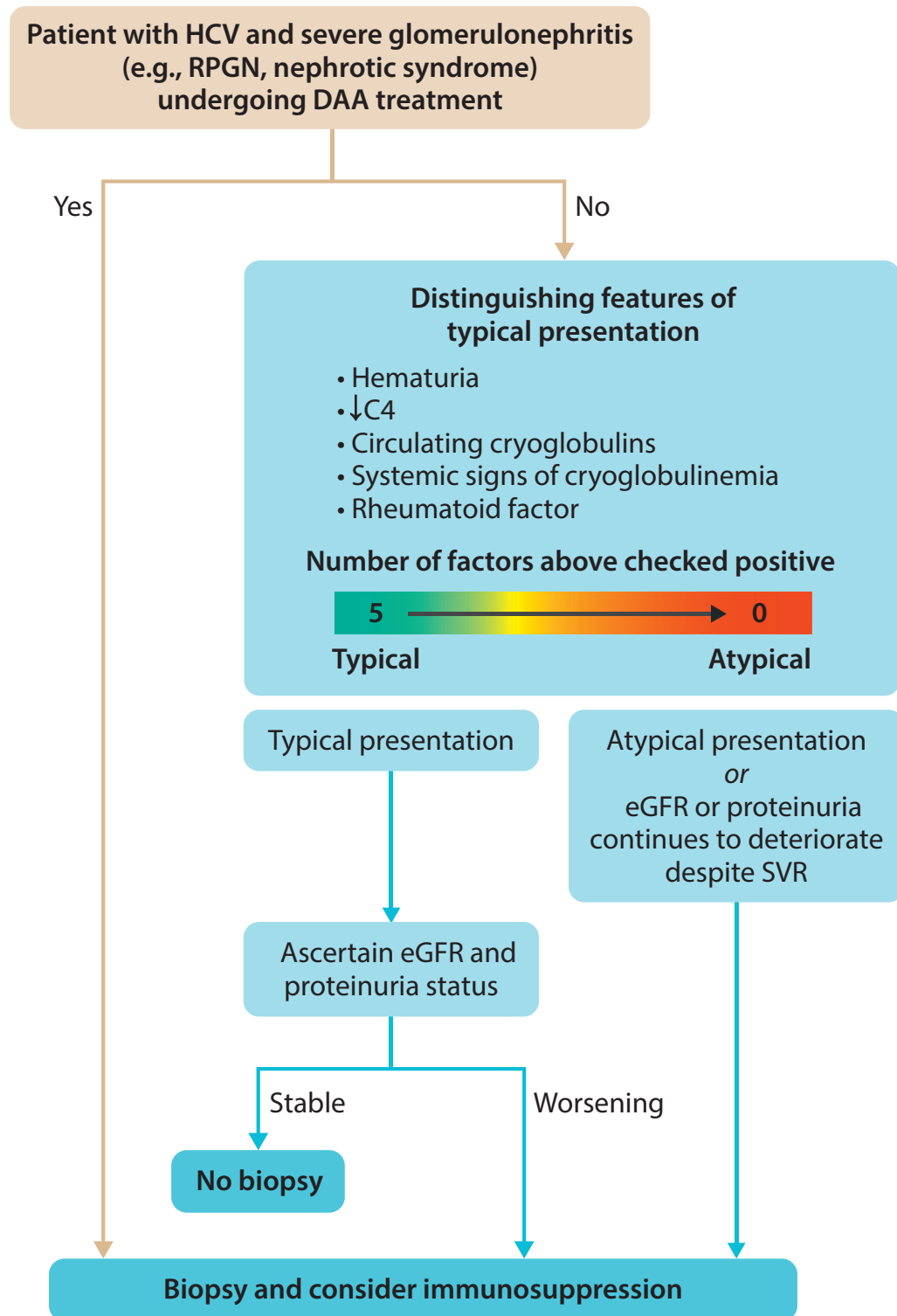


Figure 4 | Indications for biopsy in patients with hepatitis C virus (HCV) and severe glomerulonephritis. Algorithm above assumes that patient with HCV and with HCV and chronic kidney disease (CKD) is already receiving direct-acting antiviral (DAA) treatment. Systemic signs of cryoglobulinemia include skin lesions such as purpura, arthralgias, and weakness. eGFR, estimated glomerular filtration rate; RPGN, rapidly progressive glomerulonephritis; SVR, sustained virologic response.

Chapter 1: Detection and evaluation of HCV in CKD

1.1 Screening patients with chronic kidney disease (CKD) for hepatitis C virus (HCV) infection

Patients receiving maintenance hemodialysis and subgroups of patients with CKD not yet on dialysis are known to have a high prevalence of HCV infection. The reasons for testing patients with CKD for HCV infection include early detection and treatment of HCV infection, diagnostic evaluation of the cause of CKD, identification of infection control lapses in hemodialysis centers, and guidance on decisions surrounding kidney transplantation care.

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 an immunoassay followed by nucleic acid testing (NAT) if immunoassay is positive (1A).

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

1.1.2.1: We recommend using NAT alone or an immunoassay followed by NAT if immunoassay is positive (1A).

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

1.1.4: We recommend screening all patients for HCV infection at the time of evaluation for kidney transplantation (1A).

Rationale

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 an immunoassay followed by nucleic acid testing (NAT) if immunoassay is positive (1A).

Any CKD patient who has a risk factor for HCV infection should be tested.¹ Additionally, HCV testing is warranted for the evaluation of CKD because: (i) the prevalence of HCV infection may be higher in patients with CKD not yet on dialysis than in the general population^{2,3}; (ii) HCV infection increases the risk of developing CKD⁴; and (iii) HCV infection can accelerate progression of CKD.^{5–7}

Diagnosis of HCV infection relies on various assays.^{8,9} Serological assays that detect HCV antibody (anti-HCV)

are based on enzyme immunoassays or chemoluminescence immunoassays. Anti-HCV tests are unable to distinguish between resolved HCV infection and current HCV infection. Detection of HCV viremia relies on NAT technologies. Qualitative and quantitative HCV RNA methods are available and have similar limits of detection (10–20 international units [IU]/ml). HCV antigen tests that detect core antigen alone or in combination with other HCV proteins have the potential to be less costly than NAT, but their limit of detection is higher (equivalent to about 150–3000 IU/ml).^{8,10–12}

The most usual strategy for diagnosis of HCV infection consists of initial screening with an inexpensive serological assay and, if the assay is positive, subsequent NAT. However, in high prevalence settings or very high risk groups, immediate NAT is an appropriate alternative.

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

1.1.2.1: We recommend using NAT alone or an immunoassay followed by NAT if immunoassay is positive (1A).

The prevalence of HCV infection in patients undergoing hemodialysis (CKD G5 on dialysis) is higher than in the general population^{13,14} and has been associated with the number of years one has been on hemodialysis. Patient-to-patient transmission of HCV infection in outpatient hemodialysis centers has occurred repeatedly despite widespread knowledge of this risk and published guidelines for prevention. Identification of HCV transmission within a dialysis facility should prompt immediate reevaluation of infection control practices and determination of appropriate corrective action (see Chapter 3).^{15–19} The majority of persons with HCV infection are asymptomatic, making screening necessary to detect infection in high-risk populations, particularly in patients on hemodialysis in whom signs or symptoms of acute HCV infection are rarely recognized. Screening of patients on maintenance hemodialysis for HCV infection is recommended by the United States (US) Centers for Disease Control and Prevention (CDC) and also the US Preventive Services Task Force.^{20,21} Goals of screening in this patient population include early detection of HCV infection, treatment of infection, and detection of dialysis-related transmission. HCV screening is indicated in patients starting

in-center maintenance hemodialysis and also in patients who transfer from another dialysis facility or modality. In dialysis units with a high prevalence of HCV, initial testing with NAT should be considered. An anti-HCV–negative, HCV RNA–positive (i.e., NAT–positive) profile strongly suggests acute HCV infection.

Samples collected to test for HCV by NAT should be drawn before dialysis, because hemodialysis sessions reduce viremia level, although the mechanism remains unclear.²²

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

HCV transmission has typically been described in the context of in-center hemodialysis. In this setting, blood contamination on the hands of staff members or on medications, supplies, and equipment can contribute to HCV transmission. The current risk of health care–related HCV infection among patients who receive peritoneal dialysis or home hemodialysis has not been quantified. Many of these patients will require in-center hemodialysis at some point during their care, and may be at risk of acquiring HCV infection during that time. Screening of peritoneal dialysis and home hemodialysis patients should be considered upon initiation of dialysis to document baseline HCV infection status. If these patients transiently receive in-center hemodialysis, they should undergo HCV infection screening as per the recommendations for in-center hemodialysis patients, with consideration of continued screening until 6 months after the completion of in-center hemodialysis (and transition to a different modality).

1.1.4: We recommend screening all patients for HCV infection at the time of evaluation for kidney transplantation (1A).

Kidney transplantation candidates should be tested for HCV infection during evaluation for transplantation. Determination of HCV status in recipients is essential for optimal management and potentially for acceptance of kidneys from HCV-infected donors (see Chapter 4).

1.2 Follow-up HCV screening of in-center hemodialysis patients

1.2.1: We recommend screening for HCV infection with immunoassay or NAT in in-center hemodialysis patients 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: In units with a new HCV infection, we recommend that all patients be tested for HCV infection and that the frequency of subsequent HCV testing be increased (1A).

1.2.1.3: We recommend that hemodialysis patients with resolved HCV infection undergo repeat

testing every 6 months using NAT to detect possible re-infection (1B).

1.2.2: We suggest that patients have serum alanine aminotransferase (ALT) level checked upon initiation of in-center hemodialysis or upon transfer from another facility (2B).

1.2.2.1: We suggest that hemodialysis patients have ALT level checked monthly (2B).

Rationale

1.2.1: We recommend screening for HCV infection with immunoassay or NAT in in-center hemodialysis patients 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: In units with a new HCV infection, we recommend that all patients be tested for HCV infection and that the frequency of subsequent HCV testing be increased (1A).

1.2.1.3: We recommend that hemodialysis patients with resolved HCV infection undergo repeat testing every 6 months using NAT to detect possible re-infection (1B).

Patients who are not infected with HCV should be screened for presence of new infection every 6 months.²⁰ This recommendation includes anti-HCV–negative patients and anti-HCV–positive, HCV RNA–negative (i.e., NAT–negative) patients screened initially by immunoassay, as well as HCV RNA–negative patients screened initially by NAT. Patients who are anti-HCV–positive and HCV RNA–negative have resolved infection but remain at risk for re-infection if exposed.²³ Therefore, these patients should also undergo repeat screening. For patients on dialysis who are anti-HCV–positive and HCV NAT–negative, screening for HCV reinfection should be conducted every 6 months using NAT.

The purpose of the repeat screening is to identify new infections (i.e., newly acquired infections) that could represent transmission within the dialysis center. The baseline HCV testing results should be reviewed for any patient who has a positive HCV screening test result to determine whether there was a change in infection status indicating a new infection, and results must be communicated to the patient. Any patient with a current infection, whether new or pre-existing, should be linked to HCV care and considered for antiviral therapy.

Acute HCV infection in a patient on hemodialysis should be reported to the appropriate public health authority. Reporting may be mandated by law, as in the US, where a documented negative HCV antibody or NAT laboratory test result followed within 12 months by a positive HCV test result (test conversion) must be reported to public health authorities.²⁴ Acute HCV infection in a patient on hemodialysis should be investigated and considered health care–

related until proven otherwise.²⁵ Behavioral risk factors, along with dialysis and nondialysis health care exposures, should be evaluated by public health authorities. Molecular sequencing of HCV RNA from other patients in the facility may help to identify a source.^{19,26–28}

Acute HCV infection should also prompt immediate evaluation of all other patients in the same facility to identify additional cases. The status of all patients should be reviewed at the time a new infection is identified, and all patients previously known to be uninfected should be retested for HCV infection. The frequency of repeat screening should also be increased for a limited time: for example, monthly testing for 3 months, followed by testing again in 3 months, and then resumption of screening every 6 months if no additional infections are identified.^{17,20} This strategy can help to identify delayed seroconversions (from the same exposure period as the index case) or other cases resulting from recurrent breaches. Use of this strategy has led to the detection of additional new cases in several reported outbreaks.^{19,29}

For anti-HCV–positive patients with chronic HCV infection who become HCV NAT–negative with a sustained virologic response (SVR) to HCV therapy, initiate NAT screening 6 months after documentation of SVR. SVR is determined based on results of NAT testing ≥ 12 weeks after the conclusion of therapy.

For patients with spontaneous resolution of acute HCV infection as documented by a negative test for HCV RNA at ≥ 6 months after the onset of acute infection, NAT screening should begin 6 months after documented resolution of infection.

1.2.2: We suggest that patients have serum alanine aminotransferase (ALT) level checked upon initiation of in-center hemodialysis or upon transfer from another facility (2B).

1.2.2.1: We suggest that hemodialysis patients have ALT level checked monthly (2B).

A baseline serum ALT test, followed by monthly testing, in susceptible patients has been recommended to enable early detection of new HCV infection in patients on hemodialysis.²⁰ Newly infected patients may have an increase in ALT levels prior to antibody conversion, which should prompt additional evaluation. If an unexplained elevation (i.e., to greater than upper-limit normal) of ALT occurs, the patient should be tested for HCV infection. The exact predictive value of ALT screening for detection of HCV infection has been assessed in a single study and found to be moderate.³⁰ However, ALT monitoring is an inexpensive way to ensure that patients on hemodialysis are assessed for possible acquisition of infection between regular antibody or NAT screenings. Because few hemodialysis patients with a new HCV infection report symptoms or have symptoms documented in their dialysis medical records, ALT levels are also often used retrospectively to define the likely exposure period for patients who acquired infection. Thus, monthly ALT levels are valuable to help narrow the focus of an HCV case

investigation to the most likely exposure and source. The value of monthly ALT testing in patients who have resolved HCV infection has not been studied.

1.3 Liver testing in patients with CKD and HCV infection

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

1.3.2: We recommend an initial noninvasive evaluation of liver fibrosis (1B).

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

1.3.4: We recommend assessment for portal hypertension in CKD patients with suspected advanced fibrosis (F3–4) (1A).

Rationale

Evaluation of liver fibrosis in HCV-infected patients with CKD. In the prior Kidney Disease: Improving Global Outcomes (KDIGO) HCV guideline published in 2008,³¹ liver biopsy had been considered the gold standard to assess liver fibrosis in patients with CKD, including candidates for transplantation and transplant recipients. The primary objective of liver biopsy in patients with advanced CKD had been to diagnose cirrhosis. Because of the risk of liver-related mortality after kidney transplantation, cirrhosis had been considered a contraindication to kidney transplantation alone and led to consideration of combined liver–kidney transplantation.

Current evidence suggests that biochemical noninvasive markers (FibroTest/FibroMeter, aspartate aminotransferase-to-platelet ratio index [APRI], Forns, or FIB-4 index) and morphological evaluation (liver stiffness by elastography) may have comparable accuracy in evaluating liver fibrosis in patients with CKD G4–G5 as in the general population.³² Noninvasive methods, especially elastography, are sufficiently reliable to detect extensive fibrosis and/or cirrhosis (F3–F4)^{33,34} though noninvasive tests other than elastography may be less accurate (Supplementary Tables S1 and S2). Furthermore, although serious complications of liver biopsy are uncommon, patients are often reluctant to consider it, and its validity may be diminished by sampling as well as interpretation errors. Liver biopsy use in HCV-infected patients generally has declined.

Because SVR can now be anticipated in the vast majority of patients treated for HCV, the management of the HCV-infected kidney transplant candidate, even with cirrhosis, has evolved. SVR is associated with sustained and long-lasting suppression of necroinflammation and may even result in regression of cirrhosis, potentially resulting in decreased disease-related morbidity and improved survival.³⁵ Even in the absence of regression of cirrhosis, kidney transplantation alone is feasible in the absence of major complications of portal hypertension, just like in patients with hepatitis B virus (HBV)–related cirrhosis.³⁶

Thus, the role of liver biopsy in evaluation of liver fibrosis in HCV-infected patients with CKD G4-G5 will evolve given the high SVR rates obtained with current direct-acting antiviral (DAA) regimens. Defining the severity of cirrhosis involves assessment for clinically significant portal hypertension (hepatic-vein wedge-pressure gradient of ≥ 10 mm Hg).³⁷ Methods include upper endoscopy, noninvasive radiological evaluation, or direct portal pressure measurement. Based on the Baveno VI consensus,³⁸ portal hypertension is very unlikely (and hence an upper endoscopy can be avoided with $> 90\%$ reliability) in patients with compensated cirrhosis but elastography < 20 kPa and platelet count $> 150,000/\text{mm}^3$. Whether this approach is also valid for patients on hemodialysis remains unknown.

In summary, all HCV-infected patients with kidney failure should undergo a noninvasive biochemical and/or morphological evaluation to stage fibrosis and determine the role of antiviral therapies (see Chapter 2) and to facilitate the choice of kidney or combined liver-kidney transplantation in cirrhotic patients. When results between biochemical and morphological evaluation are discordant, or when liver comorbidities are suspected, liver biopsy is suggested.³⁹

1.4 Other testing of patients with HCV infection

Although HCV infection predominantly causes liver disease, it is also associated with extrahepatic manifestations including kidney disease.⁴⁰ HCV has been shown to infect both hepatocytes and lymphocytes; thus, lymphoproliferative disorders such as lymphoma and mixed cryoglobulinemia are linked to HCV infection.⁴¹ HCV has also been implicated in derangements of multiple organ systems including cardiovascular, endocrine, muscular, nervous, ocular, respiratory, skeletal, cutaneous, and urinary systems. In addition, HCV can have a deleterious impact on psychosocial status.⁴²

The relationship between HCV infection and CKD is complex. HCV infection and CKD are prevalent in the general population and are associated in various ways: patients on chronic hemodialysis are at increased risk of acquiring HCV, and some types of kidney disease are precipitated by HCV infection. Conventional risk factors for CKD such as aging, diabetes, hypertension, and metabolic syndrome do not fully explain the current frequency of CKD in the adult general population of developed countries. In addition to these conventional risk factors, accumulating evidence in the last decade has implicated HCV infection as a cause of kidney disease. HCV co-infection has also been implicated as a risk factor for CKD in HIV-infected patients.⁴³ A meta-analysis⁴ of observational studies^{44–52} demonstrated a relationship between anti-HCV-positive serologic status and an increased incidence of CKD in the adult general population, with an adjusted hazard ratio (HR) of 1.43 (95% confidence interval [CI]: 1.23–1.63). Based on current information, patients with HCV infection should be regarded as being at increased risk of CKD, regardless of the presence of conventional risk factors for kidney disease.

1.4.1: We recommend assessing all patients for kidney disease at the time of HCV infection 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 up 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 against hepatitis A virus (HAV) and hepatitis B virus (HBV), and screened for human immunodeficiency virus (HIV) (1A).

Rationale

1.4.1: We recommend assessing all patients for kidney disease at the time of HCV infection diagnosis (1A).

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

The prevalence of CKD, defined by a reduction in glomerular filtration rate (GFR) and/or increased urinary albumin excretion,⁵³ exceeds 10% in the adult general population, according to numerous population-based studies. The prevalence of low GFR alone is around 5% to 6% but increases sharply with older age. Testing for CKD appears logical in HCV-infected individuals, as many authors have suggested a potential role of HCV infection as a cause of CKD. However, epidemiologic supporting data regarding the prevalence of CKD in HCV-infected patients were until recently limited and used variable criteria for the definition of CKD; the demographic/clinical characteristics of the representative patient population were variable as well. According to 3 studies performed in the US,^{44,49,52} the unadjusted prevalence of low GFR (< 60 ml/min per 1.73 m^2) ranged at baseline between 5.1% and 8.0% among middle-aged anti-HCV-seropositive individuals. The unadjusted prevalence of abnormal kidney function (serum creatinine > 1.5 mg/dl [$> 133 \mu\text{mol/l}$]) in 1 large study of anti-HCV-seropositive veterans from the US was 4.8%.⁵⁴ In another large cohort of HCV-positive, HIV-positive patients from North America, the unadjusted frequency of low GFR (< 60 ml/min per 1.73 m^2) at baseline ranged between 3.7% and 4.0%.⁵⁵

Kidney involvement in HCV infection was first recognized more than 2 decades ago; however, the association between HCV and CKD (low GFR or presence of proteinuria) in the adult general population was controversial until a few years ago. An increasing body of evidence has recently highlighted

the detrimental impact of HCV infection on the risk of CKD (Supplementary Tables S3 and S4). One meta-analysis⁴ reported an HR of 1.43 (95% CI: 1.23–1.63) between positive HCV serologic status and increased incidence for CKD, while another recent study⁵⁶ demonstrated that patients with HCV had a 27% increased risk of CKD compared with patients without HCV. This study also revealed that HCV-positive patients experienced a 2-fold higher risk of membranoproliferative glomerulonephritis (MPGN) and a nearly 17-fold higher risk of cryoglobulinemia. Effective antiviral treatments have been shown to reduce risk for development of CKD by 30%. Cohort studies performed in patients with HIV and HCV co-infection,⁷ patients with diabetes,^{5,57} and patients with biopsy-proven chronic glomerulonephritis (GN)⁶ have confirmed a significant relationship between anti-HCV–positive serologic status and accelerated progression of CKD. The prevalence of anti-HCV in serum was significantly greater in patients with CKD before reaching kidney failure (formerly described as end-stage kidney disease [ESKD]) than in a healthy population.^{2,3} Among liver transplant recipients infected with HCV who were treated with antiviral therapy, SVR led to improved eGFR in those with CKD G2 (GFR 60–89 ml/min per 1.73 m²) before treatment.⁵⁸ HCV co-infection is a risk factor for increased health care resource utilization in HIV-infected individuals in the US; a multivariate Poisson model showed that HCV co-infection was associated with higher frequency of emergency department visits: adjusted relative risk (RR) 2.07 (95% CI: 1.49–2.89). In particular, emergency department visits related to kidney disease were much more common among co-infected patients (37%) than among those with HIV infection alone (10%).⁵⁹ Another meta-analysis of observational studies⁶⁰ reported a relationship between positive anti-HCV serologic status and an increased risk of reduced GFR among HIV-infected individuals, with an adjusted HR of 1.64 (95% CI: 1.28–2.0), compared with those having HIV infection alone.

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).

The recommendation to repeat testing for proteinuria or GFR in anti-HCV–positive, HCV NAT–positive patients comes from epidemiologic data. In 1 study, serial measurements of eGFR and proteinuria were obtained in a large cohort of US metropolitan residents. The prevalence of CKD was greater among anti-HCV–positive, HCV NAT–positive patients compared with matched anti-HCV–negative controls (9.1% vs. 5.1%, $P = 0.04$).⁶¹ In addition, using data from the Third National Health and Nutrition Examination Survey, at least 2 studies have observed an increased risk of albuminuria in patients with HCV.^{62,63} Classically, HCV infection predisposes to cryoglobulinemic MPGN; however, HCV-positive individuals may also be at risk for kidney injury related to decompensated cirrhosis, injection drug use, and

HIV or HBV co-infection. Overall, multiple studies have now shown that HCV infection is associated with an increased risk of developing CKD, as summarized in a recent meta-analysis.⁴ It is possible that accelerated atherosclerosis also contributes to the increased risk of developing kidney disease among HCV-infected individuals.⁶⁴

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

Although studies are heterogeneous and some controversy persists,⁶⁵ overall, HCV-infected patients appear to be at greater risk for incidence and progression of kidney disease and require monitoring as outlined in the KDIGO CKD guideline.⁵³ In the Women's Interagency HIV study, anti-HCV–positive serologic status was independently associated with a net decrease in eGFR of approximately 5% per year (95% CI: 3.2–7.2) compared with women who were seronegative.⁶⁶

Of note, antiviral therapy for HCV significantly improves hepatic and extrahepatic outcomes in the general population^{67,68} and among patients co-infected with HIV and HCV.⁶⁹ Six studies have addressed the impact of interferon (IFN)-based regimens on the progression of CKD.^{61,70–74} Five multivariate analyses^{61,70–73} suggested that treatment of HCV infection may improve renal survival *per se*. In a nationwide cohort study from Taiwan, patients who had received antiviral treatment (pegylated IFN plus ribavirin [RBV]) had a calculated 8-year cumulative incidence of ESKD of 0.15% versus 1.32% in untreated patients ($P < 0.001$).⁷² Multivariate-adjusted Cox regression revealed that antiviral treatment was associated with lower risks of ESKD (HR: 0.15; 95% CI: 0.07–0.31). Antiviral treatment was also associated with an adjusted HR of 0.77 (95% CI: 0.62–0.97) for acute coronary syndrome, and 0.62 (95% CI: 0.46–0.83) for ischemic stroke.⁷² These favorable associations were not observed in patients treated for less than 16 weeks, suggesting that shorter-duration therapy was inadequate.

In a study on 650 Japanese patients with liver cirrhosis,⁷⁰ multivariate Cox proportional hazards analysis showed that failure to achieve SVR was a predictor of development of CKD, with an adjusted HR of 2.67 (95% CI: 1.34–5.32). In a hospital-based study from the US, 552 HCV-infected patients were evaluated, and 159 received IFN therapy during a 7-year follow-up. Multivariate logistic regression indicated that a history of IFN treatment was a significant independent negative predictor for CKD (odds ratio [OR]: 0.18; 95% CI: 0.06–0.56).⁶¹ Finally, a recent meta-analysis of controlled and uncontrolled studies (11 studies; $n = 225$ patients) that evaluated efficacy and safety of antiviral treatment for HCV-related glomerular disease found that the summary estimate of the mean decrease in serum creatinine levels was 0.23 mg/dl (20 μ mol/l) (95% CI: 0.02–0.44) after IFN α -based therapy.⁷⁵

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 against hepatitis A virus (HAV) and hepatitis B virus (HBV), and screened for human immunodeficiency virus (HIV) (1A).

HCV is a blood-borne pathogen and shares routes of transmission with HBV and HIV. Although hepatitis A virus (HAV) infection is frequently mild in healthy individuals, superinfection with HAV and HBV in patients with liver disease (including chronic HCV) may result in significant morbidity and mortality.⁷⁶ Thus, as HAV⁷⁷ and HBV⁷⁸ are vaccine-preventable infections, appropriate vaccination should be encouraged, although response rates to vaccination are diminished in patients with advanced CKD.

Research recommendations

- Studies are needed to examine HCV antigen testing as an alternative to NAT to diagnose HCV viremic infection.
- The clinical utility of HCV antigen immunoassays and antigen and antibody combination assays should be determined.
- The predictive value of different levels of ALT for identifying HCV infection and the additive value of ALT screening to the current generation of immunoassays or NAT testing should be investigated. Data should already exist to address this question among dialysis providers that perform routine screening of their patients. The utility of ALT testing after resolved HCV infection should be studied.
- With the availability of effective treatments for HCV, the role of DAAs in preventing and slowing the progression of CKD in the HCV-infected population should be assessed.

Chapter 2: Treatment of HCV infection in patients with CKD

Introduction of highly effective, well-tolerated oral DAA regimens has enabled treatment of patients with HCV across all stages of CKD and has made IFN and RBV obsolete. Current DAA regimens always incorporate 2 or more drugs with different mechanisms of action to disrupt HCV replication, with the goals of enhancing efficacy and preventing emergence of viral resistance. Although recent studies indicate that most DAA regimens can be used irrespective of kidney function, GFR measurements or estimations may still be relevant depending on accessibility to specific drugs in different parts of the world and how they may be labelled for use in people with reduced GFR. If eGFR is used, we suggest using the combined creatinine and cystatin C-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula or, alternatively, the creatinine-based CKD-EPI formula,^{79,80} bearing in mind that creatinine-based formulas do not perform well in patients with cirrhosis.^{81,82}

Multiple studies have established a survival benefit in patients with HCV who achieve SVR,⁸³ an endpoint for clinical trials and drug approval.⁸⁴ SVR at 12 weeks is considered a virological cure.⁸⁵

For most patients with CKD, as in the general population, the potential benefits of antiviral treatment outweigh possible harm.⁸⁶ However, some patients may not be expected to live long enough to benefit from therapy (e.g., those with metastatic cancer). The Work Group was hesitant to specify a minimum life expectancy that would justify treatment, given the inaccuracy of predictions and the need to individualize this decision. However, as noted in the American Association for the Study of Liver Diseases/Infectious Diseases Society of America (AASLD/IDSA) guidance, little evidence exists to support initiation of HCV treatment in patients with a limited life expectancy (<12 months).⁸⁷

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, 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).

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).

Rationale

Development of DAA therapy has been based on mapping the HCV genome which contains non-structural (NS) proteins and the identification of its replication cycle which includes amplification of the HCV genome by the RNA polymerase NS5B. Several protease inhibitors, which all end in “-previr,” are active against the NS3/NS4 serine protease; these have been introduced with more recent additions having a high barrier to antiviral resistance and greater efficacy (Figure 2⁸⁸). The NS5A protein, although not an enzyme, is key to the assembly of virions, and these NS5A inhibitors, which all have “-asvir” in the suffix, have excellent antiviral activity but a relatively low barrier to antiviral resistance. A key event in HCV replication is amplification of the HCV genome by the RNA polymerase NS5B. Its actions can be disrupted by nucleotide or non-nucleotide inhibitors whose names end in “-buvir” (Figure 2). A number of studies have been published that have established the safety and efficacy of DAA therapy in CKD. As discussed in later sections, some regimens are effective against all HCV genotypes (“pangenotypic”), whereas others are limited by specific genotype (GT), thus necessitating GT determination prior to DAA therapy.

CKD G1–G3b (GFR ≥ 30 ml/min per 1.73 m²). Patients with CKD G1–G3b can be treated using the evidence-based guidelines for

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.

^aThe figure 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. ^bThe 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 [Supplementary Tables S5–S7](#)). ^cEstimated glomerular filtration rate (eGFR) ≥30 ml/min per 1.73 m². ^deGFR <30 ml/min per 1.73 m², not dialysis-dependent. ^eRegimens in kidney transplant recipients (KTRs) should be selected to avoid drug–drug interactions, particularly with calcineurin inhibitors. ^fStrength of evidence for CKD G4T–G5T is very low for all regimens. ^gEvidence 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.

the general population. The AASLD/IDSA and the European Association for the Study of the Liver (EASL) 2020 guidelines recommend no dosage modifications for individuals with mild to moderate reductions in GFR.^{87,89} As recommended drugs and dosage may change, clinicians should consult the latest guidelines from AASLD/IDSA

(<https://www.hcvguidelines.org/unique-populations/renal-impairment>) or EASL⁸⁹ (<http://www.easl.eu/research/our-contributions/clinical-practice-guidelines>) for the most up-to-date treatment information.

CKD G4–G5 (GFR < 30 ml/min per 1.73 m², not on dialysis) and G5D (on dialysis). DAAs have variable elimination by the kidney, although recent evidence shows that the clinical importance of reduced renal elimination in CKD G4–G5 is limited. However, advanced CKD, if present, may be a consideration in the choice of agent depending on drug labeling in the local jurisdiction.

Pangenotypic regimens. Sofosbuvir-based regimens. Sofosbuvir (SOF), a polymerase inhibitor, is the cornerstone of several DAA regimens. It is predominantly cleared by the kidney (80%) and thus, it had previously been licensed for use only in individuals with GFR ≥ 30 ml/min per 1.73 m² (CKD G1–G3b). However, recent data on SOF-based regimens in patients with advanced CKD (G4–G5D) suggest that SOF is

well-tolerated and safe, including for those who require hemodialysis ([Supplementary Tables S8–S12](#)). In an early study, reduced-dose SOF (400 mg three times a week or 400 mg every other day) was efficacious and well-tolerated in 62 patients on hemodialysis.⁹⁰ Other studies in patients with advanced CKD have come to the same conclusion.^{91,92} More recent studies have provided further reassurance about the safety and efficacy of SOF in advanced CKD at full dose^{93,94}; thus, dose adjustment of SOF in patients with CKD G4–G5 and G5D is not required. Across 16 studies of patients on dialysis that evaluated SOF-based regimens and reported serious adverse events, no serious adverse events were reported in 803 patients on hemodialysis (full-dose SOF in 628 patients, 12 studies; reduced-dose SOF in 175 patients, 5 studies; 1 study examined both full-dose and reduced-dose SOF). Across 17 of 18 studies that evaluated SOF-based regimens and reported discontinuations due to adverse events, only 1 of 904 patients had this outcome (one study of full-dose SOF/velpatasvir [VEL] reported 5 of 105 discontinuations due to adverse events, but no serious drug-related adverse events⁹⁵) ([Supplementary Tables S6 and S10](#)). Similarly, across 5 studies of patients with CKD G4–G5ND (non-dialysis) on SOF-based regimens, no serious adverse events were reported in 210 patients (162 on full-dose SOF) and only 4 of 183 patients (2 on reduced-dose

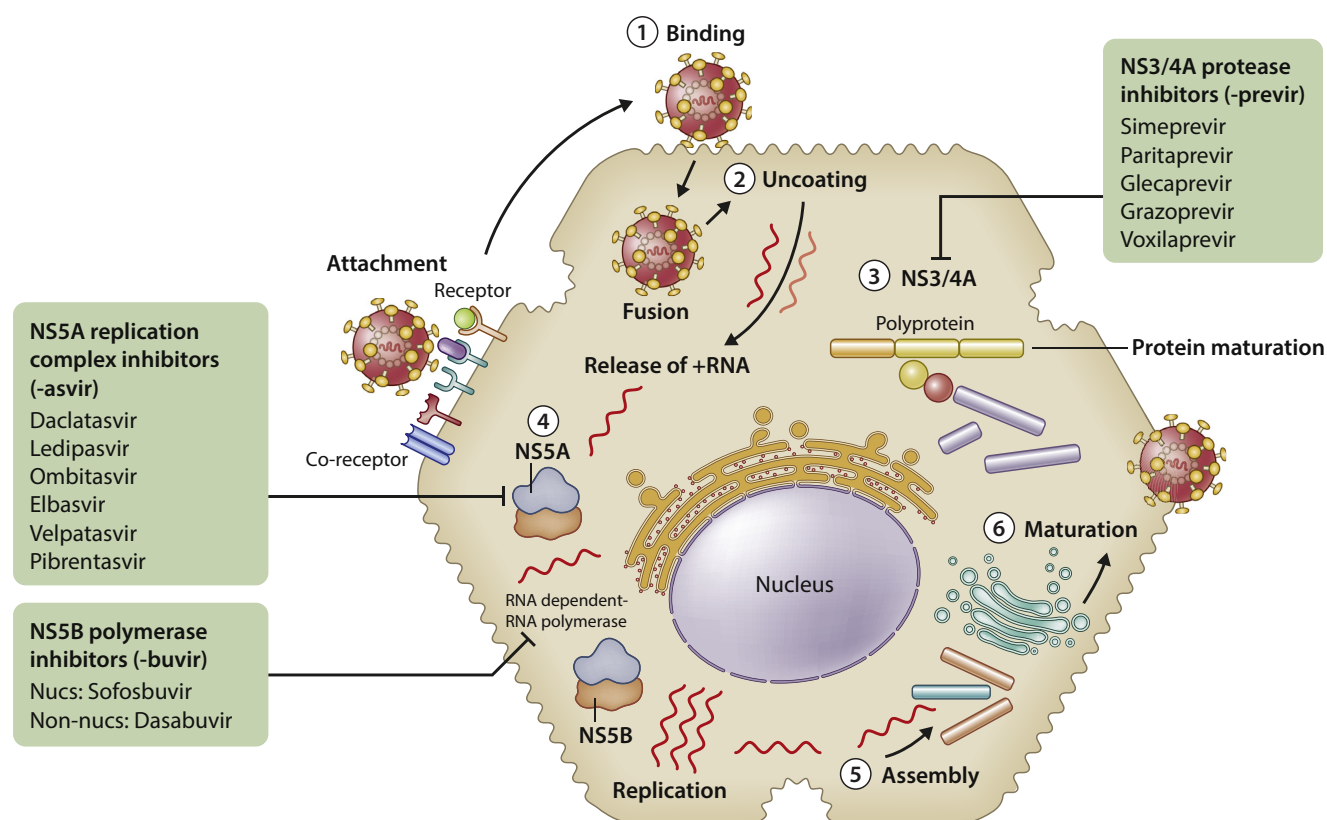


Figure 2 | Summary of currently available direct-acting antiviral (DAA) treatment targets in hepatitis C virus (HCV) life cycle. Infection is initiated by (1): virus binding and internalization, followed by (2) cytoplasmic release and uncoating; (3) translation and polyprotein processing; (4) RNA replication; (5) packaging and assembling; and (6) virion maturation and release. Adapted with permission from Stanciu C, Muzica CM, Girleanu I, et al. An update on direct antiviral agents for the treatment of hepatitis C. *Expert Opin Pharmacother* 2021;22:1729–1741,⁸⁸ reprinted by permission of the publisher (Taylor & Francis Ltd, <http://www.tandfonline.com>). NS3/4A, nonstructural protein proteases; NS5A, nonstructural phosphoprotein; NS5B, nonstructural protein RNA-dependent RNA polymerase.

and 2 on full-dose SOF and RBV, all from 1 study⁹⁶) discontinued treatment due to adverse events (Supplementary Tables S5 and S8). SOF is currently approved for all stages of CKD by the US Food and Drug Administration (FDA) and the European Medicines Agency.

SOF-based regimens that have been evaluated by at least 2 studies that reported SVR12 and safety information specifically in CKD G4–G5ND or CKD G5D populations include SOF/DCV (daclatasvir), SOF/LDV (ledipasvir), and SOF/VEL (velpatasvir). Another SOF-based regimen (SOF/SIM [simeprevir] has been evaluated by a single study only in each population (CKD G4–G5ND and CKD G5D), with similar findings; Supplementary Tables S5, S6, and S8–S12). Monotherapy with SOF alone is not recommended due to inferior efficacy (SVR12 72% in CKD G4–G5ND and 92% in CKD G5D, with inconsistent findings across studies; Supplementary Tables S5, S6, S8, and S10).

Glecaprevir/Pibrentasvir (GLE/PIB). The pangenotypic regimen GLE/PIB was studied in the open-label EXPEDITION-4 study which included 102 patients with CKD G4–G5D, 82% of whom were dialysis-dependent. Duration of treatment was 12 weeks. SVR12 was 100% on modified intention-to-treat analysis, and no serious adverse events related to the regimen were reported⁹⁷ (see Table 1). EXPEDITION-5 was

another open-label, non-randomized, multicenter study that included a shorter treatment arm in which 84 patients without cirrhosis (out of 101) with CKD G3b–G5D were treated for 8 weeks as long as they did not have GT 3. Cirrhotics, treatment-experienced and GT 3 patients were treated for 12 weeks (13 patients) or 16 weeks (4 patients). SVR12 was 97.0% in the study.⁹⁸ However, EXPEDITION-4 was excluded from our analysis of SVR12 because results were not reported separately for the CKD G4–G5ND and CKD G5D populations. EXPEDITION-5 was excluded from our analysis of CKD G4–G5ND because patients with CKD G3b were included in their analysis.

In the pooled estimate of the 3 studies of patients with CKD G4–G5ND included in our evidence review, 8-week treatment with GLE/PIB had a SVR12 of 98.5% (95% CI: 94.1%–99.6%). Two of the studies reported no serious adverse events (0 of 67), but 2 patients (3.0% total) discontinued the drug due to adverse events (Supplementary Tables S5 and S8).⁹⁹ Across 11 studies with 529 patients with CKD G5D, our meta-analysis demonstrated a SVR12 of 96.9% (95% CI: 95.1%–98.3%). Adverse events were rare; 0.5% (2 of 435) reported serious adverse events and 1.6% (4 of 352) discontinued DAAs due to adverse events (Supplementary Tables S6 and S10). Therefore, GLE/PIB

combination can be safely used in patients with CKD G4-G5ND and G5D without dose adjustment. A treatment duration of 8 weeks is sufficient for most patients without cirrhosis.

Genotype-specific regimens. Since not all regimens are pangenotypic, other regimens such as grazoprevir-elbasvir, paritaprevir-ritonavir-ombitasvir with or without dasabuvir (PrOD), and daclatasvir-asunaprevir can also be safely used in appropriate patients with CKD G4-G5ND and G5D (Figure 1 and Supplementary Tables S5 and S6)

Grazoprevir/Elbasvir (GZR/ELB). Grazoprevir-elbasvir (GZR/ELB) combination is licensed for patients with HCV GTs 1 and 4, with safety and efficacy data available in patients with CKD G4-G5 and G5D. Both agents are metabolized by CYP3A and primarily (>90%) excreted in feces with minimal renal clearance (<1%).¹⁰⁰

The C-SURFER trial evaluated 12 weeks of GZR/ELB in patients with CKD G4-G5ND and G5D with HCV GT 1; 81% of patients had CKD G5, and 76% were on hemodialysis. Patients were randomized in this double-blind trial to either immediate 12 weeks therapy or deferred treatment.¹⁰¹ The majority had GT 1a (52%), and 80% were treatment-naïve. SVR12 was 99%, with 1 relapse 12 weeks after the end of treatment, with no significant difference between GTs 1a and 1b, nor between those undergoing hemodialysis and those with advanced CKD not on dialysis therapy. Tolerability was excellent, and adverse events were comparable in the treatment and control arms. Renal events such as acute kidney injury, decrease in GFR, and need to start hemodialysis were comparable in both groups.^{101,102} These results have been confirmed in a real-world French cohort study.¹⁰³ For patients with CKD G4-G5ND, across 5 studies (n = 857) SVR12 was 96.7% (95% CI: 95.4%–97.8%); however, only 1 of these studies (n = 14) reported on adverse events (Supplementary Tables S5 and S8). For patients with CKD G5D, across 11 studies (n = 962), SVR12 was 96.5% (95% CI: 94.9%–97.8%) with only 0.6% (1 of 163) experiencing serious adverse events, and 2.5% (n = 166) discontinuing treatment due to adverse events (Supplementary Tables S5 and S10).

Ritonavir-boosted paritaprevir with ombitasvir and dasabuvir (PrOD). The combination of ritonavir-boosted paritaprevir with ombitasvir and dasabuvir (PrOD, also known as 3D regimen) for 12 weeks was evaluated in the open-label RUBY-1 study in patients with HCV GT 1 and CKD G4-G5 including patients on hemodialysis, which demonstrated excellent efficacy with SVR12 of 90%. One treatment failure was non-virological (unrelated death after conclusion of treatment), and there was 1 relapse.^{104,105} RBV was used in combination with the PrOD regimen in patients with HCV GT 1a. However, even with a reduced dose of 200 mg RBV daily, 9 out of 13 patients with GT 1a had to interrupt RBV treatment due to anemia, and 4 patients required erythropoiesis-stimulating agents.¹⁰⁵

The RUBY-2 trial investigated a 12-week RBV-free treatment course of PrOD in 19 patients with CKD G4 and G5 (including dialysis) with HCV GT 1a or 4.¹⁰⁶ The SVR12 rate

in this trial was also high, even among patients with GT 1a, and there were no adverse events due to anemia.

Real-world PrOD regimen data from the ERCHIVES study and several case series also demonstrated high SVR rates.^{107–113} Our meta-analysis included 16 studies conducted in patients with CKD G5D (n = 582) in which PrOD was used with or without RBV for 12 weeks to treat HCV GTs 1 and 4. SVR12 was 96.8% (95% CI: 95.2%–98.1%), with 0.2% (1 of 406) having serious adverse events and 1.8% patients (n = 446) discontinuing DAAs due to adverse events (Supplementary Tables S6 and S10). PrOD has been less extensively evaluated in patients with CKD G4-G5ND. Across 3 studies (n = 103), the estimate of SVR12 is somewhat imprecise (89.4%; 95% CI: 75.7%–97.8%), with no serious adverse events or discontinuations due to adverse events reported (Supplementary Tables S5 and S8).

Daclatasvir/asunaprevir (DCV/ASV). Daclatasvir (DCV, an NS5A inhibitor) and asunaprevir (ASV, an NS3/NS4A protease inhibitor) in combination have been studied primarily in Japanese patients with HCV GT 1b on hemodialysis with SVR rates reported between 76% and 100%. A large post-marketing study of all patients receiving DCV/ASV in Japan reported an overall SVR rate of 88.4% with 24 weeks of treatment with this regimen,^{114–116} but adverse events were more frequent in patients with eGFR < 30 ml/min per 1.73 m² (implicitly including both patients who were and were not treated with dialysis). Concerns associated with this regimen include possible lower SVR in patients with HCV GT 1b with resistance-associated variants.^{117–119} For the general population, the Asian Pacific Association for the Study of the Liver (APASL) suggests this regimen can be used in patients with HCV GT 1b and impaired kidney function if resistance-associated variants are absent.¹²⁰ Among patients on dialysis, our meta-analysis across 9 studies (n = 341) conducted mostly in Japan SVR12 was 93.6% (95% CI: 89.5%–96.8%) with 0.4% (n = 274) reporting a serious adverse event, but 3.8% (n = 341) discontinuing treatment due to an adverse event (Supplementary Tables S6 and S10). The regimen has not been adequately evaluated in patients (n = 10) with CKD G4-G5 not on dialysis (Supplementary Table S8).

Toxicity. A particular concern with SOF had been the putative cardiac toxicity,^{121,122} although subsequent analyses could not confirm such observations.¹²³ However, post-marketing symptomatic bradycardia has been reported when it was administered with amiodarone.¹²⁴ Another early concern had been whether DAA therapy might accelerate the decline of kidney function in CKD, but recent data have provided reassurance regarding SOF. Sise *et al.*¹²⁵ reported that in patients with CKD G3a–G3b who received SOF-based regimens, HCV cure was associated with a 9.3 ml/min per 1.73 m² improvement in eGFR during the 6-month post-treatment follow-up. Other reports have also indicated that loss of eGFR is not a consequence of SOF use.^{123,126–130} Our review suggests that serious adverse events, discontinuations due to adverse events, or decrements in kidney function were rare in patients with CKD G4-G5ND and CKD G5D (Supplementary Tables S5, S6, and S8–S12).

No evidence of a deleterious effect of other DAAs on eGFR has been reported with non-SOF-based regimens.¹³¹ Reddy *et al.*¹³² identified 32 patients with CKD G3a-G3b included in trials with GZR/ELB and found no evidence of deterioration of kidney function as a result of treatment with these agents. [Supplementary Table S9](#) lists various studies of patients with CKD G4-G5ND that reported mean change in eGFR across various stages of CKD after treatment with various DAAs, including SOF 200 mg and 400 mg (in combination with DCV, LDV, VEL), PrOD and GLE/PIB. There was no significant decline in GFR at the end of treatment with any regimen, and in 1 study, patients with CKD G4 had a small improvement in mean GFR (1.6 ml/min; 95% CI: -0.1 to 3.3) after treatment with a SOF 400 mg/VEL regimen.¹³⁰

Protease inhibitors (“-previrs” such as simeprevir, paritaprevir, and grazoprevir) are contraindicated in patients with cirrhosis, Child-Pugh class B or C, due to hepatotoxicity.¹³³

In summary, we recommend treatment of HCV in patients with CKD G4-G5ND and G5D with a RBV-free DAA-based regimen. The combination SOF-based regimens SOF/DCV, SOF/LDV, and SOF/VEL have been shown to be safe and effective in patients with CKD G4-G5, with or without dialysis ([Supplementary Tables S5 and S6](#)). In Europe and the US, labeling for SOF has been expanded to include patients with CKD G4-G5, including those on dialysis¹²³ (see SOF/VEL, SOF/VEL/voxilaprevir, SOF/LED at <https://www.ema.europa.eu/en> and in US product inserts).

Regimens such as GLE/PIB (for all GTs) and GZR/ELB (for GTs 1 or 4) are also safe and effective in patients with CKD G4-G5ND and G5D. In addition, for patients on dialysis, PrOD (for GTs 1 or 4) and DCV/ASV (for GT 1b) are safe and effective ([Supplementary Tables S5 and S6](#)).

Our systematic review found no evidence to recommend specific DAA regimens in patients on peritoneal dialysis, but it is reasonable to follow guidance for patients on hemodialysis.¹²⁶

Our guidance is in overall concordance with that provided by AASLD (<https://www.hcvguidelines.org/unique-populations/renal-impairment>) and EASL (<http://www.easl.eu/research/our-contributions/clinical-practice-guidelines>), but given that recommended drugs and dosages are constantly evolving, clinicians should consult these resources for the most up-to-date management information.

Kidney transplant recipients (CKD G1T-G5T). DAA therapy in kidney transplant recipients with HCV is effective and well tolerated ([Supplementary Tables S7 and S13–S15](#)). In a trial comparing 12 and 24 weeks of SOF/LDV in 114 kidney transplant recipients with HCV GTs 1 and 4 (96% GT1) and eGFR ≥ 40 ml/min per 1.73 m² (median 56 ml/min per 1.73 m²), SVR12 rates were close to 100%, without differences between arms, suggesting that a 12-week regimen is appropriate in this population.¹³⁴ Smaller cohort studies recently also reported excellent results in kidney transplant recipients with SOF-based regimens.^{135–137} Pooled analysis of 6 studies from India (n = 117) showed that SOF use in combination with RBV alone had a SVR12 of 94.8% (88.2%–99.8%) in

kidney transplant recipients ([Supplementary Tables S7 and S13](#)). Across 12 studies using SOF-based regimens, 5 of 436 patients (1.1%, in 2 studies) had serious SOF-related adverse events and, in 14 studies, only 3 of 510 patients (0.6%) discontinued treatment due to adverse events ([Supplementary Table S13](#)).

Across 10 studies (n = 300), SOF/LDV had high SVR12 (97.3%; 95% CI: 94.9%–99.0%) with few serious adverse events (2.6%, n = 170) or discontinuations due to adverse events (1.7%, n = 224) ([Supplementary Tables S7 and S14](#)). In 3 studies (n = 84), 1.2% (95% CI: 0.2%–0.8%) of patients on SOF/LDV experienced graft loss, and in 4 studies (n = 109), 6.2% (95% CI: 2.3%–12.0%) experienced acute rejection.

SOF/DCV had a similarly high SVR12 (99.7%; 95% CI: 97.6%–100%) in 6 studies (n = 290) and no serious adverse events (n = 166) or discontinuation due to adverse events (n = 186) ([Supplementary Table S13](#)). In 2 studies, no episodes of graft loss occurred in 141 patients, and in 3 studies, 3.4% of patients (n = 246) experienced acute rejection ([Supplementary Table S14](#)).

Reau *et al.*¹³⁸ described the use of GLE/PIB in 100 organ transplant recipients, 20 of whom had received a kidney transplant, with high SVR and excellent tolerability, but no other study reported on GLE/PIB use specifically in kidney transplant recipients (KTRs). Furthermore, Fabrizi *et al.*¹³⁹ recently reported that various DAAs were highly effective in a retrospective study on 95 patients after kidney transplantation (SVR 93.7%). These findings are similar to those in other recent reports.¹⁴⁰

In summary, kidney transplant recipients with GFR ≥ 30 ml/min per 1.73 m² (CKD G1T-G3bT) can receive pan-genotypic treatments such as SOF-based regimens and GLE/PIB. If they are not available, GZR/ELB or PrOD can be considered for GTs 1a, 1b, and 4, though caution should be exercised with calcineurin inhibitors (CNIs) as elaborated below. For kidney transplant recipients with GFR < 30 ml/min per 1.73 m² (CKD G4T-G5T), the same regimens proposed for patients with CKD G4-G5ND apply. Our guidance is in general concordance with that provided by AASLD (<https://www.hcvguidelines.org/unique-populations/kidney-transplant>) and EASL (<http://www.easl.eu/research/our-contributions/clinical-practice-guidelines>), but given that recommended drugs and dosages are constantly evolving, clinicians should consult these resources for the most up-to-date treatment information.

Drug–drug interactions. Drug–drug interactions are an important factor in the choice of a DAA regimen. Important drug interactions of DAAs occur with immunosuppressants, such as tacrolimus and cyclosporine in transplant recipients which may result in increased or diminished plasma levels of immunosuppressive agents. Protease inhibitors have a significant risk for drug–drug interactions, particularly in patients who are treated with immunosuppressive agents such as CNIs and mammalian target of rapamycin (mTOR) inhibitors.^{104,141} NS5B inhibitors such as SOF or NS5A inhibitors such as LDV

and DCV are associated with a low risk of drug–drug interaction with CNIs and mTOR inhibitors, but may have interactions with other concomitant medications. Concurrent use of GZR/ELB and cyclosporine is not recommended, as it results in a 15-fold increase in GZR area under the curve (AUC) and a 2-fold increase in elbasvir AUC. GZR/ELB increases levels of tacrolimus by 43%; thus, close monitoring of levels is indicated, and dose reductions of tacrolimus may be needed. Other protease inhibitors such as paritaprevir have similar drug–drug interactions with cyclosporine, tacrolimus, and everolimus. There are no significant drug–drug interactions with these protease inhibitors and mycophenolate mofetil (MMF). No significant interactions between NS5A and NS5B polymerase inhibitors such as SOF and CNIs have been described, but close monitoring of immunosuppressive drugs is mandatory because changes in liver metabolism concurrent with HCV eradication may require modification of immunosuppressive drug doses.

Of note, GZR is a substrate of OATP1B1/3, and co-administration with drugs that inhibit OATP1B1/3 (such as enalapril, statins, digoxin, some angiotensin-receptor blockers) may result in increased levels of GZR that may lead to clinically significant hyperbilirubinemia. GZR and ELB are substrates of CYP3A, and co-administration with strong CYP3A inducers (such as rifampin, phenytoin, and St John's wort) is contraindicated, as it may result in decreased plasma concentrations and potentially reduced antiviral activity of both agents. The Hepatitis Drug Interactions website from the University of Liverpool (<http://www.hep-druginteractions.org>) is a valuable resource for determining the risk and management recommendations for drug–drug interactions. This tool can inform the selection of optimal DAAs and concomitant medications, and the potential suspension of specific pharmacotherapies in order to avoid drug–drug interactions.

Reactivation of HBV infection with DAA therapy. A number of reports have recently described apparent reactivation of

hepatitis B virus (HBV) infection in individuals following otherwise successful therapy of HCV infection with DAA-based regimens,^{142,143} which has prompted a US FDA warning.¹⁴⁴ The European Medicine Agency (www.ema.europa.eu), EASL, and APASL have expressed similar concerns.¹⁴⁵ As part of routine evaluation of patients with HCV and CKD, HBV serological markers (i.e., hepatitis B surface antigen [HBsAg], anti-HBc and anti-HBs [antibodies to HBV core and surface antigens, respectively]) should be obtained prior to antiviral therapy. If HBsAg is present, patient should undergo assessment for HBV therapy. If HBsAg is initially 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 liver function tests rise during DAA therapy (see also <https://www.hcvguidelines.org/evaluate/monitoring>, <https://easl.eu/wp-content/uploads/2018/10/HepB-English-report.pdf>¹⁴⁶).

Research recommendations

- Studies of patients with CKD should clearly and transparently report separate results for patients with CKD G1–G3, CKD G4–G5ND, and CKD G5D. Studies are needed in patients receiving peritoneal dialysis.
- Studies examining understudied DAAs, especially affordable therapies for potential use in low- and middle-income countries,¹⁴⁷ should also be investigated in various CKD populations.
- Studies should be conducted on the re-treatment of DAA regimen failures in CKD. Furthermore, optimal therapy prior to and after kidney transplantation in some specific groups such as prior non-responders should be evaluated, as well as treatment of NS5A-resistant variants.
- The impact of treating HCV infection on CKD progression should be further investigated.
- Studies should investigate the survival benefit for patients with CKD G5D and HCV following successful DAA therapy.

Chapter 3: Preventing HCV transmission in hemodialysis 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 (see [Table 1](#)) (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 that 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 that 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*).

Rationale

The prevalence of HCV infection in patients on hemodialysis is usually higher than in the general population.¹⁴⁸ HCV prevalence rates range from about 4%–9% in most high-income countries, but are significantly higher in other countries, particularly those in the Middle East, North and Sub-Saharan Africa, Asia, and Eastern Europe^{13,149–151} ([Table 2](#)^{152–160}). Rates also vary during times of social crisis,

war, or economic downturn.^{161–163} According to a recent systematic review of studies in patients on hemodialysis based on data up to 2006, the overall global incidence rate of HCV infection was 1.47 per 100 patient-years: 4.44 per 100 patient-years in low- to middle-income countries, and 0.99 per 100 patient-years in high-income countries.¹⁶⁴

HCV is easily transmitted parenterally, primarily through percutaneous exposure to blood. Dramatic reductions were noted in the incidence following introduction of screening for HCV in blood donors and reduction in blood transfusion requirements following introduction of erythropoiesis-stimulating agents,¹⁶⁵ leaving nosocomial transmission as the main method of spread of HCV in dialysis units. Several studies have confirmed nosocomial transmission in dialysis units using epidemiologic and phylogenetic data obtained by viral sequencing.^{18,31,166–169} These data are further supported by the observation of decline in infection rates following routine implementation of infection control practices and virological follow-up to detect anti-HCV using sensitive, specific new-generation serological tests.^{14,170} A multicenter survey revealed that prevalence of anti-HCV positivity for a Belgian cohort of patients on hemodialysis ($n = 1710$) dropped steadily from 13.5% in 1991 to 6.8% in 2000, and the same survey revealed significant drops in other European countries including France (42% to 30%), Italy (28% to 16%), and Sweden (16% to 9%).¹⁷⁰ [Table 2](#) provides an overview of HCV prevalence in patients on hemodialysis as summarized from some recent studies.

Nevertheless, more than 50% of all health care–associated HCV outbreaks from 2008 to 2015 reported to the CDC occurred in hemodialysis settings.¹⁷¹ As a result, the CDC recently provided guidance on improving infection control practices to stop HCV transmission in dialysis units.¹⁷²

Infection control. Infection control lapses responsible for HCV transmission contribute to transmission of other pathogens; hence implementation of improvement efforts will have broader salutary effects. Most importantly, HCV transmission can be prevented effectively through adherence to currently recommended infection control practices. There are

Table 1 | Infection control practices (“hygienic precautions”) particularly relevant for preventing HCV transmission

- Proper hand hygiene and glove changes, especially between patient contacts, before invasive procedures, and after contact with blood and potentially blood-contaminated surfaces/supplies
- Proper injectable medication preparation practices following aseptic techniques and in an appropriate clean area, and proper injectable medication administration practice
- Thorough cleaning and disinfection of surfaces at the dialysis station, especially high-touch surfaces
- Adequate separation of clean supplies from contaminated materials and equipment

Table 2 | Recent reported HCV prevalence in hemodialysis patients

Country	N	Year of testing	HCV prevalence (%)	Source
Australia-New Zealand	393	2012	3.8	DOPPS 5 ¹⁵²
Belgium	485	2012	4.0	DOPPS 5 ¹⁵²
Brazil	798	2011	8.4	Rodrigues de Freitas ¹⁵³
Canada	457	2012	4.1	DOPPS 5 ¹⁵²
China	1189	2012	9.9	DOPPS 5 ¹⁵²
Cuba	274	2009	76	Santana ¹⁵⁴
Egypt	—	2007–2016	50	Ashkani-Esfahani ¹⁵⁵
France	501	2012	6.9	DOPPS 4 ¹⁵²
Germany	584	2012	4.5	DOPPS 5 ¹⁵²
Gulf Cooperation Council	910	2012	19.3	DOPPS 5 ¹⁵²
India	216	2012	16	NephroPlus
	1050	2013	11	
	3068	2014	8	
Iran	—	2006–2015	12	Ashkani-Esfahani ¹⁵⁵
Iraq	—	2008–2015	20	Ashkani-Esfahani ¹⁵⁵
	7122	2015	10	
	7673	2016	9	
Italy	485	2012	11.5	DOPPS 5 ¹⁵²
Japan	1609	2012	11.0	DOPPS 5 ¹⁵²
Jordan	—	2007–2015	35	Ashkani-Esfahani ¹⁵⁵
Lebanon	3769	2010–2012	4.7	Abou Rached ¹⁵⁶
Libya	2382	2009–2010	31.1	Alashek ¹⁵⁷
Nigeria	100	2014	15	Ummate ¹⁵⁸
Palestine	—	2010–2016	18	Ashkani-Esfahani ¹⁵⁵
Romania	600	2010	27.3	Schiller ¹⁵⁹
Russia	486	2012	14.0	DOPPS 5 ¹⁵²
Saudia Arabia	—	2007	19	Ashkani-Esfahani ¹⁵⁵
Senegal	106	2011	5.6	Seck ¹⁶⁰
Spain	613	2012	8.9	DOPPS 5 ¹⁵²
Sweden	426	2012	6.0	DOPPS 5 ¹⁵²
Syria	—	2009	54	Ashkani-Esfahani ¹⁵⁵
Turkey	383	2012	7.0	DOPPS 5 ¹⁵²
United Kingdom	397	2012	4.6	DOPPS 5 ¹⁵²
United States	2977	2012	7.3	DOPPS 5 ¹⁵²

DOPPS, Dialysis Outcomes and Practice Patterns Study; HCV, hepatitis C virus.

no reports of transmission of HCV in dialysis units that had all infection control practices in place. Publication bias is unlikely to explain this observation. Additionally, in the experience of the authors, centers that have had HCV transmission identified and that subsequently responded with increased attention to appropriate infection control practices have not had continued transmission. This observation applies to unpublished outbreaks and transmission events.

Three systematic reviews have examined the reasons behind transmission of HCV in hemodialysis units.^{31,167,173}

Root cause analysis of confirmed nosocomial outbreaks^{19,26,28,174,175} has revealed lapses in infection control to be associated with transmission of HCV infection between patients in dialysis units. For several reasons, including the long latency period of HCV infection, the number of dialysis treatments occurring during a patient's likely exposure period (based on multiple treatments per week), and sparse documentation of details in the dialysis treatment record, retrospective investigation to determine an exact cause of dialysis-related HCV acquisition is challenging. Rarely, the exact cause can be surmised using epidemiologic and molecular virology data. More often, transmission is documented among patients in the same clinic, who lack other common exposures and/or risk factors, and lapses in infection control are identified in

the clinic that could logically lead to transmission (Table 3). Other causes of infection such as undergoing dialysis during travel to developing countries, and nondialysis health care exposures (e.g., procedures performed in a common vascular access surgical center) can occur and are considered before concluding that transmission occurred in the dialysis unit.

Mishandling of parenteral medications has been implicated frequently in transmission. Medication vials can become contaminated with HCV when accessed with used needles or syringes, or through environmental or touch

Table 3 | Factors and lapses in infection control practices associated with transmission of HCV infection in dialysis units

- Preparation of injections in a contaminated environment (including at patient treatment station)
- Reuse of single-dose medication vial for more than 1 patient
- Use of mobile cart to transport supplies or medications to patients
- Inadequate cleaning or disinfection of shared environmental surfaces between patients
- Failure to separate clean and contaminated areas
- Failure to change gloves and perform hand hygiene between tasks or patients
- Hurried change-over processes
- Low staff-to-patient ratio

HCV, hepatitis C virus.

contamination of the vial diaphragm by health care personnel hands. The US CDC's *One & Only Campaign* on safe injection practices (<http://www.oneandonlycampaign.org/>) should help address the former issue by promoting single use of syringes. The latter issue concerning contamination is more likely to occur when medications are stored or prepared in contaminated areas and blood-contaminated items are handled in close proximity. Sharing of multidose heparin or other medication vials or spring-triggered devices for glucose monitoring can lead to transmission. Inadequate cleaning and disinfection of shared environmental surfaces also increases risk of transmission. This may include failure to adequately clean and disinfect external surfaces of hemodialysis machines, treatment chairs, and other surfaces in the treatment station, and failure to clean blood spills.

It should be emphasized that blood contamination of environmental surfaces and equipment both at the patient treatment station and outside the immediate treatment area can be present, even in the absence of visible blood. HCV RNA has been detected on external surfaces of dialysis machines, a dialysate connector, on a shared waste cart, and in hand washings of dialysis personnel.^{176–182} Blood that is visible or not visible to the naked eye, as evidenced by chemical tests, has also been detected on dialysis treatment station surfaces that underwent routine cleaning procedures following an outbreak of HCV.¹⁸ HCV can persist in an infectious state for at least 16 hours, and potentially much longer, on surfaces at room temperature.^{181,183} Hand hygiene also plays an important role in prevention of nosocomial transmission.¹⁸⁴ Lack of adherence to standard practices, such as hand-washing and glove use and removal practices, has been documented in several audits. In most HCV outbreaks in US hemodialysis centers reported to the CDC, multiple lapses in infection control were identified, involving practices such as hand hygiene and glove use, injectable medication handling, and environmental surface disinfection.¹⁷¹

Petrosillo *et al.*¹⁸⁵ conducted a multicenter study in 58 Italian hemodialysis centers and found that the adjusted risk of transmission was correlated with dialysis in units with a high prevalence of HCV-infected patients at baseline and those with a low personnel-patient ratio. A study of 87 US hemodialysis centers similarly found that baseline HCV prevalence of greater than 10%, low staff-to-patient ratio, and ≥ 2 -year duration of treatment in the facility were independently associated with frequency of HCV infections that were likely to be acquired in the facility.¹⁸⁶

Implementation of infection control practices can be advanced by establishing a list of evidence-based interventions, such as those recommended by the CDC, and regularly assessing and reinforcing adherence to practice through observational audits. Infection control practices that may be most critical to improve (based upon observation of breaches in outbreak situations that are likely to transmit HCV) are shown in Table 1. The CDC has checklists and audit tools to assist facilities in implementing and assessing many of these practices.¹⁸⁷

Isolation. Isolating HCV-infected patients (or patients awaiting HCV screening results) during hemodialysis is defined as physical segregation from others for the express purpose of limiting direct or indirect transmission of HCV. The traditional definition of contact isolation is that used for HBV infections in hemodialysis centers (i.e., dedicated room, machine, equipment, gowns, and personnel). However, “isolation” as considered for HCV control has involved multiple varied approaches and policies, including the use of a dedicated dialysis machine, personnel, room, or shift, and/or other barrier precautions (e.g., aprons, gowns, or gloves) by health care professionals attending these patients.

Whereas the complete isolation of HBV-infected patients (by room, thus including machine, equipment, and staff) has proven invaluable in halting the nosocomial transmission of HBV within hemodialysis units,¹⁸⁸ there are multiple reasons that argue against recommending isolation of HCV-positive patients¹⁸⁹:

- (i) Isolation purely for HCV will have no impact on transmission of other infections. Segregation of patients can create a false sense of reassurance around practices that could easily result in bloodstream infections (BSIs) or transmission of multi-drug resistant organisms or other blood-borne pathogens.
- (ii) Segregating patients on the basis of HBV and HCV would create 4 separate cohorts, which creates a significant logistical challenge. The treatment of HCV infection in patients on dialysis raises an additional logistical difficulty of how to assign cohort patients undergoing therapy.
- (iii) Isolating only on HCV infection status may expose the isolated patient to infection with a second HCV GT.
- (iv) HCV seroconversion may be delayed for several months in newly infected patients on hemodialysis and serological testing cannot be relied on to exclude recent infection.¹⁹⁰
- (v) Starting and maintaining isolation is likely to impose large costs on already expensive dialysis programs.

The evidence for the use of isolation of HCV-infected patients during hemodialysis is weak, based on very low-quality evidence (Supplementary Tables S16 and S17). The KDIGO 2008 HCV guideline³¹ stated that hemodialysis units should ensure implementation of and adherence to strict infection control procedures designed to prevent transmission of blood-borne pathogens, including HCV, but isolation of HCV-infected patients was not recommended as an alternative to strict infection control procedures (unless in cases of continued health care-acquired transmission, where a local isolation policy may be deemed necessary).

A recent Cochrane review¹⁹¹ examined the impact of isolation as a strategy for controlling transmission of HCV infection in hemodialysis units. Of the 123 full-text articles identified, the authors could find only 1 randomized controlled trial (RCT).¹⁹² This cluster RCT included a total of 12 hemodialysis centers (593 patients) assigned to either dedicated hemodialysis machines for HCV-infected patients or no dedicated machines. Two follow-up periods were included in the study, and each was 9 months long. Staff was

educated on standard infection control practices. Although the original article reported a significant reduction in the proportion of new infections in the second follow-up period among the facilities using dedicated versus nondedicated machines (calculated using chi-square test), based on a more standard risk ratio analysis, the Cochrane review concluded that the use of dialysis machines dedicated for HCV-infected individuals, as compared with the use of nondedicated machines, made no difference in terms of reducing the incidence of HCV infection during the follow-up period. In addition, the quality of evidence was rated as “very low” due to several methodological issues.

Other studies examining isolation as a means of reducing HCV transmission reported a reduction of transmission, but they were observational and had very poor-quality evidence with methodological challenges.^{193–195} The isolation policies studied included implementing the isolation or cohorting of infected patients in a separate room; using exclusive machines; or employing dedicated machines, room, and staff. Most studies have adopted a “before-and-after” design, and compared their results with their own historical controls.^{196–199} Thus, it is unclear whether the reported improvement resulted from the isolation policy or rather from the simultaneous raising of awareness and reinforcement of the application of hygienic precautions. Furthermore, in some studies, there might be other contributing factors such as changes in baseline prevalence and injection safety and hygienic practices over time.

In contrast to these studies, a DOPPS (Dialysis Outcomes and Practice Patterns Study) multicenter study and an Italian multicenter study both concluded that isolation did not protect against transmission of HCV in patients on hemodialysis,^{13,185} and some prospective observational studies have shown reduction of transmission after adoption of universal precautions.²⁰⁰ A prospective observational study showed a reduction in the annual incidence of HCV seroconversion from 1.4% to 0% after the reinforcement of basic hygienic precautions, without any isolation measures.²⁰¹

The CDC does not recommend the isolation of HCV-infected patients in its infection-prevention guidelines.²⁰ The UK Renal Association also states that patients with HCV do not need to be dialyzed in a segregated area; however, more experienced staff should be assigned. They further recommend that if nosocomial transmission continues to occur despite reinforcement and audit of the precautions, a local segregation policy may be deemed necessary.²⁰² The European Best Practice Work Group considers implementation of universal hygienic measures to be the standard of care.²⁰³

Finally, several experts and guidelines acknowledge that because transmission can be effectively prevented by adherence to currently recommended practices, considering isolation of seropositive patients indicates a failure of adherence to the current standard and would have a negative impact on the implementation and reinforcement of basic hygienic measures in the unit as a whole.

Dedicated dialysis machines. Evidence of HCV transmission through internal pathways of the modern single-pass dialysis machine has not been demonstrated.³¹ Transmission would require the virion to cross the intact dialyzer membrane, migrate from the drain tubing to the fresh dialysate circuit, and pass again through the dialyzer membrane of a second patient. However, the virus does not cross the intact membrane, and even in the event of a blood leak, transmission would require HCV to reach fresh dialysate used for a subsequent patient and enter the blood compartment for that patient through back-filtration across the dialyzer membrane, a highly unlikely scenario. Almost all the studies included in the various systematic reviews have conclusively excluded transmission via the internal dialysis pathway. In a few cases, a role for the dialysis circuit could not be excluded, but the environmental surfaces are more likely to have contributed to transmission.¹⁸

Receiving dialysis next to, rather than sharing the same dialysis machine with, an HCV-infected patient has been found to be a risk factor for HCV acquisition.²⁰⁴ In outbreak investigations with phylogenetic viral sequencing analysis, transmission is sometimes documented from an infected patient to a subsequent patient treated at the same station on the next shift, and also from an infected patient to patients treated in nearby stations during the same or subsequent shifts, which indicates transmission independent of the machine. Hurried and incomplete disinfection of external machine surfaces and other surfaces at the station (e.g., side table, dialysis chair, blood pressure cuff, or prime waste container) are lapses commonly identified in these outbreaks. In some investigations, transmission involving the dialysis machine was essentially ruled out.¹⁶⁹ In several studies included in the systematic reviews of HCV transmission, nosocomial spread was documented despite the existence of a policy of dedicated machines. Taken together, this information confirms that contamination of dialysis machine components cannot be the sole contributor to transmission, and may have little to no role in HCV spread. While contaminated external surfaces of dialysis machines might facilitate HCV spread, other surfaces in the dialysis treatment station are likely to have the same impact, diminishing the purported value of using dedicated machines. Similar to the concern about the risks of isolating dialysis patients with HCV, it should be stressed that using dedicated machines may trigger the perception that there is no longer a risk of nosocomial HCV transmission and thus reduce the attention devoted by hemodialysis staff members to body fluid precautions.

Reuse. During the reuse procedure, patient-to-patient transmission can take place if the dialyzers or blood port caps are switched between patients and not sterilized effectively or if there is spillage of contaminated blood or mixing of reused dialyzers during transport. These situations can be eliminated by adherence to standard hygienic precautions and appropriate labeling. Two large studies have not identified reuse as a risk factor for HCV transmission,^{201,205} whereas a weak association was shown in 1 study, likely due to unmeasured confounders.²⁰⁶

Table 4 | Hygienic precautions for hemodialysis (dialysis machines)**Definitions**

- The 'transducer protector' is a filter (normally a hydrophobic 0.2- μ m filter) that is fitted between the pressure-monitoring line of the extracorporeal circuit and the pressure-monitoring port of the dialysis machine. The filter allows air to pass freely to the pressure transducer that gives the reading displayed by the machine, but it resists the passage of fluid. This protects the patient from microbiologic contamination (as the pressure-monitoring system is not disinfected) and the machine from ingress of blood or dialysate. An external transducer protector is normally fitted to each pressure-monitoring line in the blood circuit. A back-up filter is located inside the machine. Changing the internal filter is a technical job.
- A "single-pass machine" is a machine that pumps the dialysate through the dialyzer and then to waste. In general, such machines do not allow fluid to flow between the drain pathway and the fresh pathway except during disinfection. "Recirculating" machines produce batches of fluid that can be passed through the dialyzer several times.

Transducer protectors

- External transducer protectors should be fitted to the pressure lines of the extracorporeal circuit.
- Before commencing dialysis, staff should ensure that the connection between the transducer protectors and the pressure-monitoring ports is tight, as leaks can lead to wetting of the filter.
- Transducer protectors should be replaced if the filter becomes wet, as the pressure reading may be affected. Using a syringe to clear the flooded line may damage the filter and increase the possibility of blood passing into the dialysis machine.
- If wetting of the filter occurs after the patient has been connected, the line should be inspected carefully to see if any blood has passed through the filter. If any fluid is visible on the machine side, the machine should be taken out of service at the end of the session so that the internal filter can be changed and the housing disinfected.
- Some blood tubing sets transmit pressure to the dialysis machine without a blood-air interface, thus eliminating the need for transducer protectors.

External cleaning

- After each session, the exterior of the dialysis machine and all surfaces in the dialysis treatment station should be cleaned with a low-level disinfectant if not visibly contaminated. Pay particular attention to high-touch surfaces that are likely to come into contact with the patient (e.g., arm rests, blood pressure cuff) or staff members' hands (e.g., machine control panel).
- Disinfection of external machine surfaces should not commence until the patient has left the dialysis treatment station. A complete (unit-wide) patient-free interval between shifts might facilitate more thorough cleaning and disinfection of the unit.
- If a blood spillage has occurred, the exterior should be disinfected with a commercially available tuberculocidal germicide or a solution containing at least 500 p.p.m. hypochlorite (a 1:100 dilution of 5% household bleach) if this is not detrimental to the surface of dialysis machines. Advice on suitable disinfectants, and the concentration and contact time required, should be provided by the manufacturer.
- If blood or fluid is thought to have seeped into inaccessible parts of the dialysis machine (e.g., between modules or behind blood pump), the machine should be taken out of service until it can be dismantled and disinfected.

Disinfection of the internal fluid pathways

- It is not necessary for the internal pathways of single-pass dialysis machines to be disinfected between patients, even in the event of a blood leak. Some facilities may still opt to disinfect the dialysate-to-dialyzer (Hansen) connectors before the next patient.
- Machines with recirculating dialysate should always be put through an appropriate disinfection procedure between patients.

Management of a dialyzer membrane defect leading to blood leak. As HCV is transmitted by percutaneous exposure to blood from an infected person, effective implementation of the dialysis precautions recommended in the KDIGO 2008 HCV guideline³¹ and by the CDC should prevent nosocomial transmission. The risk that the virus leaving the dialyzer could be trapped in the Hansen connector and transferred to the fresh dialysate side through accidental misconnection is vanishingly low, hence the CDC does not recommend disinfection of "single-pass" machines between treatments on the same day, even when a blood leak has occurred.²⁰ The KDIGO 2008 HCV guideline, however, recommends disinfection of both the internal fluid pathways and the Hansen connectors before the next patient if a leak has occurred, as a matter of abundant caution, and justified it based on the rarity of such events³¹ (Table 4). We reaffirm our previous recommendation.

Audits. Audits and use of surveillance data to implement prevention steps are critical to any infection control program. Routine observational audits of various infection control practices, combined with feedback of results to clinical staff, allows for regular assessment of actual practices and identification of gaps. Data from audits can facilitate immediate interventions to correct practice and should also inform

broader quality improvement efforts, including unit-wide staff education and retraining. In the US, most dialysis centers use infection control audit tools (including tools developed by the CDC or the dialysis company) as part of their continuous quality improvement process.

Although there are no RCTs that examined the impact of audits on transmission of HCV infection in dialysis units, observational studies as part of quality improvement programs have shown reduction in the rates of BSIs following implementation of regular audits and an evidence-based intervention package. In a study from the US, 17 centers reported monthly event and denominator data to the National Healthcare Safety Network and received guidance from the CDC. The feedback included advice on chlorhexidine use for catheter exit site care, staff training and competency assessments focused on catheter care and aseptic technique, hand hygiene and vascular access care audits, and feedback of infection and adherence rates to staff. Modeled rates decreased 32% ($P < 0.01$) for BSIs and 54% ($P < 0.001$) for access-related BSIs.²⁰⁷ In a follow-up study, the reduction in access-related BSI rates was sustained for 4 years after the initial intervention implementation.²⁰⁸ The overrepresentation of hospital-based centers and lack of a control group limit generalization of these data. However, the

ongoing simplification of audit tools for ease of reporting with the use of information technology—as used in this study—precludes the need of infection control professionals on site, and leaves little justification to not recommend implementation of audits. Moreover, the scope of such audits goes beyond measuring 1 particular outcome, such as HCV transmission, and permits wider implementation of infection control measures.

Audits done in other dialysis center studies routinely show suboptimal adherence to hygienic practices. A Spanish study showed that gloves were used on 93% of occasions, and hands were washed only 36% of the time after patient contact and only 14% of the time before patient contact.²⁰⁹ In a 2002 US survey, only 53% of US outpatient ESKD facilities reported preparing injected medications in a dedicated room or area separated from the treatment area; 25% prepared these medications at a medication cart or other location in the treatment area, and 4% prepared medications at the dialysis station.²⁰⁵ A survey of 420 dialysis personnel from 45 facilities reported on hand hygiene practices and knowledge regarding HCV infection risk.²¹⁰ At these facilities, percentages of dialysis staff reported to always wash their hands and change gloves during the following activities were: 47% when going from one patient treatment station to another, 55% between administering intravenous medications to different patients, and 57% immediately before starting patients on dialysis. Other studies have shown similar findings.

Observational audits of hygienic precautions that were carried out in outbreak investigations have identified a range of problems, including lack of basic hand hygiene, failure to change gloves when touching the machine interface, or when urgently required to deal with bleeding from a fistula; carrying contaminated blood circuits through the ward unbagged; lack of routine decontamination of the exterior of machines and other surfaces even when blood spillages had occurred; and failure to change the internal transducer protector when potentially contaminated. On the other hand, when hygienic practice was reviewed through interviewing staff after an outbreak rather than by observation, no obvious breaches in procedure could be identified.

The frequency at which routine audits of infection control procedures should be carried out will depend on audit type, staff turnover and training, and on the results of previous audits. When setting up a new program, audits should be at intervals of no greater than 6 months to enable staff to gain experience with the process and ensure that any remedial actions taken have been effective. The CDC recommends that audits be performed as often as monthly to establish and constantly reinforce recommended practices. Observational audits should be conducted on various days of the week and different shifts to capture all staff, and should include particularly busy times of day such as shift changes. These factors and the number of opportunities (e.g., for hand hygiene) and procedures (e.g., injectable medication administration) observed will determine the representativeness of the results.

The CDC website (<http://www.cdc.gov/dialysis/prevention-tools/audit-tools.html>) has a number of audit tools and checklists intended to promote CDC-recommended practices for infection prevention in hemodialysis facilities. The audit tools and checklists can be used by individuals when assessing staff practices. They can also be used by facility staff themselves to help guide their practices. In some centers, audit tools have been shared with patients, who are asked to assess staff practice as a means of engaging patients in the infection control efforts of the facility and improving the culture of safety in units.²¹¹ Patients should be educated on correct practices and should feel empowered to speak up when they observe a breach in hand hygiene or other staff practice.

It is known that hand hygiene practices improve when study participants are aware they are under observation. In 1 study, video monitoring of hand hygiene (performed via review of video surveillance footage) was shown to be a more accurate method than direct observation.²¹² Video surveillance for hand hygiene adherence should be considered, and other innovative approaches to monitoring staff adherence to recommended infection control practices should be explored.

Screening. Screening for HCV infection is essential to identifying transmission in hemodialysis units. The CDC recommends that all patients on maintenance hemodialysis be screened for anti-HCV and ALT level upon admission and that anti-HCV testing be repeated semiannually and ALT testing be repeated monthly for susceptible patients.²⁰ This is discussed in Chapter 1. Detection of seroconversions should prompt an aggressive evaluation of infection control practices to correct lapses and prevent additional cases from occurring (Table 5).²⁵ Importantly, HCV screening should not be used as a substitute for regular infection control audits.

Infrastructure requirements. Audit data show that despite the existence of guidelines to prevent transmission of infections in hemodialysis units, their implementation remains suboptimal, leading to a large preventable burden of infections that not only adversely impacts clinical outcomes, but imposes large costs on the health care system. Experience from public health interventions shows that interventions that depend on behavior change require large effort, which can undermine their impact. In contrast, making systemwide changes, such as imposition of regulations and creating an environment that discourages unhealthy behavior, is likely to have greater impact. This impact has been shown in many fields such as smoking cessation and containing HIV infection.²¹³ Examples in the dialysis field include endorsement of dialysis event BSI measure by the US National Quality Forum, and implementation of the Medicare Quality Initiative. Recommendation of uniform validated measures such as those used by the National Healthcare Safety Network are critical for comparisons and to facilitate interventions. Other systemwide changes that are likely to have a beneficial impact on infection prevention and control practices include increasing staff-to-patient ratios and instituting staff training and education requirements. Physical infrastructure changes to facilities might also be beneficial—for example,

Table 5 | Steps to initiate concurrently and undertake following identification of a new HCV infection in a hemodialysis patient (Adapted from CDC Health Alert²⁵)

- A. Report the infection to appropriate public health authority.
 - Assess risk factors of the affected patient in conjunction with public health.
- B. Determine HCV infection status of all patients in the hemodialysis unit.
 - Test all patients treated in the center for HCV infection (Chapter 1) unless they are already known to have active infection. Follow-up and testing of patients who were treated in the center and those subsequently transferred or discharged may be warranted.
- C. Conduct a thorough root cause analysis of the infection and address infection control lapses.
 - Perform rigorous assessments of staff infection control practices to identify lapses. This should minimally include assessments of hand hygiene and glove change practices; injectable medication preparation, handling, and administration; and environmental cleaning and disinfection practices.
 - Share findings with all staff members and take action to address lapses. Staff education and retraining may be necessary.
 - Consider hiring a consultant with infection prevention expertise to provide recommendations for improvement of practices and work flow and/or to help implement actions to address identified lapses.
 - Conduct regular audits to ensure improved adherence to recommended practice.
 - Demonstrations of cleaning adequacy such as use of Glo Germ (Moab, UT) or luminol might be helpful for staff education.
- D. Communicate openly with patients.
 - Inform all patients of the reason for additional HCV testing and the results of their HCV tests.
 - If transmission within the center is suspected or confirmed, inform all patients of this. Patients should also be made aware of steps being taken to assess and improve practices.

CDC, Centers for Disease Control and Prevention; HCV, hepatitis C virus.

establishing minimum space requirements between treatment stations, creating walls around individual treatment stations to establish separate rooms instead of large open spaces, and using walls to separate clean and dirty processes (e.g., separate room for medication preparation). Such possibilities should be explored, along with strategies to improve work flow and reduce unnecessary staff maneuvers that add to the already substantial number of occasions during dialysis care when glove change and hand hygiene are warranted. As such, regulatory and accrediting agencies should issue and/or incorporate recommendations to favor compliance with basic infection control practices in dialysis units, and efforts to make the desired infection control behavior the simplest or

most logical approach to care processes should be pursued (Table 6). Table 7 provides a summary of important hygienic precautions for hemodialysis center staff to follow.

Treatment of HCV infection as a means for prevention of transmission. With the availability of DAAs, there is a possibility that dialysis units might take recourse to starting HCV-infected patients on these agents with the hope that this will cure the infection and prevent transmission to uninfected patients. Several studies have shown that facility prevalence of HCV infection is associated with incidence of infection. Thus, it stands to reason that successful treatment of patients could reduce the likelihood of HCV spread in dialysis centers. However, it should be noted that transmission can occur even

Table 6 | Strategies to support adherence to infection control recommendations in hemodialysis centers

- It is important for the designers of dialysis units to create an environment that makes infection control procedures easy to implement. Adequate hand-washing facilities must be provided, and the machines and shared space should make it easy for staff to visualize individual treatment stations. Certain jurisdictions specify the area around a hemodialysis machine.
- The unit should ensure that there is sufficient time between shifts for effective decontamination of the exterior of the machine and other shared surfaces.
- The unit should locate supplies of gloves at enough strategic points to ensure that staff has no difficulty obtaining gloves in an emergency.
- When selecting new equipment, ease of disinfection should be considered.
- There are indications from the literature that the rate of failure to implement hygienic precautions increases with understaffing. Understaffing has been associated with hepatitis C outbreaks. Certain jurisdictions specify a specific nurse-to-patient ratio (e.g., 1:4 in France). Formal healthcare training of all staff should be required (e.g., in the US, technicians provide most direct hemodialysis care but lack standardized training). Dialysis units that are changing staff-to-patient ratios, or introducing a cohort of new staff, should review the implications on infection control procedures and educational requirements.
- Resource problems should be handled by carrying out a risk assessment and developing local procedures. For example, if blood is suspected to have penetrated the pressure-monitoring system of a machine but the unit has no on-site technical support and no spare machines, an extra transducer protector can be inserted between the blood line and the contaminated system so that the dialysis can continue until a technician can attend to the problem.

The following are useful CDC and WHO informational resources to improve hand hygiene, environmental cleaning and disinfection and injection safety:

http://www.cdc.gov/dialysis/PDFs/collaborative/Env_notes_Feb13.pdf

http://www.cdc.gov/dialysis/PDFs/collaborative/Env_checklist-508.pdf

<http://www.cdc.gov/dialysis/PDFs/dialysis-Station-Disinfect-Tool-508.pdf>

<http://www.cdc.gov/dialysis/PDFs/collaborative/Hemodialysis-Hand-Hygiene-Observations.pdf>

<http://www.cdc.gov/dialysis/PDFs/collaborative/Hemodialysis-InjectionSafety-Checklist.pdf>

<http://www.cdc.gov/dialysis/PDFs/collaborative/Hemodialysis-InjectionSafety-Observations.pdf>

Hand Hygiene in Outpatient and Home-based Care and Long-term Care Facilities: http://apps.who.int/iris/bitstream/handle/10665/78060/9789241503372_eng.pdf (See Figure 9 of document and p. 44-49)

CDC, Centers for Disease Control and Prevention; US, United States; WHO, World Health Organization.

Table 7 | Key hygienic precautions for hemodialysis staff^a**Definitions**

- A "dialysis station" is the space and equipment within a dialysis unit that is dedicated to an individual patient. This may take the form of a well-defined cubicle or room, but there is usually no material boundary separating dialysis stations from each other or from the shared areas of the dialysis unit.
- A "potentially contaminated" surface is any item of equipment at the dialysis station that *could* have been contaminated with blood, or fluid containing blood, since it was last disinfected, even if there is no visual evidence of contamination.

Education

- A program of continuing education covering the mechanisms and prevention of crossinfection should be established for staff caring for hemodialysis patients.
- Staff should demonstrate infection control competency for the tasks they are assigned. Infection control competencies (e.g., use of aseptic technique) should be assessed upon hire and at least yearly thereafter.
- Appropriate information on infection control should also be given to nonclinical staff, patients, caregivers, and visitors. Patients should be encouraged to speak up when they observe an infection control practice that is concerning to them.

Hand hygiene

- Staff should wash their hands with soap or an antiseptic hand-wash and water, before and after contact with a patient or any equipment at the dialysis station. An alcohol-based hand rub may be used instead when their hands are not visibly contaminated.
- In addition to hand washing, staff should wear disposable gloves when caring for a patient or touching any potentially contaminated surfaces at the dialysis station. Gloves should always be removed when leaving the dialysis station.
- Patients should also clean their hands with soap and water, or use an alcohol-based hand rub or sanitizer, when arriving at and leaving the dialysis station.

Injection Safety

- Medication preparation should be done in a designated clean area.
- All vials should be entered with a new needle and a new syringe, which should be discarded at point of use.
- Medications should be administered aseptically, after wearing a disposable glove and disinfecting the injection port with an antiseptic.
- Hand hygiene must be performed before and after administration of injection.
- All single-dose vials must be discarded and multidose vials, if used, should not be stored or handled in the immediate patient care area.

Equipment management (for management of the dialysis machine, see Table 4)

- Single-use items required in the dialysis process should be disposed of after use on 1 patient.
- Nondisposable items should be disinfected after use on 1 patient. Items that cannot be disinfected easily (e.g., adhesive tape and tourniquets) should be dedicated to a single patient and discarded after use.
- The risks associated with use of physiologic monitoring equipment (e.g., blood pressure monitors, weight scales, and access flow monitors) for groups of patients should be assessed and minimized. Blood pressure cuffs should be dedicated to a single patient or made from a light-colored, wipe-clean fabric.
- Medications and other supplies should not be moved between patients (e.g., on carts or by other means). Medications provided in multiple-use vials, and those requiring dilution using a multiple-use diluent vial, should be prepared in a dedicated central area and taken separately to each patient. Items that have been taken to the dialysis station should not be returned to the preparation area.
- After each session, all potentially contaminated surfaces at the dialysis station should be wiped clean with a low-level disinfectant if not visibly contaminated. Surfaces that are visibly contaminated with blood or fluid should be disinfected with a commercially available tuberculocidal germicide or a solution containing at least 500 p.p.m. hypochlorite (a 1:100 dilution of 5% household bleach).

Waste and specimen management

- Needles should be disposed of in closed, unbreakable containers, which should not be overfilled. A "no-touch" technique should be used to drop the needle into the container, as it is likely to have a contaminated surface. If this is difficult due to the design of the container, staff should complete patient care before disposing of needles.
- All blood and other biologic specimen handling should occur away from dedicated clean areas, medications, and clean supplies.
- The used extracorporeal circuit should be sealed as effectively as possible before transporting it from the dialysis station in a fluid-tight waste bag or leak-proof container for disposal. Avoid draining or manipulating the used circuit. If it is necessary to drain the circuit to comply with local regulatory requirements, or to remove any components for reprocessing, this should be done in a dedicated area away from the treatment and preparation areas.

^aIn addition to standard precautions.

in centers with very low HCV prevalence.¹⁶⁸ A study that modeled HCV transmission in hemodialysis centers found that HCV prevalence influenced incidence (as did staff-to-patient ratio), but the compliance rate with hand hygiene and glove change between patients was a much stronger determinant of transmission.¹⁸⁴ Thus, even in the setting of low HCV prevalence, rigorous adherence to infection control practices is necessary. HCV prevention programs that focus solely on treatment of patients are likely to have a deleterious effect on observance of routine infection control practices, leading to paradoxically increased risk of transmission. Furthermore, reliance on HCV treatment to prevent

transmission goes against the principle of treating patients primarily for their individual benefit. Use of treatment alone as an infection control measure might place patients at increased risk of HCV and other blood-borne infections from other sources.

Implementation issues. Despite such strong data, adherence to recommended practices remains suboptimal, often due to misconceptions of the dialysis staff. A survey of 420 dialysis personnel from 45 hemodialysis facilities showed that only 35% of dialysis personnel strongly believed that patients were at risk of acquiring HCV infection in the hemodialysis facility. In contrast, 46% strongly perceived themselves to be at risk of

acquiring HCV infection through occupational exposure.²¹⁰ Personnel also were much more likely to report knowing how to protect themselves from acquiring a blood-borne pathogen infection than knowing how to protect their patients. On the basis of their observational results, which included high compliance with glove use (93%) in contrast to poor hand hygiene compliance (36%), Arenas *et al.*²⁰⁹ similarly concluded that dialysis personnel had greater concern for patient-to-staff transmission and lacked awareness of their role in facilitating pathogen transmission to patients. These data support the need for improved training and education to address knowledge gaps, as well as other initiatives focused on optimizing adherence to recommended infection control practices (Table 7). As mentioned above, implementation is more likely when guidelines are accompanied by changes in regulations.

Research recommendations

- Further observation studies should be conducted to ascertain features of facilities that do not have incident cases (e.g., staffing, physical layout, policies and practices, and baseline prevalence).
- Large, multicenter long-term RCTs of good quality are required to answer the questions concerning the benefits and harms of isolating HCV-positive patients during hemodialysis. These studies should ideally evaluate costs, patient perceptions, and complications associated with isolation. These studies should ensure the physical separation of either the center or room, or separation by treatment shift; these programs should have strict isolation strategies in place that include staff. Studies should randomize centers to either the standard of care (i.e., efforts to adhere to recommended infection control practices) or the standard of care plus isolation; they should describe the infection control efforts and compliance rates in both sets of centers, and should ensure data assessors are blinded to the interventions. The above-suggested trials remain of interest because HCV therapies may not be universally available, affordable, or prioritized for all hemodialysis patient populations. In particular, we need innovative, effective strategies to improve infection control, and it is still important to overcome barriers to identification and treatment of all infected patients (e.g., costs and reimbursement for screening and treatment regimens) in hemodialysis centers; this has implications for improved infection control practices for other endemic and emerging infections even if HCV is eradicated from hemodialysis patient populations.
- Studies should determine whether isolation of HCV-positive patients influences rates of transmission of HCV or other infections.
- The costs and impact of improved facility staffing strategies, including higher staff-to-patient ratios, on HCV transmission should be further evaluated.
- Future research should examine standard measures for detecting dialysis-associated HCV infection that do not require viral sequencing and phylogenetic analysis.
- Future research should devise innovative approaches that accurately measure infection control processes at a reasonable cost.

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

HCV infection remains more prevalent in patients with CKD G5 compared with the general population.²¹⁴ Although HCV infection can cause HCV-associated glomerular disease resulting in kidney failure,^{148,215} kidney transplant candidates may also have acquired HCV infection within a dialysis unit²¹⁶ or may have been infected when they received a previous transplant or were transfused in the era before systematic screening for HCV.^{215,217,218} Because of the deleterious effects of HCV infection in kidney transplant patients, evaluation of disease severity and need for antiviral therapy is crucial.^{219–225} Screening for HCV in kidney transplant candidates has been addressed in Chapter 1.

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).

Rationale

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

Several studies have shown that kidney transplantation is the best therapeutic option for patients with kidney failure (Supplementary Tables S18 and S19). Survival is significantly greater in patients with CKD G5 who have undergone kidney transplantation compared with those who have remained on the waiting list, irrespective of recipient age and/or comorbidities.^{226,227} As in the uninfected population, in patients with HCV, it has also been clearly shown that survival is significantly lower in dialysis patients than in kidney transplant recipients.^{221,228–230} In addition, the approval of DAAs for HCV treatment in dialysis and kidney transplant patients (see Chapter 2) allows successful HCV clearance in nearly all patients before or after transplantation. Patients who achieve SVR before transplantation do not relapse after transplantation, despite the use of potent immunosuppressive drugs.^{231,232} Thus, eligible patients should be considered for kidney transplantation regardless of their HCV status.

Prior to the era of DAA therapy, survival of patients with persistent HCV viremia after kidney transplantation was inferior compared with HCV-uninfected kidney transplant patients,^{222–224} but still higher than if they had remained on dialysis.^{221,228,229} Graft survival is significantly decreased in untreated HCV-infected kidney transplant patients compared with HCV-uninfected patients (Supplementary Tables S20 and S21).^{219,222–224,233,234} Although liver fibrosis progression in HCV-NAT positive kidney transplant patients is variable, development of cirrhosis and hepatocellular carcinoma (HCC) has been reported.^{235–238} As HCC typically develops only in HCV-infected patients with stage 3 or 4 fibrosis, surveillance for HCC should be offered if extensive fibrosis is present. It is important to note that the above associations between HCV infection and decreased graft and patient survival were derived from the era prior to the advent of DAAs for HCV infection.

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).*

HCV-NAT positive patients who are candidates for kidney transplantation should be evaluated for the presence of cirrhosis using either a noninvasive fibrosis-staging method or, on occasion, a liver biopsy. The choice of method is discussed in Chapter 1. Absence of varices on endoscopy and portal pressure gradient < 10 mm Hg suggest that cirrhosis is compensated.

In patients with compensated cirrhosis without clinically significant portal hypertension (i.e., patients with a hepatic venous pressure gradient ≥ 10 mm Hg or evidence of portal hypertension on imaging or exam, e.g., ascites, esophageal varices, collaterals on imaging),^{37,239} isolated kidney transplantation is recommended. HCV clearance following treatment halts the progression of liver disease and may even induce regression of liver fibrosis.²⁴⁰ The Consensus Conference Group on simultaneous liver–kidney transplantation proposed that combined liver–kidney transplantation should be performed if patients have decompensated cirrhosis and/or clinically significant portal hypertension.²⁴¹ Treatment of HCV in patients with decompensated cirrhosis is associated with increased risks of adverse effects, and the benefits in a patient waitlisted for a simultaneous liver–kidney transplantation are outweighed by the risks. The Portal Hypertension Collaborative Group stated that hepatic venous-pressure gradient predicts clinical decompensation in patients with compensated cirrhosis.²⁴² Patients with cirrhosis who, despite having achieved SVR, have major hepatic complications such as ascites, hepatic encephalopathy, or worsening hepatocellular function should be evaluated for combined liver–kidney transplantation. Timing of antiviral therapy for HCV in candidates for combined liver–kidney transplant should be determined by the transplant program, recognizing that organ allocation practices including use of organs from HCV-infected donors vary by country.

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).*

The use of DAAs has transformed the paradigm of treating HCV before and after kidney transplantation. DAAs can safely be used in patients on dialysis as well as post-transplant, with cure rates ($> 95\%$) similar to those in the broader population with HCV (see Chapter 2). The main consideration, currently, is timing of HCV therapy in relation to transplantation. Other considerations for planning therapy include living versus deceased donor, wait-list time by donor type, center-specific policy for acceptance of organs from HCV-infected deceased donors, and severity of liver fibrosis (Figure 3). Other factors such as candidate sensitization and patient preference can also be considered when choosing the timing of treatment. In HCV-infected patients who elect to undergo transplantation prior to DAA therapy, treatment with DAAs in the early post-transplant period is suggested in order to quickly eradicate HCV and prevent deleterious sequelae of persistent HCV viremia.

In patients with compensated cirrhosis without clinically significant portal hypertension, if living-donor kidney transplantation is anticipated without a long wait, HCV therapy can be deferred until after transplantation out of concerns for potential drug–drug interactions peritransplant. If living-donor kidney transplantation is likely to be delayed more than 24 weeks, then HCV therapy can be offered before or after transplantation; this will allow 12 weeks of therapy and 12 weeks of follow-up to confirm SVR12.

Potential kidney recipients who are infected with HCV and have compensated cirrhosis without clinically significant portal hypertension, and who are listed for kidney transplantation from a deceased donor at a center where kidneys from HCV-infected donors are available without a long wait, may wish to defer antiviral therapy to allow receipt of an organ from an HCV-infected donor. This determination should be made in consultation with a hepatologist to ensure the patient is not at increased risk of progressive liver disease with deferred treatment.²⁴³ However, the patient needs to provide written informed consent to receive a kidney from an HCV-infected donor (even though the recipient is already infected). Of note, though, in regions where kidneys from

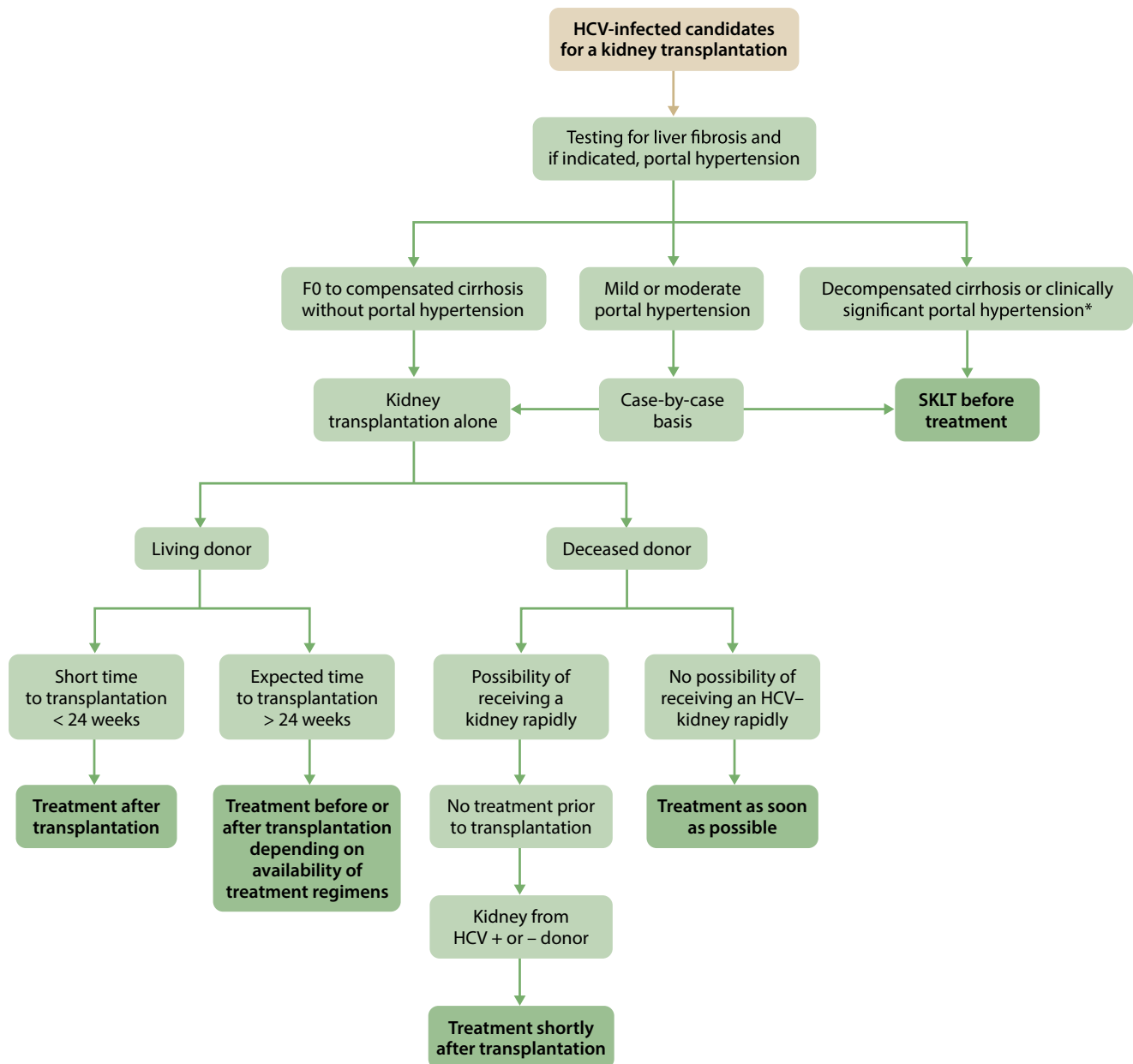


Figure 3 | Proposed management strategy in a hepatitis C virus (HCV)-infected kidney transplant candidate. *Clinically significant portal hypertension is defined as hepatic venous pressure gradient ≥ 10 mm Hg or evidence of portal hypertension on imaging or exam, e.g., ascites, esophageal varices, collaterals on imaging. F0, no scarring or fibrosis; SKLT, simultaneous kidney–liver transplantation.

HCV-infected donors are being transplanted into HCV-uninfected recipients, the increased use of kidneys from HCV-infected donors has diminished the previous waiting time advantage that HCV-positive recipients who received HCV-infected donor kidneys may have had.²⁴⁴ In contrast, when the expected waiting time for a kidney allograft from an HCV-infected donor is long, the patient should be offered HCV therapy before transplantation.

Twice-yearly surveillance for HCC is indicated in any patient with cirrhosis, regardless of the cause. Evaluation for complications of cirrhosis is indicated irrespective of whether the patient receives antiviral therapy or not.

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 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).

Rationale

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

In 1991, Pereira et al. demonstrated that HCV was transmitted by organ transplantation.²¹⁸ Several experiences published soon after the first description on the transplantation of kidneys from HCV RNA-positive donors corroborated unequivocally the transmission of HCV infection by organ transplantation.²⁴⁵ For this reason, organ procurement organizations and international guidelines have strongly recommended that all organ donors should be tested for HCV infection.^{31,246}

The diagnosis of HCV infection in organ donors is suspected when anti-HCV is detected by enzyme-linked immunosorbent assay.^{31,246} If HCV-NAT testing is widely available, all deceased donors should be tested for HCV NAT prior to organ procurement, and ideally before the organ is offered to potential recipients. Organs from anti-HCV positive donors with negative NAT may be used without an increased risk of HCV transmission^{247,248} though it would be prudent to perform NAT testing in recipients after transplantation to confirm the absence of HCV transmission.

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).

Potential living donors with HCV infection should be treated for HCV as in the general population and liver fibrosis should be assessed (see Chapter 2). Kidney function and proteinuria should be monitored during and after DAA therapy. In the absence of severe hepatic fibrosis, or evidence of kidney disease, living donation is feasible. If both the donor and

recipient are infected with HCV, one can delay treatment of the donor if timely transplant has benefits to the recipient (e.g., avoiding dialysis in a recipient with limited vascular access), with little expected harms to the donor. If the recipient is HCV-uninfected, treatment of the donor should occur prior to transplantation in order to minimize any risks to the recipient, and added costs of treating 2 patients (donor and recipient).

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).

Prior to 2014, kidneys from HCV-infected donors were almost exclusively transplanted into HCV-infected patients. This was due to the limited HCV treatment options, despite the increased risk of death and graft loss compared with HCV recipients who received kidneys from HCV-uninfected donors.²⁴⁹ However, with the advent of DAA therapy, and the rapid increase in the number of deceased donors infected with HCV in some parts of the world due to the opioid epidemic, kidneys from HCV-infected patients are increasingly being transplanted into HCV-uninfected patients.

The first 2 prospective studies of transplanting kidneys from HCV-infected donors into HCV-uninfected patients were published in 2017²⁵⁰ and 2018,²⁵¹ each with 10 participants. The THINKER trial transplanted donors with GT 1 or 4 HCV and began DAAs day 3 post-transplant, and the EXPANDER trial transplanted donors with any genotype and began DAAs just prior to the transplant surgery; in both trials, all patients were cured of HCV (SVR12).^{250–252} Since those initial publications, there have been multiple studies published on the safety and efficacy of transplanting kidneys from HCV-infected donors into HCV-uninfected patients (Supplementary Table S22). These studies have varied from formal prospective trials with institutional review board approval, registration in clinicaltrials.gov, and prospective ascertainment of outcomes and adverse events, to ‘standard-of-care’ center protocols with retrospective data collection. The published studies have also varied in the DAA regimen used, the timing of initiation of DAAs (ranging from pre-transplant to >90 days post-transplant), and treatment duration (ranging from ultra-short courses [e.g., 4 days] to full-course therapy of 12 weeks; Supplementary Table S22).

There have been 16 published studies with at least 10 participants in which kidneys from HCV-infected donors

were transplanted into HCV-uninfected recipients. Among 525 HCV-uninfected patients who were transplanted with a kidney from an HCV-infected donor, followed by DAA treatment, the overall HCV cure (SVR12 weeks post-transplant or SVR12) rate was 97.7% (95% CI: 96.3%–98.8%). Post-transplant outcomes were excellent with 98% 1-year patient and graft survival (Supplementary Table S23). However, studies were mostly non-comparative, and outcome reporting was typically unclear, resulting in only low strength of evidence in the outcome estimates. Reported hepatic complications were rare, although the retrospective studies did not have formal ascertainment of adverse events and serious adverse events, and/or pre-specified definitions of liver injury. In 12 studies (n = 457 with reported liver injury), there were 3 reported cases of fibrosing cholestatic hepatitis, all of which occurred in patients with initiation of DAAs more than 30 days post-transplant. The other reported complications are shown in Supplementary Table S22, but overall, are in line with what is expected in kidney transplant recipients.

The published data on transplanting kidneys from HCV-infected donors into HCV-uninfected recipients demonstrate that the practice can be associated with HCV cure rates that equal those with chronic HCV infection, with excellent 1-year post-transplant outcomes.^{244,252} These data therefore demonstrate that 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. However, this recommendation is associated with several caveats. First, the published data have focused on short-term outcomes, and data beyond 1 year are limited. A recent study published after our guideline systematic review reported that the 5-year mean allograft survival was not statistically different from donors who were HCV-RNA positive versus those who were not.^{252a} Secondly, there have been reports of higher-than-expected cytomegalovirus and BK viremia in HCV-uninfected recipients of a kidney from an HCV-infected donor,²⁵³ and this needs to be studied in a prospective fashion with matched comparators. Third, all HCV-uninfected patients received formal education about the risks and unknowns of being transplanted with a kidney from an HCV-infected donor, and this practice, along with a formal informed consent process, must be part of any protocol that involves transplanting kidneys from HCV-infected donors into HCV-uninfected patients.²⁵⁴ Because the only reported cases of fibrosing cholestatic hepatitis in the setting of transplanting kidneys from HCV-infected donors into HCV-uninfected recipients occurred with delayed initiation of therapy (two of the cases were >80 days post-transplant), DAA therapy should be initiated as early as possible. However, there are insufficient data to determine the exact time point at which DAA therapy should be started (e.g., just prior to transplantation vs. 3 days vs. 7 days vs. 28 days after transplantation). But because of the potential for insurance delays and/or denials for DAA therapy given their off-label use in the setting of transplanting kidneys from HCV-infected donors into HCV-uninfected recipients, it is critical that

any center performing such transplants have a plan to ensure patients can be treated in the setting of insurance denials, or delays that could lead to avoidable HCV-related liver or kidney injury.^{255–257} Lastly, although there have been trials of ultra short-course therapy (i.e., 1 week or less), more data are needed to determine whether such treatment durations are associated with similar HCV cure rates, and at this time, it is recommended that patients be treated with a full course of DAAs as suggested by the AASLD/IDSA guidelines.

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).

Rationale

DAAs are highly effective and the degree of immunosuppression has not been associated with a reduced probability of HCV cure. DAAs directly act on the virus's replicative machinery, in contrast to IFN, which relied in part on the patient's own immune system. The primary concern as it relates to immunosuppression and HCV treatment is the interaction between the different DAAs and transplant immunosuppression. The primary interaction is between cyclosporine and DAA therapy.²⁵⁸ Concomitant use of CNIs and DAAs requires close monitoring and dose reduction given that some DAAs can increase immunosuppressant levels several-fold.²⁵⁸ Examples include ombitasvir/paritaprevir with dasabuvir. In addition, DAA levels may be raised by cyclosporine use, for instance GLE/PIB, and this DAA regimen can raise tacrolimus levels, mandating close monitoring of tacrolimus levels.²⁵⁹ Further details can be found in the section on drug–drug interactions in Chapter 2, and the reader is advised to consult the Hepatitis Drug Interactions website from the University of Liverpool (<http://www.hep-druginteractions.org>) or the AASLD/EASL guidelines for the latest guidance.^{87,89}

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).

Rationale

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).*

Kidney transplantation outcomes in patients with HCV without extensive fibrosis who are successfully treated before transplantation should be equivalent to those in uninfected transplant recipients. With achievement of SVR12, viral relapse is highly unlikely, although kidney transplant recipients with unexplained hepatic dysfunction should undergo HCV testing as part of the routine diagnostic workup to exclude HCV reacquisition.

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).*

Kidney transplant recipients with cirrhosis require surveillance for complications of their liver disease, such as HCC, as outlined in the AASLD/EASL guidelines on management of cirrhosis in the general population, as chronic liver disease is a significant cause of morbidity and mortality in kidney transplant recipients.²⁶⁰

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).*

HCV infection has been reported as a risk factor for the development of proteinuria in kidney transplant recipients.²⁶¹ Several different types of glomerular lesions have been

described after kidney transplantation in HCV NAT-positive patients including recurrent or *de novo* cryoglobulinemic or non-cryoglobulinemic MPGN,²⁶² membranous nephropathy,²⁶³ acute transplant glomerulopathy,²¹⁵ anti-cardiolipin-related thrombotic microangiopathy,²⁶⁴ and chronic transplant glomerulopathy.²⁶⁵ MPGN and membranous nephropathy are the most frequent lesions related to HCV infection. The most common presentation is proteinuria with or without microhematuria, or nephrotic syndrome. The pathogenesis of MPGN seems to be related to the deposition of immune complexes containing HCV RNA in the glomerulus.³¹

After HCV NAT-positive patients have undergone kidney transplantation, clinicians should screen for proteinuria and microhematuria, although there are no data to recommend the exact timing. In the case of urine protein-creatinine ratio > 1 g/g or 24-hour urine protein (protein excretion rate) greater than 1 g on two or more occasions, a graft biopsy is indicated. Pathological examination should include immunofluorescence and electron microscopy. In the case of suspected transplant glomerulopathy, electron microscopy is mandatory to make the differential diagnosis with HCV-related MPGN.^{215,265}

For HCV-related glomerular disease, DAA therapy is indicated.^{266–275} In severe HCV-related cryoglobulinemic MPGN, in addition to antiviral therapy with DAAs, rituximab and, in severe cases, plasmapheresis should be considered.²¹⁵ This is discussed in detail in Chapter 5.

Research recommendations

- Optimal timing of antiviral therapy in candidates for kidney transplantation should be clarified. Because the time to transplantation with kidneys from deceased donors is unpredictable, delaying treatment carries higher vascular, metabolic, and malignancy risks as well as the risk of drug-drug interactions with CNIs after transplantation. As such, treatment before transplantation may be more appropriate. However, in regions where the prevalence of anti-HCV-positive donors is high, post-kidney transplant therapy should be considered.
- Future studies are needed to determine the long-term outcomes of transplantation of HCV-viremic kidneys into HCV-uninfected transplant recipients. The National Institutes of Health is sponsoring a multi-center trial of transplanting kidneys from HCV-infected donors into HCV-uninfected recipients (NCT04075916) that began on April 15, 2021 that seeks to address several knowledge gaps: (i) HCV cure rates with high precision; (ii) longer-term post-transplant kidney function; (iii) survival benefit of agreeing to being transplanted with a kidney from an HCV-infected donor; (iv) risk of post-transplant cytomegalovirus disease versus matched comparators; and (v) evidence of chronic kidney pathology in kidneys from HCV-infected donors versus matched comparators.
- Future studies are needed to determine the preferred timing of DAA treatment after transplantation with an HCV-

infected kidney, including an assessment of the benefits of earlier DAA therapy (e.g., peri-transplant or immediate post-transplant) and the risks of delayed therapy (e.g., beyond 4 weeks post-transplant). This would allow better consideration of how long DAA therapy can safely be delayed.

- More data are needed about the safety and efficacy of treating with short-course DAA therapy, including the potential prevention of HCV.²⁷⁶ Such studies should also include an examination of the logistics of implementing protocols in standard-of-care practice.

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

In addition to chronic liver disease, HCV infection may also lead to extrahepatic manifestations, including kidney disease and mixed cryoglobulinemia. Although chronic HCV infection may result in tubulointerstitial injury, HCV-associated GN is the most frequent type of kidney disease associated with HCV, with MPGN being the most common.^{277,278} However, the incidence of HCV-associated GN is low, as recently confirmed by large-scale studies. Moorman *et al.*²⁷⁹ found a frequency of nephrotic syndrome of 0.3% in a large cohort of HCV RNA viremic patients. In the same cohort, the frequency of cryoglobulinemia was 0.9%. Identical results have been offered by the Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project, which examined the comorbidities in patients diagnosed with HCV hospitalized in the US during 2004–2011. The rate of “nephrotic syndrome or MPGN” ranged between 0.47% and 0.36%.²⁸⁰ According to a retrospective cohort study of Veterans Affairs patients with a positive HCV RNA test who received a first course of DAAs between 2012 and 2016 ($n = 45,260$), the baseline prevalence of GN (International Classification of Diseases [ICD]-9/10 diagnosis) was around 2.6%.²⁸¹

The extrahepatic burden of HCV infection was also evaluated by El-Serag *et al.*, who performed a hospital-based case-control study among US male veterans from 1992 to 1999. They identified 34,204 patients infected with HCV (cases) and 136,816 randomly selected patients without HCV (controls).²⁸² A greater rate of MPGN (0.36% vs. 0.05%, $P < 0.0001$) but not membranous nephropathy (0.33% vs. 0.19%, $P = 0.86$) was found among patients with HCV. HCV-induced GN occurs frequently in association with mixed cryoglobulinemia, a systemic vasculitis characterized by involvement of small, and less frequently, medium-size vessels.^{277,278,283–285} Mixed cryoglobulinemia represents 60% to 75% of all cryoglobulinemia cases and is observed in patients with connective tissue diseases, chronic infections or lymphoproliferative disorders, all grouped under the term “secondary mixed cryoglobulinemia.” HCV has been implicated in the etiology of 80% to 90% of previously “idiopathic” mixed cryoglobulinemia cases.^{283,284} In general, HCV is associated with type II mixed cryoglobulinemia (cryoglobulins consisting of polyclonal IgG and monoclonal IgM with rheumatoid factor activity), although it is also less frequently associated with type III mixed cryoglobulinemia (cryoglobulins consisting of polyclonal IgG and polyclonal IgM).

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 4) (Not Graded).

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).

Rationale

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 4) (Not Graded).

Clinical manifestations of glomerular disease in HCV-infected patients include the presence of proteinuria and/or microscopic hematuria, with or without a reduction in GFR. It remains unclear why only a minority of patients with HCV infection develop kidney abnormalities, although polymorphisms in several genes have been suggested as risk factors for onset of cryoglobulinemia.^{286–288} Glomerular disease associated with HCV infection has been described in the presence or absence of significant liver disease.^{289,290}

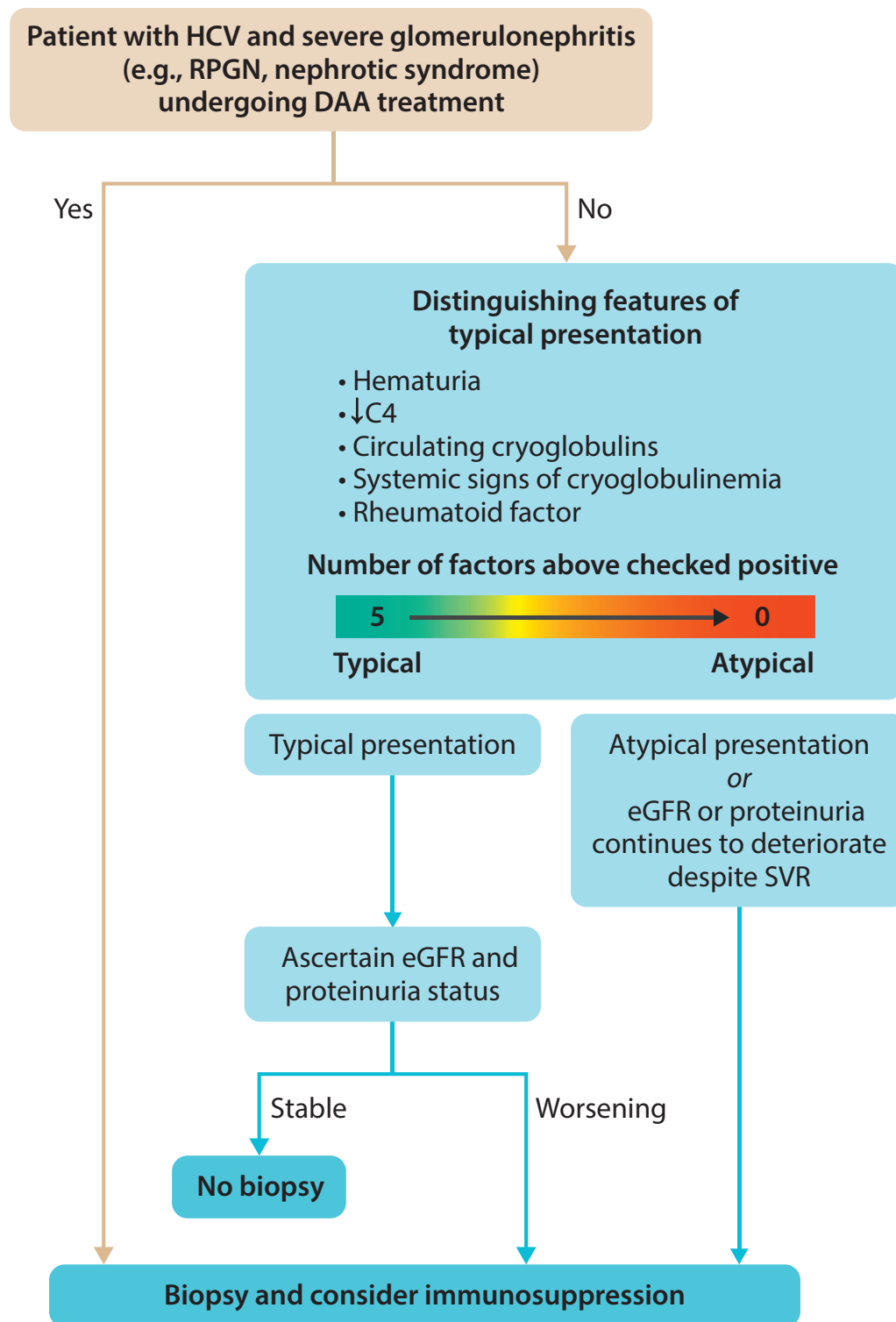


Figure 4 | Indications for biopsy in patients with hepatitis C virus (HCV) and severe glomerulonephritis. Algorithm above assumes that patient with HCV and with HCV and chronic kidney disease (CKD) is already receiving direct-acting antiviral (DAA) treatment. Systemic signs of cryoglobulinemia include skin lesions such as purpura, arthralgias, and weakness. eGFR, estimated glomerular filtration rate; RPGN, rapidly progressive glomerulonephritis; SVR, sustained virologic response.

The indications for a kidney biopsy in patients with HCV infection and signs of glomerular disease are not markedly different from the usual indications prompting a kidney biopsy in other glomerular diseases.²⁹¹ Kidney biopsy remains

invaluable to assess the precise histological picture of the disease and the probability that the observed lesions are causally related to HCV infection. Other glomerular diseases (e.g., diabetic nephropathy) are not infrequently reported among patients

with HCV infection.²⁹² This may partly result from the fact that the incidence of diabetes is known to be greater in HCV-infected patients than in the general population.^{293,294} In addition, the histology will provide an assessment of the extent of active lesions that may be amenable to immunosuppressive treatment versus chronic lesions that are unlikely to respond to immunosuppression. Thus, some patients may be able to avoid immunosuppression in the presence of severe chronic lesions, as long as there is no extrarenal indication warranting immunosuppression.²⁹¹

As almost all patients with chronic HCV (with or without GN) should be treated with DAAs, a kidney biopsy may not change management in the majority of patients with HCV and renal involvement. Most patients with HCV GN can be managed without a biopsy if there is strong suggestion of active GN based on typical clinical presentation (hematuria, proteinuria, slowly declining GFR). In a recent study by Perez de Jose *et al*,²⁹⁵ more than 50% of patients with HCV-mixed cryoglobulinemia with kidney involvement were treated with DAAs based on clinical presentation, without a kidney biopsy. Treatment with DAAs should not be delayed or postponed while waiting for a kidney biopsy. This is particularly true in patients with chronic liver disease who have a prohibitively high risk of bleeding after a kidney biopsy (e.g., due to severe thrombocytopenia, coagulopathy, concern for retroperitoneal varices, etc.). However, if clinical signs of kidney disease (hematuria, reduced GFR, albuminuria) do not improve or at least stabilize despite achieving SVR, or if there is evidence of rapidly progressive disease, a kidney biopsy may be warranted to confirm the diagnosis prior to initiating immunosuppressive therapy.

A biopsy is therefore not a prerequisite for initiating DAAs for the treatment of HCV-associated GN; kidney biopsy should, however, be performed if immunosuppressive therapy is planned or an alternative diagnosis other than HCV-related GN is suspected (Figure 4). With such a strategy, the small but not insignificant risk of complications from a kidney biopsy may be avoided in most patients. Systematic reviews^{296,297} have found that after a kidney biopsy, the risk of bleeding to the extent of requiring transfusion is around 1%–1.5%; the need for interventions required to stop bleeding is around 0.3%; and the risk of death is approximately 0.06%.

The most common type of HCV-related GN on a kidney biopsy is immune complex-mediated MPGN, usually reflecting the presence of type II cryoglobulinemia. Distinctive histological features of cryoglobulinemic GN, especially in patients with progressive deterioration of kidney function, include intraglomerular deposits, which are commonly seen in a subendothelial location. Cryoglobulin deposits may sometimes occlude the capillary lumen (seen as eosinophilic intraluminal thrombi on light microscopy). Glomeruli may show prominent hypercellularity as a result of infiltration of glomerular capillaries by mononuclear and polymorphonuclear leukocytes. Glomeruli frequently show accentuation of lobulation of the tuft architecture with a combination of increased matrix and mesangial cells, capillary endothelial swelling, splitting of capillary basement

membrane, and accumulation of eosinophilic material representing precipitated immune complexes or cryoglobulins. The glomerular basement membrane often exhibits a double contour caused by the interposition of monocytes between the basement membrane and the endothelium. On electron microscopy, large subendothelial deposits are present. Vasculitis of small renal arteries is present in 30% of cases.²⁹⁸ Histological features of exudative or lobular MPGN are associated with the occurrence of nephrotic and/or nephritic syndromes, whereas mesangial proliferation and matrix expansion are prevalent in cases with intact kidney function and isolated proteinuria and/or microscopic hematuria.²⁹⁸

Cases of HCV-associated MPGN without cryoglobulinemia have not infrequently been reported.²⁷⁸ In these patients, the clinical picture, histological features, and laboratory data are indistinguishable from “classical” idiopathic immune complex-mediated MPGN. Both subendothelial and mesangial immune complexes can be identified by electron microscopy, typically without a distinctive substructure. In both forms of HCV-associated GN, immunofluorescence commonly reveals deposition of IgM, IgG, and C3 in the mesangium and capillary walls.

Phospholipase A2 receptor (PLA2R)-negative membranous nephropathy is also observed in association with chronic HCV infection.²⁶³ Whether this is a true association is unclear. Other glomerular diseases that have been occasionally reported in chronic HCV infection are acute proliferative GN, focal segmental glomerulosclerosis,²⁹⁹ immunoglobulin A (IgA) nephropathy,³⁰⁰ thrombotic microangiopathy,²⁶⁴ rapidly progressive GN,³⁰¹ fibrillary GN, and immunotactoid glomerulopathy.³⁰² However, their pathogenic link with HCV remains even more uncertain than the link with membranous nephropathy.

The pathogenesis of glomerular disease associated with HCV infection involves immune-mediated damage (including effects from cryoglobulinemia) as well as direct effects of virus on renal tissue. HCV is thought to bind and penetrate into the renal parenchymal cells via the CD81 and SR-B1 receptors.^{303,304} HCV RNA has been found in mesangial cells, tubular epithelial cells, and endothelial cells of glomerular and tubular capillaries. The deposition of immune complexes containing HCV proteins in the glomerular basement membrane has been cited in the pathogenesis of HCV-associated membranous nephropathy.^{303,304} HCV-related granular protein deposits located in the mesangium have been observed in patients with HCV-related MPGN; they are probably related to higher degrees of proteinuria.³⁰⁵ Viral antigens have been found by immunohistochemistry,³⁰⁶ *in situ* hybridization,³⁰⁶ and laser capture microdissection.³⁰⁷

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).

RCTs are lacking to help establish evidence-based recommendations to treat glomerular lesions associated with HCV infection. Until this information is available, the treatment of HCV-associated GN should be driven by the severity of proteinuria and kidney failure. However, with DAA therapy now available, all HCV-infected patients are candidates for antiviral therapy.

The development of kidney disease among patients with mixed cryoglobulinemia has particular importance because kidney involvement confers a poor prognosis.^{308–310} In view of the role of HCV in the pathogenesis of cryoglobulinemic GN, antiviral therapy has been used to cure HCV infection and ameliorate renal injury. The evidence regarding the impact of antiviral treatment of HCV-associated GN was, until recently, very limited and consisted mostly of anecdotal reports and small-sized observational studies.

With the arrival of DAAs, IFN-based regimens are now considered obsolete. These early antiviral studies^{311–313} nevertheless provided valuable insight into the etiological role of HCV in the pathogenesis of GN, as well as information about the renal benefits of anti-HCV therapy.

An older systematic review of comparative studies of IFN versus immunosuppressive regimens for HCV-induced GN suggested some benefit of IFN to reduce proteinuria, but with a highly imprecise estimate: odds ratio (OR) 1.92; 95% CI: 0.39–9.57.³¹⁴ However, in a sensitivity analysis including only controlled trials using standard IFN doses, the OR was 3.86 (95% CI: 1.44–10.3). Of note, in all patients with reduction in proteinuria, HCV RNA clearance was observed at the end of antiviral therapy.³¹⁴

A subsequent systematic review⁷⁵ concluded that IFN- α therapy decreased proteinuria in HCV-infected patients with CKD. At the end of antiviral therapy, the summary estimate of the mean decrease in proteinuria was 2.71 g/24 h (95% CI: 1.38–4.04). The decrease in proteinuria following antiviral therapy reflected HCV RNA clearance. Although serum creatinine did not significantly improve after IFN- α , stabilization of serum creatinine was achieved.

Given the remission of hematuria, proteinuria, and improvement of GFR in patients with HCV-associated GN after HCV RNA clearance by DAAs,^{266–275} antiviral therapy with DAA regimens should be considered the first-line treatment in patients without nephrotic syndrome and a relatively stable kidney function (Supplementary Tables S24–S26). In addition, standard of care for proteinuric CKD should be implemented. This includes optimal blood pressure control, frequently employing multidrug therapy including diuretics.³¹⁵ Also, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should be used to treat proteinuria.⁵³

Encouraging results have been obtained with IFN-free DAA regimens for HCV-associated GN. Our systematic review found a very high SVR12 among patients with HCV-related cryoglobulinemia (Supplementary Tables S24 and S26). Across 5 studies with 1294 patients, of whom about 479 had

GN, the SVR12 after (various) DAA treatments was 99.0% (95% CI: 97.7%–99.8%).

In addition, *de novo* HCV GN,^{316,317} persistent HCV GN,^{316,318} or persistent serum cryoglobulins³¹⁹ after successful therapy with DAAs was occasionally observed. It has been suggested that in a subset of patients, HCV GN can persist despite achieving SVR, likely due to residual B cell clones producing rheumatoid factor. Also, *de novo* HCV GN after rituximab was noted, and this was attributed to a flare-up of HCV induced by rituximab.

Of the 45,260 HCV RNA-positive patients treated with various DAA regimens (with/without RBV) (mean follow-up of 2.01 years) at the US Department of Veterans Affairs, 41,711 (92.2%) obtained SVR. The fully adjusted hazard model showed that the incidence rate for GN after SVR was significantly reduced, adjusted HR 0.61 (95% CI: 0.41–0.90; $P = 0.0126$).²⁸¹

These studies suggest that IFN-free regimens (and almost always, RBV-free regimens) with DAAs offer excellent virological and clinical response in a difficult-to-treat condition such as HCV-associated mixed cryoglobulinemia with renal involvement or non-cryoglobulinemic HCV-associated GN. In fact, the SVR rates shown above are comparable to the SVR12 rates reported with similar regimens in other non-cryoglobulinemic real-world groups. However, larger and controlled studies are welcome to confirm these results.

Our systematic review supports the notion that DAAs have a beneficial impact on patient and kidney survival (Supplementary Tables S24 and S26). In a multicenter study from Spain,²⁹⁵ 139 patients with HCV-mixed cryoglobulinemia (65 patients with biopsy-proven HCV GN) were followed for a median duration of 138 months. Among 100 patients treated with unspecified DAAs, 4% died and 6% had doubling of serum creatinine or kidney failure. In contrast, among 15 untreated patients, two-thirds died and an additional 20% had doubling of serum creatinine or kidney failure. The HR for mortality after DAA treatment was 0.12 (95% CI: 0.04–0.40), and for doubling of serum creatinine or kidney failure, the HR was 0.10 (95% CI: 0.04–0.33). Across 4 studies, with 1172 patients with HCV-related cryoglobulinemic vasculitis, of whom 506 had GN, the death rate after treatment after 1 year was 2.4% (95% CI: 1.6%–3.4%), and in 2 studies ($n = 156$), doubling of serum creatinine or kidney failure occurred in 3.8% (95% CI: 1.7%–8.3%) of patients.

Despite this impressive efficacy, antiviral treatment of HCV-associated GN has some limitations. The clinical benefit in patients who achieve SVR may occasionally be transient, and a dissociation between viral and renal responses can occur.^{278,320–322} Three long-term (1- to 2-year) studies reported high rates of marked improvement of various cryoglobulinemia-related manifestations after SVR with DAAs, but confirmed that relapses of vasculitis may occasionally occur despite achieving SVR.^{323–325}

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).

Immunosuppressive agents have been administered to patients with serious, life-threatening complications of mixed cryoglobulinemia, such as MPGN, severe neuropathy, or extensive skin disease like ulcers or necrotic purpura. Rituximab, a chimeric monoclonal antibody, targets CD20, a surface antigen of B cells. It works by depleting, normal and pathogenic B cells and has recently been used with great success to suppress the synthesis of cryoglobulins. Cyclophosphamide too has been employed to reduce cryoglobulin synthesis; steroid pulses have been given to aggressively treat glomerular inflammation, and plasma exchange has been utilized to remove circulating cryoglobulins from the plasma and consequently reduce the deposition of immune complexes in the kidneys.

In patients with rapidly progressive kidney failure or acute cryoglobulinemic flare, control of disease by immunosuppressive agents, with or without plasma exchange (3 liters of plasma thrice weekly for 2–3 weeks), should be considered before or concurrently with the initiation of DAA therapy. Potential regimens include rituximab (375 mg/m² weekly for 4 weeks, or 2 doses of 1 g given 14 days apart) with or without corticosteroids (see below), or cyclophosphamide (2 mg/kg/d, adjusted for GFR, for 2–4 months) plus methylprednisolone pulses 0.5 to 1 g/d for 3 days. However, recent trials favor the use of rituximab with or without steroids compared to older immunosuppressive regimens like cyclophosphamide or azathioprine.^{326–328} Importantly, if rituximab is combined with plasma exchange, it should be given after a plasma-exchange session and several days before the next one. As per discretion of the treating clinician, an immunosuppressive regimen alone or combined with DAA therapy is suggested as the initial approach. In patients with nephrotic syndrome, immunosuppressive treatment in addition to DAAs should be considered in patients who have significant associated complications such as thromboembolic disease, severe hypoalbuminemia or anasarca, etc. Nephrotic range proteinuria (proteinuria > 3.5 g/d) alone does not warrant the use of immunosuppressive treatment, as such patients can achieve remission of proteinuria after treatment with DAAs.²⁹⁵ Until the DAA era, combined therapy with corticosteroids and immunosuppressive agents (e.g., treatment using cyclophosphamide and azathioprine sequentially) was used while awaiting a response, if any, to IFN-based antiviral therapy. This approach was typically used because of the relatively poor prognosis of HCV-associated mixed cryoglobulinemia with GN with IFN-based treatment alone.³⁰⁹ However, given the much better prognosis with DAAs and/or rituximab, we strongly suggest that older immunosuppressive regimens should be used only if rituximab is unavailable or unaffordable.

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).

Immunosuppressive therapies are typically reserved for patients with HCV-associated mixed cryoglobulinemia with severe disease manifestations, such as progressive glomerular disease. In addition to conventional immunosuppressants, which target inflammation at the glomerular level, encouraging results have been obtained with rituximab, a human–mouse chimeric monoclonal antibody that binds to the B-cell surface antigen CD20 and selectively targets B cells.^{326–331} Rituximab interferes with synthesis of cryoglobulins, monoclonal IgM, and renal deposition of immune complexes. An important pathogenetic feature of mixed cryoglobulinemia (including cryoglobulinemic GN) is chronic stimulation of B lymphocytes by HCV and widespread autoantibody synthesis related to HCV-induced lowering of the cell activation threshold.

Two RCTs have demonstrated the superiority of rituximab monotherapy as compared with conventional immunosuppressive therapy (i.e., corticosteroids, azathioprine, cyclophosphamide, methotrexate, and plasma exchange) for the treatment of HCV-associated cryoglobulinemic vasculitis in patients who failed or were not eligible for IFN therapy. However, importantly, only a minority of the included patients had renal involvement.^{326,328} Rituximab was well tolerated and was effective in 71% to 83% of patients with HCV-associated cryoglobulinemic vasculitis. Frequent relapses may occur after finishing treatment with rituximab when B cells re-emerge in the peripheral blood; in addition, repeated rituximab infusions may expose patients to opportunistic infections.

In a recent prospective, single-center study, rituximab was administered to 31 patients (27 anti-HCV positive) with mixed cryoglobulinemia (type II in 29 individuals and type III in 2) and diffuse MPGN (n = 16 cases), peripheral neuropathy (n = 26 cases) and severe skin ulcers (n = 7 cases). Five patients were also given 3 pulses of 500 mg of methylprednisolone. No further immunosuppressive or antiviral agents were given. Complete remission of pre-treatment active manifestations was observed in all patients with purpuric lesions and non-healing vasculitic ulcers, and in 80% of the peripheral neuropathies. Sixteen patients with cryoglobulinemic nephropathy (diffuse MPGN and mixed cryoglobulinemia) who were HCV antibody-positive received rituximab at a dose of 375 mg/m², according to a “4 + 2” protocol (days 1, 8, 15, and 22, plus one dose 1 and 2 months later).³²⁷ Safety and efficacy of rituximab was evaluated over a long-term follow-up period (mean: 72.5 months). A significant improvement of cryoglobulinemic GN was found, starting from the second month after rituximab (change in serum creatinine from 2.1 ± 1.7 mg/dl [186 ± 150 μmol/l] to 1.5 ± 1.6 mg/dl [133 ± 141 μmol/l], *P* < 0.05; and change in 24-

hour proteinuria from 2.3 ± 2.1 to 0.9 ± 1.9 g/24 h, $P < 0.05$).³²⁷ Two months after the initial rituximab treatment, a marked amelioration in serum complement C4 and cryocrit was recorded. No clinically relevant side effects were recorded. Re-induction with rituximab was carried out in 9 (of 31) patients who relapsed after a mean of 31.1 (12–54) months, again with beneficial effects. Six patients died (median of 55 months) after their rituximab cycle, due to cardiovascular events (mean age of 75.3 years). The probability of being disease-activity free after a single course of rituximab was 65% at 5 years, and 50% at 5 years after a second course following relapse.

An important point of caution to note is that rituximab, which selectively targets B cells, has been associated with severe infectious complications including exceptionally, reactivation of HCV,³³² but more frequently, HBV. The risk of reactivation of HBV infection was added to the existing “Black Box” warning on the rituximab label by the US FDA in 2013.³³³ Severe bacterial infections after rituximab therapy have been observed in kidney transplant recipients and in the non-transplant setting.³³⁴ Admittedly, these complications were mostly observed in patients receiving multiple immunosuppressive agents. Infectious episodes have been frequently reported in a susceptible patient subgroup (age > 70 years, GFR < 60 ml/min per 1.73 m², and concomitant high-dose corticosteroids) and were fatal in some patients.³³⁵ Fatal cholestatic liver disease due to HCV reactivation after a single dose of rituximab has also been observed after kidney transplantation.³³²

In addition to conventional or selective immunosuppressive agents, additional immunosuppressive agents such as MMF may deserve further evaluation. Preliminary evidence suggests that MMF can be effective for maintaining remission of HCV-associated cryoglobulinemic GN.^{336,337}

In summary, patients with mild or moderate forms of HCV-associated GN with stable kidney function and without nephrotic syndrome should be managed first with a DAA regimen. Patients with severe cryoglobulinemia or severe glomerular disease induced by HCV (i.e., nephrotic syndrome with associated complications or rapidly progressive GN) should be treated with immunosuppressive agents (preferably with rituximab as the first-line agent) and/or plasma exchange in addition to DAA therapies. Patients with HCV-associated GN who do not respond to, or are intolerant of, antiviral treatment should also be treated with immunosuppressive agents. Clinical indicators that HCV-associated GN is responding to treatment with antiviral therapy include

improvement in hematuria, degree of proteinuria, and stabilization (or improvement) in GFR. Therefore, in all cases, achievement of SVR after DAA treatment, changes in kidney function, evolution of proteinuria and hematuria, and side effects from antiviral therapy must be carefully monitored. Finally, the standard of care of proteinuric CKD should be implemented. This includes optimal blood pressure control, frequently employing multidrug therapy including diuretics.³¹⁵ In addition, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers should be used to treat proteinuria.⁵³

Research recommendations

- Occult HCV infection (detectable HCV RNA in peripheral blood mononuclear cells and/or in serum after centrifugation) could be involved in the pathogenesis of glomerular disease among patients negative for HCV RNA.³³⁸ We need large-sized studies with appropriate technology to assess the relationship between occult HCV and glomerular disease.
- The efficacy and safety of DAA therapies and/or immunosuppressive agents for the treatment of HCV-associated GN should be confirmed in large controlled clinical studies with longer follow-up.
- The antiviral approach to the treatment of HCV-associated GN has improved with the introduction of IFN-free and RBV-free regimens. Typically, patients with HCV-associated GN receive a high number of concomitant drugs, including cytotoxic agents. The potential risk resulting from drug–drug interactions should be studied in patients with HCV-induced GN.
- The role of immunosuppressive agents in the management of aggressive HCV-associated GN (i.e., severe nephrotic syndrome, rapidly progressive decline of GFR) needs to be further clarified in light of ultra-short DAA treatment courses.
- Numerous questions regarding the use of rituximab in HCV-positive GN remain. Rituximab has been administered in patients with HCV GN for whom DAAs failed to induce clinical remission; alternatively, rituximab has been given as an add-on to DAAs. In this vein, what is the optimal timing and dosing of periodic rituximab infusions for relapsers? The role of rituximab as first-line or rescue therapy needs to be defined further.
- Severe infections after rituximab therapy frequently occur in patients who are older than 50 years, have kidney disease, and report concomitant use of high-dose corticosteroids. Future studies should delineate how best to avoid infections associated with immunosuppression regimens.

Methods for guideline development

Aim

The overall aim of this project was to update a portion of the KDIGO clinical practice guideline (CPG) for the management of patients with CKD and HCV infection. The guideline consists of recommendation statements, rationale text, and a summary of systematically generated evidence on relevant pre-defined clinical topics. The general guideline development method is described below.

Overview of process

The development process for the *KDIGO 2022 CPG for the Prevention, Diagnosis, Evaluation and Treatment of Hepatitis C in CKD* included the following steps:

- Appointing Work Group members and the Evidence Review Team (ERT)
- Discussing process, methods, and results
- Developing and refining topics for updating the systematic evidence review
- Identifying populations, interventions or predictors, and outcomes of interest, and other study eligibility criteria
- Developing and implementing literature search update strategies
- Screening abstracts and retrieving full-text articles on the basis of pre-defined eligibility criteria
- Creating data extraction forms
- Standardizing quality assessment methodology
- Extracting data and performing critical appraisal of the literature
- Grading quality of evidence for each outcome across studies, and assessing the overall quality of evidence across outcomes with the aid of evidence profiles
- Updating recommendation statements based on the current evidence and other considerations
- Determining the strength of recommendations on the basis of the quality of evidence and other considerations
- Finalizing guideline recommendations and supporting text
- Proffering the guideline draft for public review in February 2022
- Editing the guideline based on review feedback
- Publishing the final version of the guideline

The overall process for conducting the systematic reviews and developing the CPG follows international standards, including those from the Institute of Medicine.^{339,340}

The Work Group Co-Chairs and the ERT met regularly (approximately every 2 weeks) to review the guideline development process, determine the specific CPG topics and recommendations to be updated, determine the specific topics for which to have updated systematic reviews, determine study eligibility criteria, assess progress of the review, discuss systematic review findings, evaluate the evidence base, and review draft updated recommendations and rationale text. The Work Group, ERT, and KDIGO staff also intermittently met with Work Group members to discuss the update process, review the updated evidence, and discuss updated recommendations and rationale text.

Commissioning of Work Group and ERT. The KDIGO Co-Chairs appointed the Work Group Co-Chairs, who then assembled

the Work Group of domain experts, including individuals with expertise in adult and pediatric nephrology, transplant nephrology, hepatology, virology, infection control, and public health. The Brown University Center for Evidence Synthesis in Health in Providence, Rhode Island, USA, was contracted as the ERT to conduct systematic evidence review and provide expertise in guideline development methodology. The ERT consisted of physician-methodologists with expertise in nephrology and evidence-based CPG development, and an experienced research associate/medical librarian.

Defining scope and topics. The Work Group Co-Chairs and the ERT defined the overall scope and goals of the guideline update and drafted a preliminary list of topics and key clinical questions. The list of research and recommendation topics for update was based on the original KDIGO guideline on HCV,³¹ and the 2018 update.³⁴¹ The current ERT was also the ERT for both prior CPGs (for the original 2008 CPG, the ERT was based at Tufts Medical Center in Boston, Massachusetts, USA). The Work Group and ERT further developed and refined each topic and its eligibility criteria, literature search strategies, and data extraction forms (Table 8). Systematic reviews and screening criteria used in the prior 2018 guideline for topics not revisited in this 2022 guideline update can be found in Table 9.³¹

Establishing the process for guideline development. The ERT performed systematic literature searches and organized abstract and article screening. The ERT also coordinated the methodological and analytical processes, and defined and standardized the methodology for performing literature searches, data extraction, and summarizing the evidence. The Work Group took the primary role of writing and grading the recommendation statements and rationale text, and retained final responsibility for their content.

Formulating questions of interest. Questions of interest were formulated according to the PICOS criteria (Population, Intervention, Comparator, Outcome, Study design). Details of the PICOS criteria for this guideline update are presented in Table 8.

Ranking of outcomes. The Work Group ranked outcomes of interest on the basis of their importance for informing clinical decision making (Table 10).

Literature searches and article selection. The literature search strategies from the KDIGO 2018 HCV CPG were reviewed and replicated for this update, with minor revisions. The original systematic search strategies were developed by the ERT with input from the Work Group Co-Chairs. Modules were created for kidney disease, HCV, and study designs. Searches were conducted in MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. For topics covered in the KDIGO 2018 HCV CPG,³⁴¹ searches were limited to 2016 and later to capture new evidence. The full literature search strategies are provided in Appendix 1. In addition, the ERT searched for existing relevant systematic reviews. The final searches were conducted on February 1, 2022. The search yield was also supplemented by focused searches for DAAs, HCV, and cryoglobulinemia in conference abstracts from the 2019, 2020, and 2021 American Society of Nephrology (ASN), American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver

Table 8 | Systematic review topics and screening criteria performed for the 2022 guideline**Chapter 2: Treatment of HCV infection in patients with CKD**

Population	- CKD G4-G5ND (or equivalent) with HCV infection - CKD G5D with HCV infection - CKD G1T-G5T (any category of kidney function except dialysis) with HCV infection
Intervention	Included only results data for clearly identifiable population categories ^a Any DAA regimen, including combination regimens Within single-group studies, we included only results data for clearly identifiable DAA regimens ^b Allowed multiple (non-parsable) DAA regimens for kidney function, graft, and mortality outcomes
Comparator	Other regimen, no treatment, no comparator (single-group studies)
Outcomes	SVR (≥ 12 wk), serious AE attributable to DAA, DAA discontinuation due to AE, death, change in CKD category, QoL, eGFR (CKD G4-G5ND, CKD G1T-G5T), proteinuria (CKD G4-G5ND, CKD G1T-G5T), acute rejection (CKD G1T-G5T), graft loss (CKD G1T-G5T)
Study design	RCT, nonrandomized comparative studies, single-group studies; prospective or retrospective. Published, peer-reviewed, or presented at AASLD, APASL, EASL, ERA-EDTA, or ASN 2019, 2020, and 2021 conferences
Minimum duration of follow-up	12 wk post-treatment: SVR, kidney/graft measures and outcomes End of treatment: AEs 6 mo post-treatment: Death
Minimum N of subjects	≥ 10 (within each specified population and DAA regimen ^a)
Publication dates	All ^c

Chapter 4: Management of patients before and after kidney transplantation

Population	Graft recipient HCV negative and graft donor HCV positive (by NAT)
Intervention	Any DAA regimen, including combination regimens
Comparator	Other regimen, no treatment, no comparator (single-group studies)
Outcome	SVR (≥ 12 wk), serious AE attributable to DAA, DAA discontinuation due to AE, death, QoL, acute rejection, delayed graft function, graft loss, graft eGFR, liver damage/failure, time on waitlist (comparative studies only, vs. D-/R-)
Design	RCT, nonrandomized comparative studies, single-group studies; prospective or retrospective. Published, peer-reviewed, or presented at AASLD, APASL, EASL, ERA-EDTA, or ASN 2019, 2020, and 2021 conferences
Minimum duration of follow-up	12 wk post-treatment End of treatment: AEs
Minimum N of Subjects	≥ 10
Publication dates	All ^c

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

Population	HCV-associated glomerular disease ^d
Intervention	Any DAA regimen Any CKD treatment (e.g., corticosteroids, immunosuppressive agents)
Comparator	Other regimen, no treatment, no comparator (single-group studies)
Outcome	SVR (≥ 12 wk), serious AE attributable to DAA, DAA discontinuation due to AE, death, change in CKD category or change in kidney function, cryoglobulinemia, QoL, eGFR, proteinuria, cryocrit, complement levels
Design	RCT, nonrandomized comparative studies, single-group studies; prospective or retrospective. Published, peer-reviewed, or presented at AASLD, APASL, EASL, ERA-EDTA, or ASN 2019, 2020, and 2021 conferences
Minimum duration of follow-up	12 wk post-treatment End of treatment: AEs
Minimum N of subjects	≥ 10
Publication dates	All ^c

AASLD, American Association for the Study of Liver Diseases; AE, adverse event; APASL, Asian Pacific Association for the Study of the Liver; ASN, American Society of Nephrology; CKD, chronic kidney disease; D, dialysis; D-, donor HCV negative; DAA, direct-acting antiviral; EASL, European Association for the Study of the Liver; eGFR, estimated glomerular filtration rate; ERA-EDTA, European Renal Association-European Dialysis and Transplant Association; HCV, hepatitis C virus; NAT, nucleic acid test; ND, non-dialysis; QoL, quality of life; R-, recipient HCV negative; RCT, randomized controlled trial; SVR: sustained viral response.

^aResults data for mixed populations (e.g., CKD G4-G5D and ND, CKD G3-G5ND) were omitted. To the extent possible, we parsed data for the specific populations of interest from the reported data. However, we allowed up to 10% of participants to be in a different CKD category. If SVR12 was 100% or 0% had serious AEs (as examples) across populations, we included these results for the specific populations of interest (if we could determine the number of patients analyzed within each specific population of interest).

^bTo the extent possible, we parsed data for the specific DAA regimens from the reported data. However, we allowed up to 10% of participants to have a different DAA regimen.

^cWe re-screened all studies included for guideline Chapters 2, 4, and 5 from both the KDIGO 2008 HCV CPG and the 2018 CPG update. We conducted a *de novo* literature search update from January 1, 2016, through February 1, 2022, supplemented with studies known to the Work Group through April 2022.

^dWe also included studies of patients with HCV-associated cryoglobulinemia, of whom at least 10 had glomerular disease.

(EASL), European Renal Association–European Dialysis and Transplant Association (ERA-EDTA), and Asian Pacific Association for the Study of the Liver (APASL) meetings. The Work Group provided additional articles for screening through April 2022.

For selection of studies, all members of the ERT screened the abstracts in duplicate using an open-source online screening program, Abstrackr (<http://abstrackr.cebm.brown.edu/>). To establish relevance and consensus among reviewers, the entire team screened and achieved consensus on a series of initial batches of 100 abstracts.

A total of 2730 citations from the databases were screened, in addition to conference abstracts, studies included in the KDIGO 2008 and 2018 HCV CPGs, and articles suggested by Work Group members (Figure 5). Potentially relevant articles (or abstracts) were retrieved in full text and re-screened in duplicate for eligibility. In total, 527 articles were selected for consideration for inclusion, of which 130 studies (in 134 articles) met eligibility criteria.

Data extraction. Data extraction was performed by 1 ERT member. Extracted data from each study were reviewed by another

Table 9 | Systematic reviews and screening criteria used in the 2018 guideline for topics not revisited in the 2022 guideline**Chapter 1: Predictor analyses**

Population	Predictors of CKD progression: any (including general population) except CKD G5D (dialysis); HCV as predictor: Kidney transplant recipients
Predictor	HCV-infection (untreated), other predictors of CKD progression (if HCV-infected)
Outcome	CKD progression (change in GFR, SCr doubling, ESKD), proteinuria, patient mortality, graft loss, delayed graft function, kidney pathology (HCV-associated GN)
Design	Longitudinal, multivariable analyses; HCV-associated GN: Any (except autopsy studies)
Minimum duration of follow-up	Any
Minimum N of subjects	≥100
Publication dates	Predictors of CKD progression: any; HCV as predictor: ≥2008 (plus studies in KDIGO 2008 CPG)

Chapter 1: Liver testing

Population	Tests for cirrhosis: CKD (all stages); pre-transplant biopsy: CKD G4-G5 pre-transplantation (or equivalent)
Intervention/ Comparator	Non-invasive liver testing, including upper endoscopy (for varices), liver biopsy
Outcome	Non-invasive test performance characteristics, change in management strategy, patient mortality, graft loss
Design	Any
Minimum N of subjects	Non-invasive testing: N ≥ 10; pre-transplant biopsy: N ≥ 5
Publication dates	Any

Chapter 3: Dialysis isolation

Population	Hemodialysis (patients or units)
Intervention	Isolation, quarantine, etc.
Comparator	No isolation, less stringent standard
Outcome	HCV transmission
Design	Any
Minimum duration of follow-up	None
Minimum N of subjects	N ≥ 30 patients
Publication dates	≥2008 (plus studies in KDIGO 2008 CPG)

Chapter 4: Early versus late transplantation

Population	HCV-infected transplantation candidates
Intervention	Transplantation ("now")
Comparator	Remaining on waitlist or awaiting HCV-negative status
Outcome	Patient mortality, graft loss
Design	Any, multivariable analysis
Minimum duration of follow-up	None
Minimum N of subjects	N ≥ 100
Publication dates	≥2008 (plus studies in KDIGO 2008 CPG)

KDIGO 2008 CPG, KDIGO 2008 clinical practice guideline on hepatitis C³¹; CKD, chronic kidney disease; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; GN, glomerulonephritis; HCV, hepatitis C virus; SCr, serum creatinine; SVR, sustained virologic response.

ERT member to confirm accuracy. The ERT designed a form to capture data on design, methodology, eligibility criteria, study participant characteristics, interventions, comparators, outcomes, and results of individual studies. Methodology and outcomes were also systematically assessed for risk of bias (see the section on risk of bias assessment below). Data were extracted into the online repository Systematic Review Data Repository-Plus (SRDR+). The data are available for review at <http://srdplus.ahrq.gov/>.

Summary tables. Summary tables were developed for each reviewed topic. Summary tables report study descriptions and results for each study. For Chapter 2, the summary tables are organized by specific DAA regimen, with summary results across studies for each regimen. The summary table for Chapter 4 organizes studies first by study design (prospective with a protocol, followed by retrospective), then alphabetically by first author. For Chapter 5, studies are presented in alphabetical order by first author.

Table 10 | Hierarchy of outcomes

Hierarchy	Outcome
Critical importance	Death, graft loss, ESKD
High importance	SVR12, treatment discontinuation due to adverse events, serious adverse events attributable to DAA, change in CKD category (or SCr doubling and including incident dialysis), quality of life, allograft eGFR, fibrosing cholestatic hepatitis, cryoglobulinemia complete remission
Moderate importance	Delayed graft function, acute rejection, eGFR (native kidney), proteinuria, cryocrit, complement

CKD, chronic kidney disease; DAA, direct-acting antiviral; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HCV, hepatitis C virus; SCr, serum creatinine; SVR, sustained virologic response.

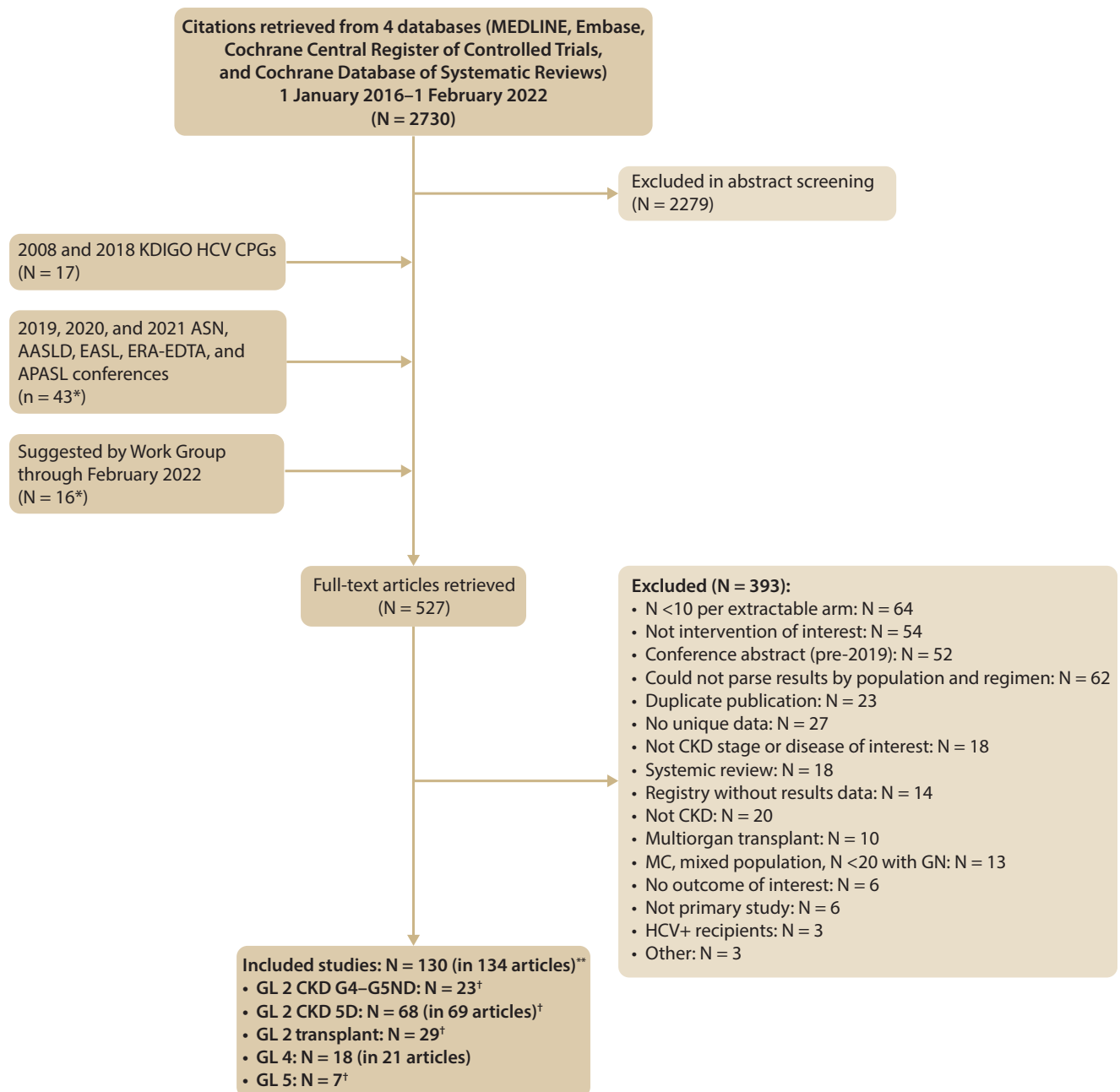


Figure 5 | Search yield. *Additional citations not included in literature searches. **Includes articles that reported data for multiple CKD populations. †Includes articles that reported data for other CKD populations. AASLD, American Association for the Study of Liver Diseases; APASL, Asian Pacific Association for the Study of the Liver; ASN, American Society of Nephrology; CKD, chronic kidney disease; CPG, clinical practice guideline; EASL, European Association for the Study of the Liver; ERA-EDTA, European Renal Association–European Dialysis and Transplant Association; GL, guideline; GN, glomerulonephritis; HCV, hepatitis C virus; KDIGO, Kidney Disease: Improving Global Outcomes; MC, mixed cryoglobulinemia; ND, non-dialysis.

For each study, the summary tables include regimen, study identifier, study country, treatment duration, HCV GT data, pre-treatment liver cirrhosis data, and results data. For SVR12 results, we include whether analyses were conducted as intention-to-treat (ITT, including if all participants were analyzed) or with another approach. For all results, we include footnotes describing caveats, explanations for missing participants; for selected outcomes (e.g., serious adverse events, death), we included reported data about details such as nature of serious adverse event or cause of death). For

all outcomes, we report either meta-analyzed, pooled, or descriptive summaries of outcomes across studies.

Work Group members reviewed and confirmed all summary table data and quality assessments. Final summary tables are available at www.kdigo.org.

Evidence profiles. Evidence profiles were constructed to assess the quality and record quality grades and descriptions of effect (or association) for each outcome across studies, as well as the quality of overall evidence and description of net benefits or harms of the

Table 11 | Work products for the 2022 guideline

Topics	Summary table	Included studies, n	Evidence profile
Chapter 2: HCV treatment			
2.1. DAA, CKD G4-G5ND	+	23	+
2.1. DAA, CKD G5D	+	68	+
2.1. DAA, KTR	+	29	+
Chapter 4: Kidney transplantation			
4.2. DAA treatment in D+/R- KTRs	+	18	+
Chapter 5: HCV-associated glomerulonephritis			
5.2. HCV-associated glomerulonephritis management	+	7	+

CKD, chronic kidney disease; D, dialysis; D+, donor HCV positive; DAA, direct-acting antiviral; HCV, hepatitis C virus; KTR, kidney transplantation recipient; ND, non-dialysis; R-, recipient HCV negative.

intervention or comparator across all outcomes. The evidence profiles aim to make the evidence synthesis process transparent. Decisions in the evidence profiles were based on data from the primary studies listed in corresponding summary tables and on judgments of the ERT and Work Group. Each evidence profile was initially constructed by the ERT and then was reviewed, edited, and approved by the Work Group. The work products created by the ERT for summarizing the evidence base for this update are listed in Table 11, together with the number of included studies. Work products from the prior 2018 guideline for topics not revisited in this 2022 guideline update are listed in Table 12.

Grading of quality of evidence for outcomes of individual studies. Studies were assessed for risk of bias and methodological quality concerns. We used the Cochrane Risk of Bias tool³⁴² to evaluate RCTs (that evaluated comparisons of interest). The tool asks about risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases. However, no eligible studies were evaluated as RCTs.

For non-randomized, observational comparative studies (that evaluated comparisons of interest), we used pertinent questions from the Cochrane Risk of Bias tool pertaining to outcome assessor blinding, incomplete outcome data (i.e., missing data and dropouts), and selective reporting. We also used selected questions from the Risk Of Bias In Non-Randomized Studies - of Interventions

(ROBINS-I) tool.³⁴³ Specifically, for comparative studies, we evaluated whether evaluated cohorts were comparable, and whether potential confounders were accounted for.

For all studies, including single-group (non-comparative) studies, we determined whether analyses were intention-to-treat (or otherwise included all participants) or were per-protocol (or other incomplete assessment), and whether selection of participants into the study was based on participant characteristics observed after the start of intervention, selective reporting, whether there was clear reporting without discrepancies, clear eligibility criteria, adequately described interventions (including dosages and treatment duration), and adequate outcome definition. For studies that reported harms, we assessed whether pre-defined or standard definitions of adverse events were used. For all studies, we also captured whether there were other potential biases or methodological problems of note. Where quality issues may have pertained only to some reported outcomes, this was noted.

For each study, assessment of quality was done by one of the reviewers, then confirmed by another, with discrepancies discussed in conference (Table 13).

Grading the quality of evidence and the strength of a guideline recommendation. A structured approach, based on Grading of Recommendations Assessment, Development and Evaluation (GRADE)³⁴⁴ and facilitated by the use of evidence profiles, was used

Table 12 | Work products from the 2018 guideline for topics not revisited in the 2022 guideline

Topics	Summary table	Included studies, ^a n	Evidence profile
1. HCV testing			
1.1 Determining which CKD patients should be tested for HCV	—	(Not searched)	
1.2 HCV testing in CKD	—	(Not searched)	
1.3 Non-invasive vs. invasive tests for cirrhosis in CKD	+	11	+
1.4 HCV as predictor of CKD progression	+	16	+
1.4 Other predictors of CKD progression	+	1	—
2. HCV treatment			
2 DAA drug dosing	—	10 PK studies	—
3. HCV transmission			
3 Dialysis isolation	+	7	+
4. Kidney transplantation			
4.1.1 Transplantation vs. waitlist	+	5	+
4.1.1 HCV as predictor, patient mortality	+	5	+
4.1.1 HCV as predictor, graft loss	+	7	+
4.1.2 Pre-transplant liver biopsy	—	1	—
4.1.3 Timing of HCV treatment vs. kidney transplantation	—	(Based on GL 2)	—
4.3 DAA and immunosuppression interaction	+	4	—
4.4 HCV-related complications	—	(Not searched)	—
5. HCV-associated glomerulonephritis			
5.1 HCV-associated kidney disease prevalence	+	5	—

CKD, chronic kidney disease; DAA, direct-acting antiviral; GL, guideline; HCV, hepatitis C virus; PK, pharmacokinetic.

^aPlus 6 case reports on miscellaneous topics.

Table 13 | Classification of study quality

Good quality	Low risk of bias and no obvious reporting errors; complete reporting of data. Must be prospective.
Fair quality	Moderate risk of bias, but problems with study or paper are unlikely to cause major bias.
Poor quality	High risk of bias or cannot rule out possible significant biases. Poor methods, incomplete data, reporting errors.

to grade the quality of the overall evidence (also known as certainty of evidence) and the strength of recommendations. For each topic, the discussion on grading of the quality of the evidence was led by the ERT, and the discussion regarding the strength of the recommendations was led by the Work Group Co-Chairs. The “strength of a recommendation” indicates the extent to which one can be confident that adherence to the recommendation will do more good than harm. The “quality of a body of evidence” refers to the extent to which our confidence in an estimate of effect is sufficient to support a particular recommendation.³⁴⁵

Grading the quality of evidence for each outcome across studies. Following the GRADE process, for each outcome, the potential grade for the quality of evidence for each intervention–outcome pair started at “high” but was then lowered if there were serious limitations to the methodological quality of the aggregate of studies, if there were important inconsistencies in the results across studies, if there was uncertainty about the directness of evidence (including limited applicability of the findings to the population of interest), if the outcome measure estimates were imprecise or based on sparse studies, or if there was thought to be a high likelihood of reporting bias. We modified the standard GRADE process in regards to study design of DAA evaluations, as described in the footnotes to Table 14. The final grade for the quality of the evidence for an intervention–outcome pair could be 1 of the following 4 grades: “high”, “moderate”, “low”, or “very low” (Table 14).

Grading the overall quality of evidence. The quality of the overall body of evidence was then determined on the basis of the quality grades for all outcomes of interest, taking into account explicit judgments about the relative importance of each outcome. The resulting 4 final categories for the quality of overall evidence were “A,” “B,” “C,” and “D” (Table 15).

Assessment of the net health benefit across all important clinical outcomes. The net health benefit was determined on the basis of the anticipated balance of benefits and harms across all clinically important outcomes (Table 16). The assessment of net benefit also involved the judgment of the Work Group and the ERT.

Developing the recommendations. Draft recommendation statements were developed by the Work Group. The health benefits, side effects, and risks associated with each recommendation were considered when formulating the guideline, as well as information on patient preferences when available. Recommendation statements were revised in a multistep process during video-conference meetings and by subsequent drafts by e-mail. Relevant recommendations from AASLD/IDSA and EASL guidelines on management of HCV were also reviewed. The final draft was sent for external public review. Based on the feedback received, it was further revised by the Work Group Co-Chairs and members. All Work Group members provided feedback on the initial and final drafts of the recommendation statements and guideline text, and approved the final version of the guideline.

Table 14 | GRADE system for grading quality of evidence

Step 1: Starting grade for quality of evidence based on study design	Step 2: reduce grade	Step 3: raise grade ^e	Final grade for quality of evidence and definition
All study designs = High ^a	<i>Study quality</i> –1 level if serious limitations –2 levels if very serious limitations <i>Consistency</i> –1 level if important inconsistency <i>Directness^b</i> –1 level if some uncertainty –2 levels if major uncertainty <i>Other</i> Reduce to Very Low if sparse^c Reduce to Very Low if imprecise^d –1 level if high probability of reporting bias	<i>Strength of association</i> +1 level if strong association^f +2 levels if very strong association^d <i>Other</i> +1 level if evidence of a dose–response gradient +1 level if all residual plausible confounders would have reduced the observed effect	High = Further research is unlikely to change confidence in the estimate of the effect Moderate = Further research is likely to have an important impact on confidence in the estimate of effect, and may change the estimate Low = Further research is very likely to have an important impact on confidence in the estimate, and may change the estimate Very Low = Any estimate of effect is very uncertain

^aGiven that it is well established that non–direct-acting antiviral (non-DAA) treatment is ineffective to achieve sustained virologic response at 12 weeks (SVR12), for this outcome we relied on primarily noncomparative, single-group studies. In contrast with the standard Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, we considered that all study designs could provide high-quality evidence (Step 1). Also, see footnote b. We did not consider confounders or strength of association as possible factors that may increase the grade because these are not relevant concepts for single-group studies.

^bFor outcomes other than SVR12, we considered studies that did not compare treatment to no treatment to provide indirect evidence of the comparative effectiveness, and downgraded by 1 level.

^cSparse if only 1 study (N < 100 per study group).

^dImprecise if there is a low event rate (0 or 1 event) in either study group. For comparative studies, imprecise if 95% confidence interval spans both 0.5 and 2.0. For single-group studies, imprecise if in our judgment, the 95% confidence intervals of incidence estimates spanned across the categories of rare, uncommon, common, or frequent.

^eOmitted from consideration for Chapter 2 because association analyses and confounding are not relevant for noncomparative studies.

^fStrong evidence of association is defined as “significant relative risk of >2 (<0.5)” based on consistent evidence from 2 or more observational studies with no major threats to validity. Very strong evidence of association is defined as “significant relative risk of >5 (<0.2)” based on consistent evidence from 2 or more observational studies with no major threats to validity.

Table 15 | Final grade for overall quality of evidence

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect is close to the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often will be far from the true effect.

Table 16 | Balance of benefits and harms

When there was evidence to determine the balance of medical benefits and harms of an intervention to a patient, conclusions were categorized as follows:

- For statistically significant benefit or harm, report as “benefit [or harm] of intervention”.
- For non-statistically significant benefit or harm, report as “possible benefit [or harm] of intervention”.
- In instances where studies are inconsistent, report as “possible benefit [or harm] of intervention”.
- “No difference” can only be reported if a study is not imprecise.
- “Insufficient evidence” is reported if imprecision is a factor.

Table 17 | KDIGO nomenclature and description for grading recommendations

Grade ^a	Implications		
	Patients	Clinicians	Policy
Level 1, strong “We recommend”	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2, weak “We suggest”	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

KDIGO, Kidney Disease: Improving Global Outcomes.

^aThe additional category “Not Graded” was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements. They should not be interpreted as being weaker recommendations than Level 1 or 2 recommendations.

Table 18 | Determinants of strength of recommendation

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the more likely a strong recommendation is warranted. The narrower the gradient, the more likely a weak recommendation is warranted.
Quality of the evidence	The higher the quality of evidence, the more likely a strong recommendation is warranted.
Values and preferences	The more variability in values and preferences, or the more uncertainty in values and preferences, the more likely a weak recommendation is warranted. Values and preferences were obtained from the literature when possible, or were assessed in the judgment of the Work Group when robust evidence was not identified.
Costs (resource allocation)	The higher the costs of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted.

Grading the strength of the recommendations. The strength of a recommendation is graded as level 1 or level 2. Table 17 shows the KDIGO nomenclature for grading the strength of a recommendation and the implications of each level for patients, clinicians, and policy makers. Recommendations can be for or against doing something. Each recommendation includes an explicit link between the quality of the available evidence and the strength of that recommendation. However, as elaborated in Table 18, the strength of a recommendation is determined not only by the quality of the evidence but also by other, often complex judgments, regarding the size of the net medical benefit (potential risks vs. benefit), values and preferences, and costs. Formal decision analyses including cost analysis were not conducted.

Ungraded statements. This category was designed to allow the Work Group to issue general advice. Although this category has now been replaced with “practice points” in recent KDIGO guidelines published after 2019, KDIGO decided to maintain this category of ungraded statements for the sake of consistency with Chapters 1 and 3, which remain unchanged from the 2018 guideline and are still current and integral to the entire CPG for the prevention, diagnosis, evaluation, and treatment of patients with HCV and CKD.³⁴¹

Typically, an ungraded statement meets the following criteria: it provides guidance based on common sense; it provides reminders of the obvious; and it is not sufficiently specific to allow for application of evidence to the issue, and therefore it is not based on systematic evidence review. As such, ungraded statements may be considered to

Table 19 | The COGS checklist for reporting clinical practice guidelines

Topic	Description	Discussed in KDIGO 2022 HCV in CKD CPG
1. Overview material	Provide a structured abstract that includes the guideline's release date, status (original, revised, updated), and print and electronic sources.	See <i>Abstract</i> and <i>Methods for Guideline Development</i> .
2. Focus	Describe the primary disease/condition and intervention/service/technology that the guideline addresses. Indicate any alternative preventative, diagnostic or therapeutic interventions that were considered during development.	Management of HCV in terms of treatment, monitoring, and prevention in adults with CKD, including both dialysis and transplant populations.
3. Goal	Describe the goal that following the guideline is expected to achieve, including the rationale for development of a guideline on this topic.	This CPG is intended to assist the practitioner caring for patients with CKD and HCV and to prevent transmission, resolve the infection, and prevent adverse outcomes such as deaths, graft loss, and progression to kidney failure while optimizing patients' quality of life.
4. User/setting	Describe the intended users of the guideline (e.g., provider types, patients) and the settings in which the guideline is intended to be used.	Target audience is practicing nephrologists and other health care providers for adults with CKD and HCV infection.
5. Target population	Describe the patient population eligible for guideline recommendations and list any exclusion criteria.	Adults with CKD (including those on dialysis therapy and kidney transplant recipients) and HCV infection.
6. Developer	Identify the organization(s) responsible for guideline development and the names/credentials/potential conflicts of interest of individuals involved in the guideline's development.	Organization: KDIGO Names/credentials/potential conflicts of interest of individuals involved in the guideline's development are disclosed in the <i>Biographic and Disclosure Information</i> section.
7. Funding source/sponsor	Identify the funding source/sponsor and describe its role in developing and/or reporting the guideline. Disclose potential conflict of interest.	This guideline is funded by KDIGO. Financial disclosures of Work Group members are published in the <i>Biographic and Disclosure Information</i> section.
8. Evidence collection	Describe the methods used to search the scientific literature, including the range of dates and databases searched, and criteria applied to filter the retrieved evidence.	Topics were triaged either to (i) systematic review, (ii) systematic search followed by narrative summary, or (iii) narrative summary. For systematic reviews, we searched PubMed, Embase, Cochrane Central Registry for trials, and Cochrane database of systematic reviews. Screening criteria for this and other topics are outlined in the <i>Methods for Guideline Development</i> chapter. The search was updated through February 2022 and supplemented by articles identified by Work Group members through April 2022. We also searched for pertinent existing guidelines and systematic reviews.
9. Recommendation grading criteria	Describe the criteria used to rate the quality of evidence that supports the recommendations and the system for describing the strength of the recommendations. Recommendation strength communicates the importance of adherence to a recommendation and is based on both the quality of the evidence and the magnitude of anticipated benefits and harms.	Quality of individual studies was graded in a 3-tiered grading system (see Table 13). Quality of the evidence and strength of recommendations were graded following the GRADE approach (Tables 14, 15, and 17). The Work Group could provide general guidance in the form of ungraded statements.
10. Method for synthesizing evidence	Describe how evidence was used to create recommendations, e.g., evidence tables, meta-analysis, decision analysis.	For systematic review topics, summary tables and evidence profiles were generated. For recommendations on interventions, the steps outlined by GRADE were followed.
11. Prerelease review	Describe how the guideline developer reviewed and/or tested the guidelines prior to release.	The guideline had undergone an external public review in February 2022. Public review comments were compiled and fed back to the Work Group, which considered comments in its revision of the guideline.

(Continued)

Table 19 | (Continued) **The COGS checklist for reporting clinical practice guidelines**

Topic	Description	Discussed in KDIGO 2022 HCV in CKD CPG
12. Update plan	State whether or not there is a plan to update the guideline and, if applicable, an expiration date for this version of the guideline.	The requirement for an update will be assessed periodically from the publication date or earlier if important new evidence becomes available in the interim. Such evidence might, for example, lead to changes to the recommendations or may modify information provided on the balance between benefits and harms of a particular therapeutic intervention.
13. Definitions	Define unfamiliar terms and those critical to correct application of the guideline that might be subject to misinterpretation.	See <i>Abbreviations and Acronyms</i> .
14. Recommendations and rationale	State the recommended action precisely and the specific circumstances under which to perform it. Justify each recommendation by describing the linkage between the recommendation and its supporting evidence. Indicate the quality of evidence and the recommendation strength, based on the criteria described in Topic 9.	Each guideline chapter contains recommendations for the management of patients with HCV and CKD. Each recommendation builds on a supporting rationale with evidence tables if available. The strength of the recommendation and the quality of evidence are provided in parentheses within each recommendation.
15. Potential benefits and harms	Describe anticipated benefits and potential risks associated with implementation of guideline recommendations.	The benefits and harm for each comparison of interventions are provided in summary tables and summarized in evidence profiles. The estimated balance between potential benefits and harm was considered when formulating the recommendations.
16. Patient preferences	Describe the role of patient preferences when a recommendation involves a substantial element of personal choice or values.	Recommendations that are level 2 or “discretionary” indicate a greater need to help each patient arrive at a management decision consistent with her or his values and preferences.
17. Algorithm	Provide (when appropriate) a graphical description of the stages and decisions in clinical care described by the guideline.	Algorithms were developed where applicable (see Figures 3 and 4).
18. Implementation considerations	Describe anticipated barriers to application of the recommendations. Provide reference to any auxiliary documents for providers or patients that are intended to facilitate implementation. Suggest review criteria for measuring changes in care when the guideline is implemented.	These recommendations are global. Local versions of the guideline are anticipated to facilitate implementation and appropriate care. Review criteria were not suggested because implementation with prioritization and development of review criteria have to proceed locally. Most recommendations are discretionary, requiring substantial discussion among stakeholders before they can be adopted as review criteria. The decision of whether to convert any recommendations to review criteria will vary globally. Research recommendations were also outlined to address current gaps in the evidence base.

CKD, chronic kidney disease; COGS, Conference on Guideline Standardization; CPG, clinical practice guideline; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HCV, hepatitis C virus; KDIGO, Kidney Disease: Improving Global Outcomes.

be relatively strong recommendations; they should not be interpreted as being weak recommendations based on limited or poor evidence. Common examples include recommendations about frequency of testing, referral to specialists, and routine medical care. We strove to minimize the use of ungraded recommendations.

This grading scheme, with 2 levels for the strength of a recommendation together with 4 levels of grading for the quality of the evidence, as well as the option of an ungraded statement for general guidance, was adopted by the KDIGO Board in December 2008. The Work Group took on the primary role of writing the recommendations and rationale statements, and retained final responsibility for

the content of the guideline statements and the accompanying narrative. The ERT reviewed draft recommendations and grades for consistency with the conclusions of the evidence review.

Format for guideline recommendations. Each chapter contains 1 or more specific recommendations. Within each recommendation, the strength of recommendation is indicated as level 1 or level 2, and the quality of the supporting evidence is shown as A, B, C, or D. The recommendation statements and grades are followed by the rationale text summarizing the key points of the evidence base and the judgments supporting the recommendation. In relevant sections, considerations of the guideline

statements in international settings and suggested audit criteria are also provided where applicable. Important key points and research recommendations suggesting future research to resolve current uncertainties are also outlined at the conclusion of each chapter

Limitations of approach

Although the literature searches were intended to be comprehensive, they were not exhaustive. MEDLINE, Embase, and Cochrane databases were searched, but other specialty or regional databases were not. Hand searches of journals were not performed, and review articles and textbook chapters were not systematically searched. Recent conference abstracts were screened from several professional society meetings, but older conference abstracts and other conference

meetings were not specifically screened. However, any important studies known to domain experts that were missed by the electronic literature searches were added to retrieved articles and reviewed by the Work Group.

Review of guideline development process

The Conference on Guideline Standardization (COGS) checklist has been developed to assess the quality of the methodological process for systematic review and guideline development.³⁴⁶ Table 19 shows the criteria that correspond to the COGS checklist and how each one is addressed in this guideline. Appendix 2 demonstrates the level of concurrence to the Institute of Medicine's standards for systematic reviews and guidelines.^{339,340}

Biographic and disclosure information

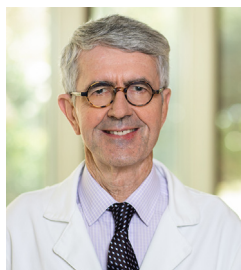


Michel Jadoul, MD (Work Group Co-Chair, KDIGO Co-Chair), received his MD degree in 1983 at the Université Catholique de Louvain (UCLouvain), Brussels, Belgium. Dr. Jadoul trained in internal medicine and nephrology under the mentorship of Professor Charles van Ypersele de Strihou. He further spent a year in Utrecht, The Netherlands under the mentorship of Professors Dorhout, Mees, and Koomans. He has served as chair at the Department of Nephrology of the Cliniques Universitaires Saint-Luc since 2003 and is currently a full clinical professor at UCLouvain. Dr. Jadoul's clinical activities focus on the follow-up of hemodialysis and CKD patients, and his main research interests include β 2-microglobulin amyloidosis, hepatitis C, and other complications (e.g., falls, bone fractures, sudden death) in hemodialysis patients, as well as cardiovascular complications after kidney transplantation and various causes of kidney disease (e.g., drug-induced).

Dr. Jadoul has coauthored over 330 scientific papers, most of them published in major nephrology journals. He is currently serving as a theme editor of *Nephrology Dialysis Transplantation*, and he is also a country co-investigator for the Dialysis Outcomes and Practice Patterns Study (DOPPS) (2001–present). In 2008, he received the international distinguished medal from the US National Kidney Foundation (NKF). He was previously a member of the European Renal Association (ERA) Council (2013–2016). Presently, Dr. Jadoul is a KDIGO Co-Chair.

MJ reports consultancy fees from Astellas, AstraZeneca, Bayer Pharmaceuticals, Boehringer Ingelheim, Fresenius Medical Care Asia Pacific, Mundipharma, Vifor Fresenius Medical Care; grants from Amgen, and AstraZeneca*; and speaker bureaus fees from Astellas, AstraZeneca, Mundipharma, and Vifor Fresenius Medical Care.*

**Monies paid to institution.*



Paul Martin, MD, FRCP, FRCPI (Work Group Co-Chair), is Professor of Medicine, Mandel Chair in Gastroenterology, and Chief of the Division of Digestive Health and Liver Diseases at the University of Miami, FL, USA. He graduated from medical school at University College Dublin, Dublin, Ireland and trained in Internal Medicine and Gastroenterology in Dublin and in Canada. He was a medical staff fellow in the Liver Unit of the National Institutes of Health (NIH). He is Emeritus Editor-in-Chief of *Liver*

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PM reports consultancy fees from AbbVie and Gilead; grants/grants pending from AbbVie and Gilead*; and fees for the development of educational presentations for SC Liver Research Consortium.*

**Monies paid to institution.*



Ahmed A. Awan, MD, FACP, is Assistant Professor of Nephrology in the Department of Medicine at Baylor College of Medicine in Houston, TX, USA, and works in the division of Nephrology and Abdominal Transplantation at Baylor St. Luke's Hospital and Medical Center. He is also the founder and director of "Hepatorenal

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AAA declared no competing interests.



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(Ciber-ehd), and Coordinator of La Fe University Research Group “Hepatology, Hepatobiliopancreatic surgery and Transplantation.”

She is well recognized for her important contributions in the field of post-transplantation HCV liver disease, where she was involved in the creation of various consensus documents on viral hepatitis and liver disease. She is also an active committee member for several national and international hepatology and liver transplantation societies.

Prof. Berenguer previously served as associate editor for the *Journal of Hepatology* and *Liver Transplantation* until December 2014, was deputy editor for *Transplantation* until 2019, and is now associate editor for the *Journal of Hepatology Reports*. She has authored more than 370 publications in peer-reviewed journals, as well as over 70 chapters in international and national textbooks.

MCB reports consultancy fees from AbbVie, Deep Genomics, Intercept, Natera, and Orphan; grants/grants pending from Gilead and Intercept; and speaker bureaus fees from AbbVie, Astellas, Chiesi, Deep Genomics, Gilead, Intercept, Novartis and Orphan.



Annette Bruchfeld, MD, PhD, FERA, is Professor of Nephrology at Linköping University and Guest Professor in Immune-mediated Kidney Diseases at Karolinska Institutet, Stockholm, Sweden, and is a senior consultant in Nephrology and Internal Medicine. She has had a long-standing interest in hepatitis C and

its impact on kidney disease and in patients with CKD. In 2003, she defended her thesis “Hepatitis C in chronic kidney disease and kidney transplantation: With special reference to epidemiology and treatment” at Karolinska Institutet. More recently, Professor Bruchfeld, who is an active clinical trialist, was one of the lead investigators in the randomized controlled C-SURFER trial, which was a landmark trial for the use of DAAs in HCV-infected CKD patients.

Other clinical and research interests include inflammatory kidney diseases, antineutrophil cytoplasmic antibody (ANCA)-vasculitis and kidney transplantation. Professor Bruchfeld has published more than 150 research papers and reviews. She is currently the chair of the ERA Immunonephrology Working Group and was the Scientific Chair of the ERA 2022 Congress in Paris and was previously a member of the ERA Council.

AB reports consultancy fees from AstraZeneca and Chemocentryx*; is on the advisory board of AstraZeneca* and Bayer*; and reports speaker bureaus fees from AbbVie, MSD/Merck, and Vifor.*

**Monies paid to institution.*



Fabrizio Fabrizi, MD, is associate director and professor of nephrology at Maggiore Policlinico Hospital and IRCCS Cà Granda Foundation, Milan, Italy. His research focuses on the understanding of the epidemiology, natural history, and treatment of viral hepatitis (HBV and HCV) in patients with CKD. He has performed clinical

trials, narrative or systematic reviews, and laboratory-based studies. He has received grants from the Italian Society of Nephrology and research fellowships from the Society of Italian-American Nephrologists as support for his research. Dr. Fabrizi has actively participated in the development of several national/international guidelines concerning the management of viral hepatitis in CKD patients, including the inaugural 2008 KDIGO HCV guideline. He currently serves on the editorial board of many journals, including the *International Journal of Artificial Organs*, *Cancer*, *Journal of Nephrology*, and *Pathogens*. He has authored more than 300 publications in peer-reviewed journals, such as *Kidney International*, the *American Journal of Kidney Diseases*, and the *Clinical Journal of the American Society of Nephrology*, among others.

FF declared no competing interests.



David S. Goldberg, MD, is an Associate Professor of Medicine in the Division of Digestive Health and Liver Diseases and Associate Professor of Public Health Sciences at the University of Miami Miller School of Medicine. Dr. Goldberg received his medical degree from the Mount Sinai School of Medicine, followed by

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Dr. Goldberg is a transplant hepatologist who dedicates most of his time to conducting epidemiology and health services research on topics related to chronic and end-stage liver disease, organ allocation and transplantation, and organ donation. He is currently the principal investigator (PI)/Co-PI of two R01 grants funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)/NIH focused on developing new models to estimate the survival benefit of liver transplantation and to develop better models to predict outcomes of kidney and liver allografts; a U01 from the NIDDK to perform a multi-center trial of transplanting kidneys from hepatitis C-infected donors into hepatitis

C-negative patients; and a U01 to participate in the NIDDK-sponsored Liver Cirrhosis Network. Dr. Goldberg has published more than 150 peer-reviewed publications including first-author papers in the *New England Journal of Medicine* and *JAMA*, and was the first author of the first trial focused on transplanting kidneys from hepatitis C-infected donors into hepatitis C-negative recipients followed by antiviral treatment.

DSG reports grants/grants pending from AbbVie and Gilead; fees for the development of educational presentations for Pfizer; and expert testimony for White and Williams.*

**Monies paid to institution.*



Jidong Jia, MD, PhD, is Professor of Medicine, Liver Research Center, Beijing Friendship Hospital, Capital Medical University & National Clinical Research Center for Digestive Diseases, Beijing, China.

As a hepatologist, his clinical expertise covers viral, autoimmune, and genetic liver diseases, with special research interests in liver fibrosis, cirrhosis, and portal hypertension. He has published over 200 papers in peer-review journals, such as *Hepatology*, *Journal of Hepatology*, and *Gastroenterology*.

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JJ reports grants/grants pending from Bristol Myers Squibb and Gilead*; and speaker bureaus fees from Gilead.*

**Monies paid to institution.*



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Dr. Kamar's interests are viral infection, particularly hepatitis E virus, HCV, BK virus, and cytomegalovirus infections that develop after solid organ transplantation, and more

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NK reports being on the advisory board and receiving speaker bureaus fees from Astellas, AstraZeneca, Biotest, Chiesi, CSL Behring, ExeViR, GSK, Hansa, MSD, Novartis, Sandoz, Sanofi, and Takeda.



Rosmawati Mohamed, MD, MRCP, MIntMed, MBBS, is a Consultant Hepatologist at the University of Malaya Medical Centre, Kuala Lumpur. Professor Rosmawati was appointed as Founding Co-chairperson of the World Health Organization (WHO) Strategic and Technical Advisory Committee for

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Locally, she is the Master, Academy of Medicine of Malaysia (AMM), the only registered body representing all medical specialties in Malaysia, embracing 12 colleges and 24 chapters. She serves on various committees of the Malaysian Medical Council governing medical specialist recognition, training, and continuous professional development.

She has worked tirelessly as a hepatitis and cancer advocate and organized nationwide campaigns for World Hepatitis Day and World Cancer Day, with non-government organizations (NGOs), the Ministry of Health, and private specialists, to increase awareness regarding hepatitis and liver cancer.

RM declared no competing interests.



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MGP is a board member of Gilead; reports consultancy fees from Gilead and Myralis; and receives speaker bureaus fees from Gilead.



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He has published more than 300 primary and review articles in the field of liver diseases.

He chaired the Inserm/Pasteur research unit 1220 studying the immune pathology of HCV infection and was the chair of the Center of Translational Research at the Pasteur Institute from 2015 to 2019. He is the recipient of several research awards and fellowships. He has previously chaired the coordinated action 24 of the French Agency for AIDS and Viral Hepatitis (ANRS: therapeutic trials in viral hepatitis) and now co-chairs the French ANRS CO-22 Hepather cohort (Viral hepatitis).

SP reports consultancy fees from Abbvie, Biotest, Gilead, Janssen, LFB, MSD, Shionogi, and ViiV Healthcare; speaker bureaus fees from Abbvie, Biotest, Gilead, Janssen, LFB, MSD, Shionogi, and ViiV Healthcare; and grants/grants pending from Bristol Myers Squibb, Gilead, MSD, and Roche.



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MES reports consultancy fees from Bioporto, Gilead, Mallinckrodt, and Travere; and grants/grants pending from AbbVie, Angion*, EMD Serono*, Gilead*, and Merck*.*

**Monies paid to institution.*

KDIGO Chair



Wolfgang C. Winkelmayer, MD, MPH, ScD, is the Gordon A. Cain Chair of Nephrology and professor of medicine at Baylor College of Medicine, Houston, TX, USA. Dr. Winkelmayer received his medical degree (1990) from the University of Vienna, Austria, and later earned a Master of Public Health in health

care management (1999) and a Doctor of Science in health policy (2001) from Harvard University, Cambridge, MA, USA. He then spent 8 years on the faculty of Brigham and Women's Hospital and Harvard Medical School, where he established himself as a prolific investigator and leader in the discipline of comparative-effectiveness research as it pertains to patients with kidney disease.

From 2009 to 2014, he was the director of clinical research in the Division of Nephrology at Stanford University School of Medicine, Palo Alto, CA, USA. He assumed his current position as chief of nephrology at Baylor College of Medicine in September 2014. His main areas of research interest include comparative effectiveness and safety research of treatment strategies for anemia, as well as of various interventions for cardiovascular disease in patients with kidney disease. Dr. Winkelmayer is a member of the American Society of Clinical Investigation. His clinical passion lies in providing quality kidney care to the predominantly disadvantaged and un(der)insured population in the public safety net health system of Harris County, TX, USA.

Dr. Winkelmayer has authored over 350 peer-reviewed publications, and he has a particular interest in medical publishing. He currently serves as associate editor for the *Journal of the American Medical Association*, was a co-editor of the *American Journal of Kidney Disease* from 2007 to 2016, and has been appointed to several other editorial boards of leading nephrology and epidemiology journals. He joined KDIGO volunteer leadership as an executive committee member in 2015 and has served as its Co-Chair since 2016.

WCW reports consultancy fees from Akebia/Otsuka, AstraZeneca, Bayer Pharmaceuticals, Boehringer Ingelheim/Lilly, GSK, Merck, Pharmacosmos, Reata, and Zydus.

Evidence Review Team (ERT)

Ethan M. Balk, MD, MPH, is associate director of the Center for Evidence Synthesis in Health and Professor of Health Services, Policy and Practice at Brown University School of Public Health in Providence, RI, USA. He has been project director of the ERT and has collaborated on numerous Kidney Disease

Outcomes Quality Initiative (KDIGO) guidelines since 2008, and prior to that on Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines since 2000. As project director for this guideline, he played a pivotal role in providing methodological expertise in the guideline development process and assisted in the collection, evaluation, grading, and synthesis of evidence and the revisions of the final evidence report. Dr. Balk also provided methodological guidance and training of Work Group members regarding topic refinement, key question formulation, data extraction, study assessment, evidence grading, and recommendation formulation. His primary research interests are evidence-based medicine, systematic review, clinical practice guideline development, and critical literature appraisal.

EMB reports no competing interests.



Craig E. Gordon, MD, MS, is associate professor of medicine at Tufts University Medical Center in Boston, MA, USA. Dr. Gordon graduated from New York University School of Medicine and received a master's degree in clinical care research from the Tufts University School of Graduate Biomedical Sciences. Dr.

Gordon previously served as the assistant project director of the ERT for the 2008 KDIGO CPG on HCV in CKD and associate director of the ERT and assistant project director for the 2018 KDIGO CPG on HCV in CKD.

Dr. Gordon provided methodologic expertise to the Work Group during the guideline development process and assisted in the collection, evaluation, grading, and synthesis of evidence for the guideline, as well as providing guidance to Work Group members in the areas of topic refinement, key question formulation, data extraction, study assessment, evidence grading, and recommendation formulation. His primary research and clinical interests are in the management of HCV in patients with CKD, polycystic kidney disease, and thrombotic microangiopathies, as well as evidence-based medicine and systematic review related to other areas of nephrology.

CEG reports consultancy fees from Alexion and Otsuka, and grants/grants pending from Alexion, Palladio Biosciences, Reata, and Sanofi Genzyme.



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GA declared no competing interests.

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individuals provided feedback during the public review of the draft guideline:

Patricia Ferreira Abreu; Laith Al-Rabadi; Salim Alatwany; Maria Almerinda Ribeiro Alves; Mariano Arriola; Elif Ari Bakir; Rommel Bataclan; Anatole Besarab; Rolando Claure Del Granado; Swapna Joseph; Nada Kanaan; Rümeyza Turan Kazancioğlu; Chao Li; Chen-Hua Liu; Aida Lydia; José M. Morales; Eugen Mota; Nuria S. Perez Romano; Deepak Sharma; Talia Weinstein; Ming-Lung Yu; and Weiming Zhang.

Participation in the review does not necessarily constitute endorsement of the content of this report by the above individuals, or the organizations or institutions they represent.

Michel Jadoul, MD
Paul Martin, MD, FRCP, FRCPI
Work Group Co-Chairs

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SUPPLEMENTAL APPENDICES

Appendix 1: Search strategies

Appendix 2: Concurrence with Institute of Medicine standards for systematic reviews and for guidelines

APPENDIX 1: SEARCH STRATEGIES

PubMed

Search 1

("kidney glomerulus"[MESH] OR "Kidney Diseases"[Mesh] OR "kidney function tests"[MESH] OR "renal replacement therapy"[MESH] OR "kidney transplantation"[MESH] OR ((kidney OR renal) AND ("transplantation"[MESH] OR "allografts"[MESH] OR transplant OR allograft* OR graft*)) OR "kidneys, artificial"[MESH] OR renal OR nephron* OR kidney OR uremia OR uraemia OR hemodialysis OR hemodialysis OR haemodialysis OR haemodialysis OR dialysis OR hemofiltr* OR haemofiltr* OR hemofiltr* OR haemofiltr*) AND ("Hepatitis C"[MESH] OR hepatitis c OR hep c OR HCV) AND (telaprevir OR "telaprevir" [Supplementary Concept] OR boceprevir OR "N-(3-amino-1-(cyclobutylmethyl)-2,3-dioxopropyl)-3-(2-(((1,1-dimethylethyl)amino)carbonyl)amino)-3,3-dimethyl-1-oxobutyl)-6,6-dimethyl-3-azabicyclo(3.1.0)hexan-2-carboxamide" [Supplementary Concept] OR danoprevir OR "danoprevir" [Supplementary Concept] OR faldaprevir OR "N-((cyclopentyloxy)carbonyl)-3-methylvalyl-4-((8-bromo-7-methoxy-2-(2-((2-methylpropanoyl)amino)-1,3-thiazol-4-yl)quinolin-4-yl)oxy)-N-(1-carboxy-2-ethenylcyclopropyl)prolinamide" [Supplementary Concept] OR vaniprevir OR "MK-7009" [Supplementary Concept] OR sovalprevir OR ACH-1625 OR simeprevir OR "Simeprevir"[Mesh] OR asunaprevir OR "asunaprevir" [Supplementary Concept] OR paritaprevir OR "ABT-450" [Supplementary Concept] OR grazoprevir OR "MK-5172" [Supplementary Concept] OR vedoprevir OR "GS-9451" [Supplementary Concept] OR daclatasvir OR "daclatasvir" [Supplementary Concept] OR ombitasvir OR "ABT-267" [Supplementary Concept] OR ledipasvir OR "ledipasvir" [Supplementary Concept] OR samatasvir OR "samatasvir" [Supplementary Concept] OR elbasvir OR MK-8742 OR GS 5816 OR ACH 3102 OR sofosbuvir OR "Sofosbuvir"[Mesh] OR mericitabine OR "2'-fluoro-2'-methyl-3',5'-diisobutyryldeoxycytidine" [Supplementary Concept] OR valopicitabine OR "valopicitabine" [Supplementary Concept] OR setrobuvir OR "setrobuvir" [Supplementary Concept] OR tegobuvir OR "tegobuvir" [Supplementary Concept] OR filibuvir OR "PF 00868554" [Supplementary Concept] OR dasabuvir OR "ABT-333" [Supplementary Concept] OR deleobuvir OR "deleobuvir" [Supplementary Concept] OR beclabuvir OR "8-cyclohexyl-N-((dimethylamino)sulfonyl)-1,1a,2,12b-tetrahydro-11-methoxy-1a-((3-methyl-3,8-diazabicyclo(3.2.1)oct-8-yl)carbonyl)cycloprop(d)indolo(2,1-a)(2)benzazepine-5-carboxamide" [Supplementary Concept] OR glecaprevir OR "ABT-493" [Supplementary Concept] OR pibrentasvir OR "pibrentasvir" [Supplementary Concept] OR velpatasvir OR "velpatasvir" [Supplementary Concept] OR voxilaprevir OR "voxilaprevir" [Supplementary Concept] OR "direct acting antiviral" OR "direct-acting antiviral" OR DAA OR ribavirin OR "Ribavirin"[Mesh] OR interferon OR IFN OR pegylated interferon OR "peginterferon alfa-2b" [Supplementary Concept] OR pegylated IFN)

Search 2

(glomerulonephritis OR "Glomerulonephritis"[MESH] OR glomerulopathy OR "Nephrotic Syndrome"[MESH] OR "Glomerulonephritis, Membranous"[MESH] OR glomerulonephrit* OR "Glomerulonephritis, Membranoproliferative"[MESH] OR membranous nephropathy OR IGA nephropathy OR immunoglobulin A nephropathy OR IGAN OR "Glomerulonephritis, IgA"[MESH] OR rapidly progressive glomerulonephr* OR RPGN OR "focal sclerosing glomerulopathy" OR FSGS OR "Glomerulosclerosis, Focal Segmental"[Mesh] OR glomerulosclerosis OR (Hypocomplementemia AND Glomerulonephritis) OR Berger's disease OR Bergers OR focal segmental glomerulo* OR Goodpasture OR Nephritis OR "Purpura, Schoenlein-Henoch"[MESH] OR ("Antibodies, Antineutrophil Cytoplasmic"[MESH] AND "vasculitis"[MESH]) OR (ANCA AND vasculitis) OR "Glomerulosclerosis, Focal Segmental"[MESH] OR "Nephrosis, Lipoid"[MESH] OR "Minimal change nephropathy" OR "minimal change disease" OR "churg-strauss syndrome"[MESH] OR "Granulomatosis with Polyangiitis"[Mesh] OR "Lupus Nephritis"[MESH] OR "Lupus nephritis" OR "renal vasculitis" OR amyloidosis OR cryoglobulinemia OR "Cryoglobulinemia"[Mesh]) AND ("Hepatitis C"[MESH] OR hepatitis c OR hep c OR HCV)

Search 1 OR Search 2

AND

Date limits: 2016-present

NOT ("address"[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "comment"[pt] OR "congress"[pt] OR "dictionary"[pt] OR "directory"[pt] OR "festschrift"[pt] OR "government publication"[pt] OR "historical article"[pt] OR "interview"[pt] OR "lecture"[pt] OR "legal case"[pt] OR "legislation"[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt] OR "comment on" OR ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] OR rat[tw] OR cow[tw] OR cows[tw] OR chicken*[tw] OR horse[tw] OR horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep[tw] OR ovine[tw] OR murinae[tw] OR cats[tw] OR cat[tw] OR dog[tw] OR dogs[tw] OR rodent[tw])

Cochrane/Embase

Search 1

("kidney glomerulus" OR "Kidney Diseases" OR "kidney function tests" OR "renal replacement therapy" OR "kidney transplantation" OR ((kidney OR renal) AND ("transplantation" OR "allografts" OR transplant OR allograft* OR graft*)) OR renal OR nephron* OR kidney OR uremia OR uraemia OR hemodialysis OR hemodialysis OR haemodialysis OR haemodialysis OR dialysis OR hemofiltr* OR haemofiltr* OR hemofiltr* OR haemofiltr*) AND (hepatitis c OR hep c OR HCV) AND (telaprevir OR danoprevir OR faldaprevir OR vaniprevir OR sovalprevir OR simeprevir OR asunaprevir OR paritaprevir OR grazoprevir OR vedoprevir OR daclatasvir OR ombitasvir OR ledipasvir OR samatasvir OR elbasvir OR sofosbuvir OR mericitabine OR valopicitabine OR setrobuvir OR tegobuvir OR filibuvir OR dasabuvir OR deleobuvir OR beclabuvir OR glecaprevir OR pibrentasvir OR velpatasvir OR voxilaprevir OR "direct acting antiviral" OR "direct-acting antiviral" OR DAA OR ribavirin OR interferon OR IFN OR pegylated interferon OR pegylated IFN)

Search 2

(glomerulonephritis OR glomerulopathy OR "Nephrotic Syndrome" OR glomerulonephrit* OR membranous nephropathy OR IGA nephropathy OR immunoglobulin A nephropathy OR IGAN OR rapidly progressive glomerulonephr* OR RPGN OR "focal sclerosing glomerulopathy" OR FSGS OR glomerulosclerosis OR Berger's disease OR Bergers OR focal segmental glomerulo* OR Goodpasture OR Nephritis OR "Schoenlein-Henoch" OR ("Antineutrophil Cytoplasmic Antibodies" AND "vasculitis") OR (ANCA AND vasculitis) OR Nephrosis OR "Minimal change nephropathy" OR "minimal change disease" OR "churg-strauss syndrome" OR "Granulomatosis with Polyangiitis" OR "Lupus nephritis" OR "renal vasculitis" OR amyloidosis OR cryoglobulinemia) AND (hepatitis c OR hep c OR HCV)

Search 1 OR Search 2

Date limits: 2016-present

APPENDIX 2: CONCURRENCE WITH INSTITUTE OF MEDICINE STANDARDS FOR SYSTEMATIC REVIEWS AND FOR GUIDELINES

IOM Standards for Systematic Reviews		Part of KDIGO Process?
2.1	Establish a team with appropriate expertise and experience to conduct the systematic review	Yes
2.1.1	Include expertise in the pertinent clinical content areas	Yes
2.1.2	Include expertise in systematic review methods	Yes
2.1.3	Include expertise in searching for relevant evidence	Yes
2.1.4	Include expertise in quantitative methods	Yes
2.1.5	Include other expertise as appropriate	Yes
2.2	Manage bias and conflict of interest (COI) of the team conducting the systematic review	Yes
2.2.1	Require each team member to disclose potential COI and professional or intellectual bias	Yes (not explicitly intellectual bias)
2.2.2	Exclude individuals with a clear financial conflict	Yes
2.2.3	Exclude individuals whose professional or intellectual bias would diminish the credibility of the review in the eyes of the intended users	Not explicitly
2.3	Ensure user and stakeholder input as the review is designed and conducted	Yes
2.3.1	Protect the independence of the review team to make the final decisions about the design, analysis, and reporting of the review	Yes
2.4	Manage bias and COI for individuals providing input into the systematic review	Yes
2.4.1	Require individuals to disclose potential COI and professional or intellectual bias	Yes (not intellectual bias)
2.4.2	Exclude input from individuals whose COI or bias would diminish the credibility of the review in the eyes of the intended users	No
2.5	Formulate the topic for the systematic review	Yes
2.5.1	Confirm the need for a new review	Yes
2.5.2	Develop an analytic framework that clearly lays out the chain of logic that links the health intervention to the outcomes of interest and defines the key clinical questions to be addressed by the systematic review	No
2.5.3	Use a standard format to articulate each clinical question of interest	Yes
2.5.4	State the rationale for each clinical question	No
2.5.5	Refine each question based on user and stakeholder input	Yes
2.6	Develop a systematic review protocol	Yes
2.6.1	Describe the context and rationale for the review from both a decision-making and research perspective	No
2.6.2	Describe the study screening and selection criteria (inclusion/exclusion criteria)	Yes
2.6.3	Describe precisely which outcome measures, time points, interventions, and comparison groups will be addressed	Yes
2.6.4	Describe the search strategy for identifying relevant evidence	Yes
2.6.5	Describe the procedures for study selection	Yes
2.6.6	Describe the data extraction strategy	Yes
2.6.7	Describe the process for identifying and resolving disagreement between researchers in study selection and data extraction decisions	Yes
2.6.8	Describe the approach to critically appraising individual studies	Yes
2.6.9	Describe the method for evaluating the body of evidence, including the quantitative and qualitative synthesis strategies	Yes

IOM Standards for Systematic Reviews		Part of KDIGO Process?
2.6.10	Describe and justify any planned analyses of differential treatment effects according to patient subgroups, how an intervention is delivered, or how an outcome is measured	Yes
2.6.11	Describe the proposed timetable for conducting the review	Yes
2.7	Submit the protocol for peer review	No
2.7.1	Provide a public comment period for the protocol and publicly report on disposition of comments	Yes (public review) No (public disposition of comments)
2.8	Make the final protocol publicly available, and add any amendments to the protocol in a timely fashion	No
3.1	Conduct a comprehensive systematic search for evidence	Yes
3.1.1	Work with a librarian or other information specialist trained in performing systematic reviews to plan the search strategy	Yes
3.1.2	Design the search strategy to address each key research question	Yes
3.1.3	Use an independent librarian or other information specialist to peer review the search strategy	Yes
3.1.4	Search bibliographic databases	Yes
3.1.5	Search citation indexes	Yes
3.1.6	Search literature cited by eligible studies	No
3.1.7	Update the search at intervals appropriate to the pace of generation of new information for the research question being addressed	Yes
3.1.8	Search subject-specific databases if other databases are unlikely to provide all relevant evidence	N/A
3.1.9	Search regional bibliographic databases if other databases are unlikely to provide all relevant evidence	N/A
3.2	Take action to address potentially biased reporting of research results	No
3.2.1	Search grey-literature databases, clinical trial registries, and other sources of unpublished information about studies	Yes
3.2.2	Invite researchers to clarify information about study eligibility, study characteristics, and risk of bias	No
3.2.3	Invite all study sponsors and researchers to submit unpublished data, including unreported outcomes, for possible inclusion in the systematic review	No
3.2.4	Handsearch selected journals and conference abstracts	Yes
3.2.5	Conduct a web search	No
3.2.6	Search for studies reported in languages other than English if appropriate	Yes
3.3	Screen and select studies	Yes
3.3.1	Include or exclude studies based on the protocol's prespecified criteria	Yes
3.3.2	Use observational studies in addition to randomized clinical trials to evaluate harms of interventions	Yes
3.3.3	Use two or more members of the review team, working independently, to screen and select studies	Yes
3.3.4	Train screeners using written documentation; test and retest screeners to improve accuracy and consistency	Yes
3.3.5	Use one of two strategies to select studies: (1) read all fulltext articles identified in the search or (2) screen titles and abstracts of all articles and then read the full texts of articles identified in initial screening	Yes (2)
3.3.6	Taking account of the risk of bias, consider using observational studies to address gaps in the evidence from randomized clinical trials on the benefits of interventions	Yes
3.4	Document the search	Yes
3.4.1	Provide a line-by-line description of the search strategy, including the date of every search for each database, web browser, etc.	Yes
3.4.2	Document the disposition of each report identified including reasons for their exclusion if appropriate	Yes
3.5	Manage data collection	Yes

IOM Standards for Systematic Reviews		Part of KDIGO Process?
3.5.1	At a minimum, use two or more researchers, working independently, to extract quantitative and other critical data from each study. For other types of data, one individual could extract the data while the second individual independently checks for accuracy and completeness. Establish a fair procedure for resolving discrepancies—do not simply give final decision-making power to the senior reviewer	One reviewer extracted data and the second checked
3.5.2	Link publications from the same study to avoid including data from the same study more than once	Yes
3.5.3	Use standard data extraction forms developed for the specific SR	Yes
3.5.4	Pilot-test the data extraction forms and process	Yes
3.6	Critically appraise each study	Yes
3.6.1	Systematically assess the risk of bias, using predefined criteria	Yes
3.6.2	Assess the relevance of the study's populations, interventions, and outcome measures	Yes
3.6.3	Assess the fidelity of the implementation of interventions	Yes
4.1	Use a prespecified method to evaluate the body of evidence	Yes
4.1.1	For each outcome, systematically assess the following characteristics of the body of evidence: Risk of bias; Consistency; Precision; Directness; Reporting bias	Yes
4.1.2	For bodies of evidence that include observational research, also systematically assess the following characteristics for each outcome: Dose–response association; Plausible confounding that would change the observed effect; Strength of association	Yes
4.1.3	For each outcome specified in the protocol, use consistent language to characterize the level of confidence in the estimates of the effect of an intervention	Yes
4.2	Conduct a qualitative synthesis	Yes
4.2.1	Describe the clinical and methodological characteristics of the included studies, including their size, inclusion or exclusion of important subgroups, timeliness, and other relevant factors	Yes
4.2.2	Describe the strengths and limitations of individual studies and patterns across studies	Yes
4.2.3	Describe, in plain terms, how flaws in the design or execution of the study (or groups of studies) could bias the results, explaining the reasoning behind these judgments	No
4.2.4	Describe the relationships between the characteristics of the individual studies and their reported findings and patterns across studies	No
4.2.5	Discuss the relevance of individual studies to the populations, comparisons, cointerventions, settings, and outcomes or measures of interest	No
4.3	Decide if, in addition to a qualitative analysis, the systematic review will include a quantitative analysis (meta-analysis)	Yes
4.3.1	Explain why a pooled estimate might be useful to decision makers	No
4.4	If conducting a meta-analysis, then do the following: • Use expert methodologists to develop, execute, and peer review the meta-analyses • Address the heterogeneity among study effects • Accompany all estimates with measures of statistical uncertainty • Assess the sensitivity of conclusions to changes in the protocol, assumptions	Yes
5.1	Prepare final report using a structured format	N/A
5.1.1	Include a report title	N/A
5.1.2	Include an abstract	N/A
5.1.3	Include an executive summary	N/A
5.1.4	Include a summary written for the lay public	N/A
5.1.5	Include an introduction (rationale and objectives)	N/A
5.1.6	Include a methods section. Describe the following:	Yes
	• Research protocol	Yes
	• Eligibility criteria (criteria for including and excluding studies in the systematic review)	Yes
	• Analytic framework and key questions	No
	• Databases and other information sources used to identify relevant studies	Yes

IOM Standards for Systematic Reviews		Part of KDIGO Process?
	• Search strategy	Yes
	• Study selection process	Yes
	• Data extraction process	Yes
	• Methods for handling missing information	No
	• Information to be extracted from included studies	Yes
	• Methods to appraise the quality of individual studies	Yes
	• Summary measures of effect size (e.g., risk ratio, difference in means)	Yes
	• Rationale for pooling (or not pooling) results of included studies	No
	• Methods of synthesizing the evidence (qualitative and meta-analysis)	Yes
	• Additional analyses, if done, indicating which were prespecified	N/A
5.1.7	Include a results section; organize the presentation of results around key questions; describe the following (repeat for each key question):	N/A
5.1.8	Include a discussion section. Include the following:	N/A ¹
	• Summary of the evidence	Yes
	• Strengths and limitations of the systematic review	Yes
	• Conclusions for each key question	No
	• Gaps in evidence	Yes
5.1.9	Include a section describing funding sources and COI	Yes
5.2	Peer review the draft report	Yes
5.2.1	Use a third party to manage the peer review process	No
5.2.2	Provide a public comment period for the report and publicly report on disposition of comments	Yes ²
5.3	Publish the final report in a manner that ensures free public access	Yes ³

¹ The systematic review is not written up as a separate report. There is no stand-alone discussion section. The evidence is summarized in individual rationale sections of the guideline as needed to support the recommendations. Gaps in the evidence are discussed as needed to support the recommendations.

² There is a public comment period for the guideline as a whole, not for the systematic review, *per se*. Disposition of comments not publicly reported.

³ The guideline is published in a manner that ensures free public access.

IOM Standards for Developing Trustworthy Clinical Practice Guidelines		Part of KDIGO Process?
1. Establishing Transparency		
1.1	The processes by which a CPG is developed and funded should be detailed explicitly and publicly accessible.	Yes
2. Management of Conflict of Interest (COI)		Yes
2.1	Prior to selection of the guideline development group (GDG), individuals being considered for membership should declare all interests and activities potentially resulting in COI with development group activity, by written disclosure to those convening the GDG:	Yes (financial interests declared at time of appointment)
	Disclosure should reflect all current and planned commercial (including services from which a clinician derives a substantial proportion of income), non-commercial, intellectual, institutional, and patient– public activities pertinent to the potential scope of the CPG.	Yes (not intellectual)
2.2	Disclosure of COIs within GDG:	
	All COI of each GDG member should be reported and discussed by the prospective development group prior to the onset of his or her work.	Reported, not discussed
	Each panel member should explain how his or her COI could influence the CPG development process or specific recommendations.	No
2.3	Divestment	
	Members of the GDG should divest themselves of financial investments they or their family members have in, and not participate in marketing activities or advisory boards of, entities whose interests could be affected by CPG recommendations.	Not explicitly
2.4	Exclusions	
	Whenever possible GDG members should not have COI.	No
	In some circumstances, a GDG may not be able to perform its work without members who have COIs, such as relevant clinical specialists who receive a substantial portion of their incomes from services pertinent to the CPG.	True for KDIGO
	Members with COIs should represent not more than a minority of the GDG.	No
	The chair or coauthors should not be a person(s) with COI.	No
	Funders should have no role in CPG development.	Yes
3. Guideline Development Group Composition		
3.1	The GDG should be multidisciplinary and balanced, comprising a variety of methodological experts and clinicians, and populations expected to be affected by the CPG.	Yes
3.2	Patient and public involvement should be facilitated by including (at least at the time of clinical question formulation and draft CPG review) a current or former patient, and a patient advocate or patient/consumer organization representative in the GDG.	No for patient involvement Question formulation and draft guideline were available for open public review
3.3	Strategies to increase effective participation of patient and consumer representatives, including training in appraisal of evidence, should be adopted by GDGs.	No
4. Clinical Practice Guideline–Systematic Review Intersection		
4.1	Clinical practice guideline developers should use systematic reviews that meet standards set by the Institute of Medicine's Committee on Standards for Systematic Reviews of Comparative Effectiveness Research.	Yes
4.2	When systematic reviews are conducted specifically to inform particular guidelines, the GDG and systematic review team should interact regarding the scope, approach, and output of both processes.	Yes
5. Establishing Evidence Foundations for and Rating Strength of Recommendations		
5.1	For each recommendation, the following should be provided:	
	An explanation of the reasoning underlying the recommendation, including	Yes
	a clear description of potential benefits and harms;	Yes

IOM Standards for Developing Trustworthy Clinical Practice Guidelines		Part of KDIGO Process?
	a summary of relevant available evidence (and evidentiary gaps), description of the quality (including applicability), quantity (including completeness), and consistency of the aggregate available evidence;	Yes
	an explanation of the part played by values, opinion, theory, and clinical experience in deriving the recommendation.	Yes
	A rating of the level of confidence in (certainty regarding) the evidence underpinning the recommendation	Yes
	A rating of the strength of the recommendation in light of the preceding bullets	Yes
	A description and explanation of any differences of opinion regarding the recommendation	Yes
6.	Articulation of Recommendations	
6.1	Recommendations should be articulated in a standardized form detailing precisely what the recommended action is, and under what circumstances it should be performed.	Yes
6.2	Strong recommendations should be worded so that compliance with the recommendation(s) can be evaluated.	Yes
7.	External Review	
7.1	External reviewers should comprise a full spectrum of relevant stakeholders, including scientific and clinical experts, organizations (e.g., health care, specialty societies), agencies (e.g., federal government), patients, and representatives of the public.	Yes
7.2	The authorship of external reviews submitted by individuals and/or organizations should be kept confidential unless that protection has been waived by the reviewer(s).	Yes
7.3	The GDG should consider all external reviewer comments...	Yes
	...and keep a written record of the rationale for modifying or not modifying a CPG in response to reviewers' comments.	Reviewed and discussed, not formally recorded
7.4	A draft of the CPG at the external review stage or immediately following it (i.e., prior to the final draft) should be made available to the general public for comment. Reasonable notice of impending publication should be provided to interested public stakeholders.	Yes
8.	Updating	
8.1	The CPG publication date, date of pertinent systematic evidence review, and proposed date for future CPG review should be documented in the CPG.	Yes; The requirement for an update will be assessed periodically from the publication date or earlier if important new evidence becomes available in the interim
8.2	Literature should be monitored regularly following CPG publication to identify the emergence of new, potentially relevant evidence and to evaluate the continued validity of the CPG.	Planned after publication
8.3	CPGs should be updated when new evidence suggests the need for modification of clinically important recommendations. For example, a CPG should be updated if new evidence shows that a recommended intervention causes previously unknown substantial harm; that a new intervention is significantly superior to a previously recommended intervention from an efficacy or harms perspective; or that a recommendation can be applied to new populations.	Planned after publication

Table S1: Summary Table
Diagnostic testing for liver fibrosis (by biopsy)
Categorical outcomes

PMID	Author	Year	Type of article	Study design	Population	Sample size	Description of Diagnostic Test		Timpoint
							Diagnostic test	Reference standard (Sensitivity threshold)	
20357753	Liu CH., Liang CC., Liu CJ., Hsu SJ., Lin JW., Chen SI., Hung PH., Tsai HB., Lai MY., Chen PJ., Chen JH., Chen DS., Kao JH.	2010	Peer-reviewed publication	Cohort study, prospective	HD	279	APRI (≥0.30)	Liver biopsy (F2-F4)	0 months
						175			12-18 months
					HD	279	APRI (≥0.40)	Liver biopsy (F2-F4)	0 months
						175			12-18 months
					HD	279	APRI (≥0.60)	Liver biopsy (F2-F4)	0 months
						175			12-18 months
					HD	279	APRI (≥0.80)	Liver biopsy (F2-F4)	0 months
						175			12-18 months
					HD	279	APRI (≥0.95)	Liver biopsy (F2-F4)	0 months
						175			12-18 months
17634962	Schiavon LL., Schiavon JL., Filho RJ., Sampaio JP., Lanzoni VP., Silva AE., Ferraz ML.	2007	Peer-reviewed publication	Cross-sectional study	HD	203	APRI (≥0.4)	Liver biopsy (F2-F4)	nd
							APRI (≥0.95)	Liver biopsy (F2-F4)	

PMID	Author	Year	Type of article	Study design	Population	Sample size	Description of Diagnostic Test		Timpoint
							Diagnostic test	Reference standard (Sensitivity threshold)	
19758273	Schiavon LL., Carvalho-Filho RJ., Narciso-Schiavon JL., Pinheiro SR., Barbosa DV., Lanzoni VP., Ferraz ML., Silva AE.	2010	Peer-reviewed publication	Cross-sectional study	Transplant	102	APRI (>0.55)	Liver biopsy (F3-F4)	nd
							APRI (≥1.00)	Liver biopsy (F3-F4)	
							APRI (>0.50)	Liver biopsy (F2-F4)	
							APRI (>1.50)	Liver biopsy (F2-F4)	
ATC-abstract 596	A. Brar, M. Salifu, M. Rampal, N. Sumrani, D. John, F. Tedla.	2012	Abstract	Cross-sectional study	HD	26	APRI	Liver biopsy (F2-F4)	nd
24353319	Jiang Y., Huang E., Mehrnia A., Kamgar M., Pham PT., Ogunorunyinka O., Brown I., Danovitch GM., Bunnapradist S.	2014	Peer-reviewed publication	Cross-sectional study	HD? (Transplant candidates)	210	APRI (≥0.4)	Liver biopsy (F3-F4)	nd
							APRI (>0.95)	Liver biopsy (F3-F4)	
21393486	Liu CH., Liang CC., Huang KW., Liu CJ., Chen SI., Lin JW., Hung PH., Tsai HB., Lai MY., Chen PJ., Chen JH., Chen DS., Kao JH.	2011	Peer-reviewed publication	Cross-sectional study	HD	304	APRI (1.5)	Liver biopsy (≥F2)	nd
							APRI (0.55)	Liver biopsy (≥F2)	nd
							APRI (0.5)	Liver biopsy (≥F2)	nd
							APRI (1.75)	Liver biopsy (F3)	nd
							APRI (0.75)	Liver biopsy (F3)	nd

PMID	Author	Year	Type of article	Study design	Population	Sample size	Description of Diagnostic Test		Timpoint
							Diagnostic test	Reference standard (Sensitivity threshold)	
16371924	Varaut A., Fontaine H., Serpaggi J., 2005 Verkarre V., Vallet-Pichard A., Nalpas B., Imbertbismuth F., Lebray P., Pol S.		Peer-reviewed publication	Cross-sectional study	HD & Transplant	110	Fibrotest (>0.6)	Liver biopsy (F2-F4)	nd
							Fibrotest (≥0.2)	Liver biopsy (F2-F4)	
							Fibrotest (>0.6)	Liver biopsy (F3-F4)	
							Fibrotest (≥0.2)	Liver biopsy (F3-F4)	
					HD	50	Fibrotest (>0.6)	Liver biopsy (F2-F4)	
							Fibrotest (≥0.2)	Liver biopsy (F2-F4)	
							Fibrotest (>0.6)	Liver biopsy (F3-F4)	
							Fibrotest (≥0.2)	Liver biopsy (F3-F4)	
					Transplant	60	Fibrotest (>0.6)	Liver biopsy (F2-F4)	
							Fibrotest (≥0.2)	Liver biopsy (F2-F4)	
							Fibrotest (>0.6)	Liver biopsy (F3-F4)	
							Fibrotest (≥0.2)	Liver biopsy (F3-F4)	

PMID	Author	Year	Type of article	Study design	Population	Sample size	Description of Diagnostic Test		
							Diagnostic test	Reference standard (Sensitivity threshold)	Timpoint
20847572	Canbakan M., Senturk H., Canbakan B., Toptas T., Tabak O., Ozaras R., Tabak F., Balci H., Sut N., Ozbay G.	2011	Peer-reviewed publication	Cross-sectional study	HD	33	Fibrotest (>0.19)	Liver biopsy (F2-F4)	nd
							Fibrotest (>0.6)	Liver biopsy (F2-F4)	
21393486	Liu CH., Liang CC., Huang KW., Liu CJ., Chen SI., Lin JW., Hung PH., Tsai HB., Lai MY., Chen PJ., Chen JH., Chen DS., Kao JH.	2011	Peer-reviewed publication	Cross-sectional study	HD	304	Fibroscan (8.8)	Liver biopsy (F2-F4)	nd
							Fibroscan (7.1)	Liver biopsy (F2-F4)	nd
							Fibroscan (5.3)	Liver biopsy (F2-F4)	nd
							Fibroscan (9.5)	Liver biopsy (F3-4)	nd
							Fibroscan (9.6)	Liver biopsy (F3-4)	nd
							Fibroscan (8.3)	Liver biopsy (F3-4)	nd
ATC-abstract 596	A. Brar, M. Salifu, M. Rampal, N. Sumrani, D. John, F. Tedla.	2012	Abstract	Cross-sectional study	HD	26	FIB-4	Liver biopsy (F2-F4)	
20847572	Canbakan M., Senturk H., Canbakan B., Toptas T., Tabak O., Ozaras R., Tabak F., Balci H., Sut N., Ozbay G.	2011	Peer-reviewed publication	Cross-sectional study	HD	33	ActiTest (>0.11)	Liver biopsy (≥A2)	

Table S1: Summary Table
Diagnostic testing for liver fibrosis (by biopsy)
Categorical outcomes

PMID	Author	Year	Outcome	Sensitivity (%)	Specificity (%)	ROC-AUC	Quality
20357753	Liu CH., Liang CC., Liu CJ., Hsu SJ., Lin JW., Chen SI., Hung PH., Tsai HB., Lai MY., Chen PJ., Chen JH., Chen DS., Kao JH.	2010	Fibrosis	97	23	0.83	Good
				76	55	0.71	
				84	51		
				50	73		
				61	90		
				45	89		
				45	95		
				33	95		
				32	96		
				14	98		
17634962	Schiavon LL., Schiavon JL., Filho RJ., Sampaio JP., Lanzoni VP., Silva AE., Ferraz ML.	2007	Fibrosis	88	54	0.80	Good
				44	93		

PMID	Author	Year	Outcome	Sensitivity (%)	Specificity (%)	ROC-AUC	Quality
				95	69	0.84	
				42	89		
19758273	Schiavon LL., Carvalho-Filho RJ., Narciso-Schiavon JL., Pinheiro SR., Barbosa DV., Lanzoni VP., Ferraz ML., Silva AE.	2010	Fibrosis	85	51	0.73	Good
				25	89		
ATC-abstract 596	A. Brar, M. Salifu, M. Rampal, N. Sumrani, D. John, F. Tedla.	2012	Fibrosis	nd	nd	0.81	Fair
24353319	Jiang Y., Huang E., Mehrnia A., Kamgar M., Pham PT., Ogunorunyinka O., Brown I., Danovitch GM., Bunnapradist S.	2014	Fibrosis	67	56	nd	Good
				27	92		
21393486	Liu CH., Liang CC., Huang KW., Liu CJ., Chen SI., Lin JW., Hung PH., Tsai HB., Lai MY., Chen PJ., Chen JH., Chen DS., Kao JH.	2011	Fibrosis	3	100	nd	Good
			Fibrosis	74	82	0.84 (0.79, 0.88)	
			Fibrosis	79	70	nd	
			Fibrosis	2	99	nd	
			Fibrosis	93	90	0.93 (0.90, 0.97)	

PMID	Author	Year	Outcome	Sensitivity (%)	Specificity (%)	ROC-AUC	Quality
16371924	Varaut A., Fontaine H., Serpaggi J., Verkarre V., Vallet-Pichard A., Nalpas B., Imbertbismuth F., Lebray P., Pol S.	2005	Fibrosis	24	92	0.66	Fair
				84	45		
				nd	nd	0.70	
				nd	nd		
				14	97	0.47	
				71	52		
				30	98	0.66	
				80	48		
				69	88	0.71	
				93	39		
				nd	nd	0.72	
				100	29		

PMID	Author	Year	Outcome	Sensitivity (%)	Specificity (%)	ROC-AUC	Quality
20847572	Canbakan M., Senturk H., Canbakan B., Toptas T., Tabak O., Ozaras R., Tabak F., Balci H., Sut N., Ozbay G.	2011	Fibrosis	64	32	0.46 (0.25, 0.67)	Poor
				13	84		
21393486	Liu CH., Liang CC., Huang KW., Liu CJ., Chen SI., Lin JW., Hung PH., Tsai HB., Lai MY., Chen PJ., Chen JH., Chen DS., Kao JH.	2011	Fibrosis	30	100	nd	Good
			Fibrosis	55	96	nd	
			Fibrosis	93	88	0.96 (0.94, 0.98)	
			Fibrosis	45	99	nd	
			Fibrosis	45	99	nd	
			Fibrosis	95	99	0.98 (0.97, 1.00)	
ATC-abstract 596	A. Brar, M. Salifu, M. Rampal, N. Sumrani, D. John, F. Tedla.	2012	Fibrosis	nd	nd	0.54	Fair
20847572	Canbakan M., Senturk H., Canbakan B., Toptas T., Tabak O., Ozaras R., Tabak F., Balci H., Sut N., Ozbay G.	2011	Activity (Necroinflammation)	36	40	0.36 (0.15, 0.57)	Poor

Table S2: Evidence profile: Diagnostic testing for liver fibrosis (by biopsy)

Diagnostic Test	# of Studies	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence, including Applicability	Other Considerations	Summary of Findings		
							Quality of Evidence for Outcome	Description of Findings	Importance of Outcome
APRI*	5 studies	995	No limitations (0)	No important inconsistencies (0)	Direct (0)	None (0)	High	F2-F4: AUC 0.73-0.83 (4 studies, transplant/HD) APRI >0.4 Sn 84-88%, Sp 51-54% (2 studies, HD) APRI >0.95 Sn 32-44%, Sp 93-96% (2 studies, HD) † F3-F4: AUC 0.84 (1 study, HD) APRI >0.4 Sn 67%, Sp 56% (1 of 2 studies, HD) ‡ APRI >0.95 Sn 27%, Sp 92% (1 of 2 studies, HD) §	High
Fibroscan 	1 study	304	No limitations (0)	NA	Direct (0)	Sparse data (-1)	Moderate	F2-F4: AUC 0.96 (1 study, HD) F3-F4: AUC 0.98 (1 study, HD)	High
Fibrotest ¶	2 studies	143	Some limitations (-1)	No important inconsistencies (0)	Direct (0)	None (0)	Moderate	F2-F4: AUC 0.46-0.47 (2 studies, HD) Fibrotest >0.2 Sn 64-71%, Sp 32-52% (2 studies)** Fibrotest >0.6 Sn 13-14%, Sp 84-97% (2 studies) †† F3-F4: AUC 0.66 (1 study, HD), AUC 0.72 (1 study, Txp)	High
FIB-4 ‡‡	1 study	26	Some limitations (-1)	NA	Direct (0)	Sparse data (-1)	Low	AUC 0.54 (1 study, HD)	High
ActiTest §§	1 study	33	Serious limitations (-2)	NA	Indirect (-1)	Sparse data (-1)	Very Low	Predicting "Activity" (necroinflammation): ActiTest >0.11 Sn 36%, Sp 40%, AUC 0.36	High

Overall summary (and Quality of Overall Evidence):

High quality evidence that APRI accurately diagnoses METAVIR F2-F4, sparse evidence that APRI accurately diagnoses F3-F4.

Sparse, moderate quality evidence that Fibroscan very accurately diagnoses F2-F4 and F3-F4.

Very Low to Moderate evidence that other tests (Fibrotest, FIB-4, ActiTest) do not accurately diagnose liver fibrosis (or necroinflammation).

Studies included in EP: 16371924, 20847572, 21393486, ATC-abstract 596, 20847572

Abbreviations: ALT = alanine aminotransferase, APRI = AST to platelet ratio index, AST = aspartate aminotransferase, AUC = area under the (receiver operating characteristics) curve, F2/F3/F4 = METAVIR scores, FIB4 = Fibrosis-4 test, GGT = γ-glutamyltranspeptidase, HD = hemodialysis, NA = not applicable (single study), Sn = sensitivity, Sp = specificity.

Annotations:

* APRI = (AST level [U/L]/upper limit of normal)/platelet counts (10⁹/liter) x 100

† Transplant population (1 study): APRI >0.50 Sn 85%, Sp 51%; APRI >1.5 Sn 25%, Sp 89%.

‡ 2nd HD study: APRI >0.55 Sn 95%, Sp 69%.

§ 2nd HD study: APRI >1.0 Sn 42%, Sp 89%.

|| Also known as transient elastography or liver stiffness measurement, based on proprietary ultrasonography.

¶ Proprietary test based on α2-macroglobulin, haptoglobin, apolipoprotein A1, GGT, total bilirubin, age and sex.

** In transplant population (1 study): Fibrotest >0.2 Sn 93%, Sp 39%.

†† In transplant population (1 study): Fibrotest >0.6 Sn 69%, Sp 88%; AUC 0.71.

‡‡ FIB4 = age (years) × AST [U/L]/platelet count[10⁹/L] × (ALT [U/L])^{1/2}

§§ Proprietary test based on α2-macroglobulin, haptoglobin, apolipoprotein A1, GGT, total bilirubin, ALT, age and sex.

Table S3: Summary Table HCV infection as independent predictor of CKD progression																	
PMID	Author	Year	Type of article	Country	Study design	Registry Name	Population	Sample Size, Total	CKD stage, baseline	Kidney function, baseline	HCV genotypes		Follow-up Time	Predictor HCV+	Predictor Definition nd	Predictor units nd	# w/Predictor or mean (95%) 100,518
25529816	Molnar	2015	Peer-reviewed publication	US	Retrospective cohort study	nd	US veterans with baseline GFR ≥60 mL.min.1.73m2 with and without HCV	1,021,049	CKD 1-2	HCV+: 93 ± 16 HCV-: 87 ± 16	nd		7.8 years (IQR 6.8, 8.4)	HCV-			920,531
														HCV+	nd	nd	100,518
														HCV-			920,531
														HCV+	nd	nd	100,518
8.0 years (IQR 7.1, 8.5)														HCV-			920,531
detectable RNA																	
23904290	Lucas	2013	Peer-reviewed publication	US	Retrospective cohort study	NA-ACCORD	HIV+ adults	63,023	CKD 0-5	GFR >90 70% GFR 60-89 26% GFR 30-59 3.4% GFR 15-29 0.4%	nd		nd	HCV viremic			57,854 pt-yr
														HCV aviremic	seropositive, undetectable RNA		4769 pt-yr
														HCV-			269,805 pt-yr
														detectable RNA			
														HCV viremic			61 833 pt-yr
														HCV aviremic	seropositive, undetectable RNA		5139 pt-yr
														HCV-			287,386 pt-yr
detectable RNA																	
20400217	Lee	2010	Peer-reviewed publication	Taiwan	Cross-sectional study	Taiwanese National Health Insurance Program	Adults	54,966	CKD 1-5	GFR ≥90: 27.7% GFR 60-89: 57.9% GFR 30-59: 13.7% GFR <0.8%	nd		nd	HCV alone	seropositive	nd	5,189
														HCV alone	seropositive	nd	5,189
														HCV alone	seropositive	nd	5,189
														HCV alone	seropositive	nd	5,189
														HCV alone			
21386707	Hofmann	2011	Peer-reviewed publication	Sweden	Retrospective cohort study	Swedish Institute for Infectious Disease Control	HCV and matched controls	43,000	nd	nd	nd		nd	MALES			
														HCV-infected	nd	nd	25,412
														HCV-infected	nd	nd	25,412
														HCV-infected	nd	nd	25,412
														HCV-infected	nd	nd	25,412
														FEMALES			
														HCV-infected	nd	nd	25,412
														HCV-infected	nd	nd	25,412

PMID	Author	Year	Type of article	Country	Study design	Registry Name	Population	Sample Size, Total	CKD stage, baseline	Kidney function, baseline	HCV genotypes	Follow-up Time	Predictor	Predictor Definition	Predictor units	# w/Predictor or mean (95%)	
													HCV-infected	nd	nd	25,412	
													HCV-infected	nd	nd	25,412	
18371161	Ishizaka	2008	Peer-reviewed publication	Japan	Cross-sectional study	General Health Screen at Mitsui Memorial Hospital	Working adults	12,535	nd	Hep B - and Hep C -: 70 ± 10	nd	nd	HCV +	HCV Ag +	nd	72	
													Hep B +: 70 ± 9 Hep C +: 67 ± 13	HCV - and HBV -	HCV Ag - and HBV Ag -	nd	12,333
														HCV +	HCV Ag +	nd	72
														HCV - and HBV -	HCV Ag - and HBV Ag -	nd	12,333
														HCV +	HCV Ag +	nd	72
													HCV - and HBV -	HCV Ag - and HBV Ag -	nd	12,333	
23311442	Cao	2013	Peer-reviewed publication	China	Cross-sectional Study	nd	HIV infected antiretroviral therapy-naïve	538	nd	Non-CKD: 113.54 ± 24.06	nd	nd	HCV +	HCV Ab +	nd	80	
CKD: 98.98 ± 34.48	HCV -	HCV Ab -	nd	444													
		seropositive	nd	178,447 pt-yr													
17592100	Tsui	2007	Peer-reviewed	US	Retrospective Cohort Study	Medicare, the Department of Veterans Affairs, and the United States Renal Data System	US Veterans	474,369	HCV+: 9.4% with any stage HCV-: 16.6% with any stage	HCV+ GFR>=60: 83% GFR 30-59: 15% GFR<30: 2%	nd	3.4y (median 3.6y)	HCV+ HCV- HCV+, eGFR >= 60 HCV-, eGFR >= 61 HCV+, eGFR 30-59 HCV-, eGFR 30-59 HCV+, eGFR <30 HCV-, eGFR <30	seronegative seropositive seronegative seropositive seronegative seropositive seronegative	nd nd nd nd nd nd nd	1,442,826 pt-yr 163,846 pt-yr 1,219,523 pt-yr 13,295 pt-yr 207,484 pt-yr 1,307 pt-yr 15,819 pt-yr	
26526451	Rogal	2016	Peer-reviewed	US	Retrospective Cohort Study	HCV Infected Veterans (ERCHIVES)	US Veterans	71,528			1: 33.14%, 2: 4.75%, 3: 5.25%, 4: 0.35%, Mixed: 0.08%, Missing: 56.43%	HCV+: 5.99 (SD 2.84)y HCV-: 4.91 (SD 2.16)y	HCV+ HCV- HCV+	nd nd	nd nd		
22554802	Su	2012	Peer-reviewed	Taiwan	Retrospective Case Control	Taiwan National Health Insurance Research Database	Taiwanese adults	37,746			nd	5.58 (SD 2.04)	HCV+ HCV-			32,648 pt-yr 176,921 pt-yr	
26817874	Hwang	2016	Peer-reviewed	Taiwan	Retrospective Case Control	Longitudinal Cohort of Diabetes Patients	DM	19,574			nd	12 y	HCV+ HCV-			nd	
16524948	Tsui	2006	Peer-reviewed publication	US	Cross-sectional	NHANES III	US general population	15029 (366 HCV+)	nd	HCV+: 110 (106-114) HCV-: 100 (99-101)	nd	nd	HCV+ HCV- HCV+ HCV+ HCV-	nd nd nd	nd nd nd	366 14,663 14,663 100,518 920,531	
19747988	Asrani	2010	Peer-reviewed publication	US	Retrospective cohort study	Conglomerate of health insurance carriers database, NOS	US adults	167,569	CKD 0-5	GFR >60 95% GFR 30-59 5.0% GFR 15-29 0.2% GFR <15 0.1%	nd	nd	HCV+ HCV - HCV+ HCV -	EIA, NAT, gentoype test EIA, NAT, genotype test		13,384 154,185 8,063 80,759	
24257691	Chen	2014	Peer-reviewed publication	Taiwan	Retrospective cohort study	Taiwan National Health Insurance Research Database	Taiwanese adults (no renal Txp)	9430 HCV+ and 3772 Non-CKD (per ICD-9)		nd	nd	~7 years	HCV +	ICD-9 codes		9,430	

PMID	Author	Year	Type of article	Country	Study design	Registry Name	Population	Sample Size, Total	CKD stage, baseline	Kidney function, baseline	HCV genotypes	Follow-up Time	Predictor HCV-	Predictor Definition	Predictor units	# w/Predictor or mean (95%)
37,720 (matched)																
25826420	Mocroft	2015	Peer-reviewed publication	Europe, U	Prospective cohort study	nd	HIV+	17,594	Healthy (not CKD)	median: 104	nd	103,185 person-years	HCV +	nd		2,262
													HCV -	nd		11,386
21185632	Butt	2011	Peer-reviewed publication	US	Retrospective cohort study	ERCHIVES	HCV infected patients, HCV-uninfected controls	43,139	Healthy (not CKD 3-5)	HCV+: 99 (22.6)	nd	HCV+: 3.15 (1.4) y	HCV +	anti-HCV Ab + or HCV RNA +		18,002
										HCV-: 92 (22.2)			HCV -	anti-HCV Ab - or HCV RNA -		25,137
22994610	Bickel	2015	Peer-reviewed publication	Germany	Prospective cohort study	nd	HIV+	9198	Not ESRD	nd	nd	5 years max	HCV +			1008
													HCV -			4330 (+3860 unknown)

Table S3: Summary Table
HCV infection as independent
predictor of CKD progression

PMID	Author	Year	Outcome	Outcome Definition	Cases (# w/Outcome)	Rate	Adjustments (reject if none)	Metric (HR, OR, RR, beta, change)	Estimate (95% CI)	Comparison	P_value	Risk of bias				
25529816	Molnar	2015	GFR<60 incidence	the presence of two consecutive eGFR values of <60 mL/min/1.73 m2 at least 90 days apart with the added stipulation that the decrease in eGFR should be at least 25% from the baseline eGFR	11,271 95,837	16.7 (16.4,17.0)/1000 pt/yr 14.9 (14.8,15.0)/1000 pt-yr	age, gender, race/ethnicity, baseline GFR, ,comorbidities, SBP, DBP, BMI, socio-demographic parameters	HR	1.15 (1.12, 1.17)	vs. HCV-	nd	LOW				
			GFR loss >5 mL/min/1.73m2/year	Rapid deterioration was defined as slopes of < −5 mL/min/1.73 m2/year (i.e., loss of eGFR of >5 mL/min/1.73 m2) /year).	nd nd	nd nd							OR	1.22 (1.19, 1.26)	vs. HCV-	nd
			ESRD	initiation of renal replacement therapy or preemptive transplant	904 2479	1.2 (1.1, 1.3)/1000 pt-yr 0.36 (0.34, 0.37)/1000 pt-yr										
23904290	Lucas	2013	CKD 3	GFR<60 for >=90 d	1666 122 5090	28.8 (27.5, 30.2)/1000 pt-yr 25.6 (21.4, 30.6)/1000 pt-yr 18.9 (18.4, 19.4)/1000 pt-yr	Age, sex, race, history of injection drug use, hepatitis B surface antigen positivity, baseline glomerular filtration rate, and time-updated covariates including calendar year, CD4 cell count, HIV RNA, antiretroviral therapy use, tenofovir use, indinavir use, lopinavir/ritonavir use, atazanavir use, hypertension, and diabetes.	HR	1.36 (1.26, 1.46) 1.19 (0.98, 1.45)	vs. HCV- vs. HCV-	nd nd	LOW				
			CKD 5	GFR<15 for >=90 d	376 23 699	6.1 (5.5, 6.7)/1000 pt-yr 4.4 (2.9, 6.7)/1000 pt-yr 2.4 (2.3, 2.6)/1000 pt-yr	Age, sex, race, history of injection drug use, hepatitis B surface antigen positivity, baseline glomerular filtration rate, and time-updated covariates including calendar year, CD4 cell count, HIV RNA, antiretroviral therapy use, tenofovir use, indinavir use, lopinavir/ritonavir use, atazanavir use, hypertension, and diabetes.	HR	1.95 (1.64, 2.31) 1.69 (1.07, 2.65)	vs. HCV- vs. HCV-	nd nd					
CKD decline	≥25% GFR decline from baseline to a GFR < 60 mL/min/1.73 m2 that persisted for at least 90 days among subjects with baseline GFR ≥ 30 mL/min/1.73 m2.	984 76 2885	16.4 (15.4, 17.5)/1000 pt-yr 15.4 (12.3, 19.2)/1000 pt-yr 10.3 (9.9, 10.7)/1000 pt-yr	Age, sex, race, history of injection drug use, hepatitis B surface antigen positivity, baseline glomerular filtration rate, and time-updated covariates including calendar year, CD4 cell count, HIV RNA, antiretroviral therapy use, tenofovir use, indinavir use, lopinavir/ritonavir use, atazanavir use, hypertension, and diabetes.	HR	1.31 (1.19, 1.44) 1.31 (1.02, 1.68)	vs. HCV- vs. HCV-	nd nd								
20400217	Lee	2010	CKD	determined by eGFR and proteinuria based on the K/DOQI definition	nd	nd	age, sex, educational status, BMA, albumin, Hb, cholesterol, uric acid, HTN, and DM	OR	1.26 (1.17, 1.38)	vs. HBV or HBV/HCV	<0.001	HIGH				
			CKD	defined using GFR estimated using the 6-variable MDRD Study equation	nd	nd	age, sex, educational status, BMA, albumin, Hb, cholesterol, uric acid, HTN, and DM									
			proteinuria	presence of urine protein of at least grade 1+ in repeated measures	nd	nd	age, sex, educational status, BMA, albumin, Hb, cholesterol, uric acid, HTN, and DM									
			low GFR	eGFR <60 mL/min/1.73 m2	nd	nd	age, sex, educational status, BMA, albumin, Hb, cholesterol, uric acid, HTN, and DM									
Hofmann		2011														
21386707												HIGH				
			glomerular diseases	risk of hospitalization for glomerular disease; ICD-9 codes: 580–583, ICD-10 codes: N00–N08	104	nd	age, sex, and interaction between HCV status and sex	HR	2.9 (2.0, 4.3)	vs. no HCV infection	nd					
			renal failure	risk of hospitalization for renal failure; ICD-9 codes: 584–586, ICD-10 codes: N17–N19	245	nd	age, sex, and interaction between HCV status and sex	HR	4.6 (3.7, 5.8)	vs. no HCV infection	nd					
			other kidney diseases	risk of hospitalization for other kidney diseases; ICD-9 codes: 587–589 and 593, ICD-10 codes:N25–N28	30	nd	age, sex, and interaction between HCV status and sex	HR	2.9 (1.4, 6.0)	vs. no HCV infection	nd					
			all noncancer kidney diseases combined	risk of hospitalization for combination of above	349	nd	age, sex, and interaction between HCV status and sex	HR	3.9 (3.2, 4.8)	vs. no HCV infection	nd					
			glomerular diseases	risk of hospitalization for glomerular disease; ICD-9 codes: 580–583, ICD-10 codes: N00–N08	34	nd	age, sex, and interaction between HCV status and sex	HR	5.1 (3.0, 8.8)	vs. no HCV infection	nd					
			renal failure	risk of hospitalization for renal failure; ICD-9 codes: 584–586, ICD-10 codes: N17–N19	59	nd	age, sex, and interaction between HCV status and sex	HR	7.2 (4.9, 10.6)	vs. no HCV infection	nd					

PMID	Author	Year	Outcome	Outcome Definition	Cases (# w/Outcome)	Rate	Adjustments (reject if none)	Metric (HR, OR, RR, beta, change)	Estimate (95% CI)	Comparison	P_value	Risk of bias
			other kidney diseases	risk of hospitalization for other kidney diseases; ICD-9 codes: 587–589 and 593, ICD-10 codes:N25–N28	4	nd	age, sex, and interaction between HCV status and sex	HR	10.0 (2.7, 37.2)	vs. no HCV infection	nd	
			all noncancer kidney diseases combined	risk of hospitalization for combination of above	94	nd	age, sex, and interaction between HCV status and sex	HR	5.8 (4.2, 7.9)	vs. no HCV infection	nd	
18371161	Ishizaka	2008	Low eGFR	eGFR<60 mL/min/1.73 m2	22	31%	age, sex, SBP, and FPG					
					1887	15%		OR	1.63 (0.95, 2.80)	vs. HCV - and HBV -	0.077	HIGH
			Albuminuria	UAER of 330 mg/g	14	19%	age, sex, SBP, and FPG	OR	2.00 (1.06, 3.76)	vs. HCV - and HBV -	0.034	
					1157	9%						
			CKD	eGFR<60 mL/min/1.73 m2, or UAER of 330 mg/g	nd	nd	age, sex, SBP, and FPG	OR	1.83 (1.10, 3.05)	vs. HCV - and HBV -	0.02	
					nd	nd						
23311442	Cao	2013	CKD	GFR < 60 mL/min per 1.73 m2 and/or isolated proteinuria (>= 1 + on urine dipstick) for 3 months	20	25%	age, HIV viral load					
					64	14%		OR	2.074 (1.036, 4.149)	vs. HCV -	0.011	HIGH
							age, sex, race/ethnicity, diabetes mellitus, hypertension, human immunodeficiency virus infection, congestive heart failure, coronary heart disease, peripheral vascular disease, chronic obstructive pulmonary disease, cerebrovascular disease, substance abuse, and baseline eGFR, also stratified by age					
17592100	Tsui	2007	ESRD	onset of chronic dialysis or renal transplantation	760	4.26 (3.97-4.57)/1000 pt-yr		HR	1.68 (1.54-1.82)	vs. HCV-	nd	LOW
					4393	3.05 (2.96-3.14)/1000 pt-yr						
					106	0.65 (0.54-0.78)/1000 pt-yr		HR	2.74 (2.13-3.51)	vs. HCV-	nd	
					308	0.25 (0.23-0.28)/1000/ pt-yr						
					228	17.15 (15.06-19.53)/1000 pt-yr		HR	2.57 (2.20-3.01)	vs. HCV-	nd	
					1039	5.01 (4.71-5.32)/1000 pt-yr						
					426	326.03 (296.49-358.50)/1000 pt-yr		HR	1.28 (1.15-1.44)	vs. HCV-	nd	
					3046	192.55 (185.83-199.51)/1000 pt-yr						
26526451	Rogal	2016	CKD 3-5		nd	nd	baseline GFR with FIB-4 included as a time-varying covariate	HR	0.86 (0.79, 0.92)	HCV+ vs. HCV-	<0.0001	LOW
			Progressive CKD	decline in eGFR of >= 30 from baseline	nd	nd	baseline GFR with FIB-4 included as a time-varying covariate	HR	0.93 (0.86, 1.00)	HCV+ vs. HCV-	0.06	
22554802	Su	2012	ESRD		77		age, sex, occupation, urbanization, and Charlson Comorbidity Index score	HR	1.53 (1.17, 2.01)	vs. HCV-	0.002	LOW
					196		results also stratified by age, sex, and followup interval					
26817874	Hwang	2016	ESRD		nd	nd	sex, age at index date and various comorbidities including hypertension, CAD, hyperlipidemia, HBV infection, gout and liver cirrhosis	HR	1.47 (1.11-1.93)	vs. HCV-	<0.05	LOW
16524948	Tsui	2006	GFR<60 prevalence	eGFR <60	366	2.0 (1.1,3.6) %	age, gender, race/ethnicity, educational status, smoking status, DM,and HTN	OR	0.89 (0.49, 1.62)	vs. HCV-	0.7	LOW
					14,663	4.3 (3.7,4.9) %						
			Albuminuria prevalence	Albuminuria	366	nd	age, gender, race/ethnicity, educational status, smoking status, DM,and HTN	OR	1.22 (1.19, 1.26)	vs. HCV-	nd	
					14,663	nd						
19747988	Asrani	2010	CKD prevalence (baseline)	GFR<60 (single measurement)	13,384	5.3%	Age, sex, cirrhosis, DM, HTN, CHF, PVD, CAD, COPD, HIV, drug/alcohol abuse, depression	OR	0.90 (0.36, 2.27)	vs. HCV-	0.7	LOW
					154,185	5.1%						
			Progression to CKD	GFR <60 without baseline CKD	8,063	3.8%	Age, sex, cirrhosis, DM, HTN, CHF, PVD, CAD, COPD, HIV, drug/alcohol abuse, depression	OR	0.92 (0.79, 1.08)	vs. HCV-		
					80,759	3.5%						
24257691	Chen	2014	CKD, incident	ICD-9 code	367	3.9% (5.46/1000 person-yr)	age per year, sex, comorbidities, geographic region, urbanization level, enrollee category, and number of medical visits in 1 year before study entry	HR	1.28 (1.12, 1.46)	vs HCV-	<0.001	LOW

PMID	Author	Year	Outcome	Outcome Definition	Cases (# w/Outcome)	Rate	Adjustments (reject if none)	Metric (HR, OR, RR, beta, change)	Estimate (95% CI)	Comparison	P_value	Risk of bias
					960	2.5%	(3.43/1000 person-yr)					
25826420	Mocroft	2015	CKD	eGFR <= 60 mL/min per 1.73 m2 (>3mo)	89	13.9%	age, sex, HIV risk, eGFR, nadir CD4 <200, HTN, prior CVD, diabetes	OR [exp(beta)]	1.40 (nd)	vs. HCV -	nd (at least <0.10)	HIGH
					391	61.0%						
21185632	Butt	2011	CKD 3-5	eGFR < 60 mL/min per 1.73 m2 for >=2 times	3,140	17.4%	age, sex, race, eGFR, HTN, smoking, COPD, diabetes, dyslipidemia, anemia, alcohol abuse, drug abuse, decompensated liver disease, ACEi/ARB use	HR	1.30 (1.23, 1.37)	vs. HCV -	< 0.0001	LOW
					3,738	14.9%						
22994610	Bickel	2015	ESRD	Initiation of RRT	~13 ~22	nd nd	race (black), intravenous drug use (sex, AIDS, HBV coinfection were NS)		0.84 (0.24, 2.86)	vs. HCV -	0.79	UNCLEAR

Table S4: Evidence profile: HCV infection as independent predictor of CKD progression

Outcome	# of Studies and Study Design*	Total N of Participants	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence, including Applicability	Other Considerations	Summary of Findings		
							Quality of Evidence for Outcome	Description of Findings	Importance of Outcome
ESRD	6 retrospective, 1 prospective cohorts	Cohorts: 9198-1,021,049	No limitations (0)	No important inconsistencies (0) [†]	Direct (0)	None	High (Moderate for HIV coinfection)	No HIV coinfection: All studies (6 of 6 analyses in 5 studies) found significantly higher rates of ESRD in HCV+ (vs. HCV-). ES range 1.47-7.2 (women)/4.6 (men). HIV coinfection: Inconsistent: One study found no significant association between HCV coinfection and RRT (ES 0.84) One found significant association with CKD 5 (ES 1.95)	Critical
CKD	10 retrospective, 1 prospective cohorts	Cohorts: 538-1,021,049	No limitations (0)	Some inconsistencies (-1)	Direct (0)	None	Moderate	No HIV coinfection: Most studies(5 of 7) found significantly higher CKD incidence in HCV+ (vs. HCV-). ES range 0.86-1.83. One study found significantly <i>lower</i> risk of CKD in patients with <i>newly acquired</i> HCV. HIV coinfection: All studies (3 of 3) found significantly higher CKD incidence in HCV+ coinfection (vs. HCV-). ES range 1.36-2.07.	High
Decline in Kidney Function	3 retrospective cohorts	Cohorts: 63,023-1,021,049	No limitations (0)	Some inconsistencies (-1)	Direct (0)	None	Moderate	No HIV coinfection: 2 studies had conflicting findings with significant association between HCV+ and GFR loss >5 mL/min (OR 1.22) in 1 study, and no association with GFR loss ≥30 mL/min (HR 0.93) in 1 study. HIV coinfection: 1 study significant association between HCV+ and GFR decline ≥25% to <60 mL/min (HR 1.31).	High
Total N	15 retrospective, 1 prospective cohorts	Cohorts: 538-1,021,049							

Association of HCV+ status and CKD:

People with HCV infection are at increased risk of CKD and ESRD compared to people without HCV infection. Among people with HIV, coinfection with HCV increases the risk for CKD, but it remains unclear whether it also increases the risk for ESRD.

Quality of Overall Evidence:

Moderate

Studies included in EP: 25529816, 23904290, 20400217, 21386707, 18371161, 23311442, 17592100, 26526451, 22554802, 26817874, 16524948, 19747988, 24257691, 25826420, 21185632, 22994610

Abbreviations: CKD: chronic kidney disease; DAA: direct-acting antivirals; GFR: glomerular filtration rate; RCT: randomized controlled trial; SVR: sustained virological response

Annotations:

* Limited to largest studies with the addition of smaller studies of HIV population and from otherwise unrepresented countries.

† For general population. Two studies of HIV population were inconsistent with each other.

Table S5. Evidence Profile: Treatment with direct-acting antiviral regimens in CKD G4-G5 non-dialysis patients

Outcome	Regimen ¹	# of Studies ²	Total N of Patients on Treatment	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings			
								Certainty of Evidence for Outcome	Description of Findings	Importance of Outcome	
Death, ~6-12 mo	Any	0							ND	Critical	
SVR12	DCV/ASV	1	10	No limitations	N/A	Direct	Sparse	Very low	100% (52, 100)	Very high SVR12 for all treatments. Mostly ~97%. No direct evidence of differences among regimens.	High
	GLE/PIB	3	132	No limitations	Consistent	Direct	None	High	98.5% (94.1, 99.6)		
	GZR/EBR	5	857	No limitations	Consistent	Direct	None	High	96.7% (95.4, 97.8)		
	PrO±D	3	103	No limitations	Inconsistent	Direct	Imprecise	Low	89.4% (75.7, 97.8)		
	SOF	2	41	No limitations	Inconsistent	Direct	Imprecise	Very Low	71.7% (29.1, 98.6)		
	SOF/DCV	4	571	No limitations	Consistent	Direct	None	High	97.1% (95.7, 98.3)		
	SOF/LDV	2	43	No limitations	Consistent	Direct	Imprecise	Very Low	100% (84, 100)		
	SOF/SIM	1	41	No limitations	N/A	Direct	Sparse	Very Low	92.7% (79.6, 97.6)		
SOF/VEL	2	99	No limitations	Consistent	Direct	Imprecise	Low	96.0% (89.7, 98.5)			
Serious AE due to DAA	DCV/ASV	0							ND	Rare, but insufficient evidence. No evidence of differences among regimens.	High
	GLE/PIB	2	67	Some limitations ³	Consistent	Direct	Imprecise	Very Low	0% (0, 11)		
	GZR/EBR	1	14	Serious limitations ⁴	N/A	Direct	Sparse	Very Low	0% (0, 39)		
	PrO±D	2	53	Serious limitations ⁵	Consistent	Direct	Imprecise	Very Low	0% (0, 13)		
	SOF	3	41	No limitations	Consistent	Direct	Imprecise	Very Low	0% (0, 17)		
	SOF/DCV	2	52	Serious limitations ⁶	Consistent	Direct	Imprecise	Very Low	0% (0, 14)		
	SOF/LDV	2	43	No limitations	Consistent	Direct	Imprecise	Very Low	0% (0, 16)		
	SOF/SIM	0							ND		
SOF/VEL	1	74	No limitations	N/A	Direct	Sparse	Very Low	0% (0, 10)			
Discontinue due to AE	DCV/ASV	0							ND	Rare, but insufficient evidence. No evidence of differences among regimens.	High
	GLE/PIB	2	67	Some limitations ⁷	Consistent	Direct	Imprecise	Very Low	3.0% (0.7, 11)		
	GZR/EBR	1	14	Serious limitations ⁸	N/A	Direct	Sparse	Very Low	0% (0, 39)		
	PrO±D	2	53	Serious limitations ⁹	Consistent	Direct	Imprecise	Very Low	0% (0, 13)		
	SOF	2	41	No limitations	Inconsistent	Direct	Imprecise	Very Low	11% (1.2, 28)		
	SOF/DCV	2	25	Serious limitations ¹⁰	Consistent	Direct	Imprecise	Very Low	0% (0, 25)		
	SOF/LDV	2	43	No limitations	Consistent	Direct	Imprecise	Very Low	0% (0, 16)		
	SOF/SIM	0							ND		
SOF/VEL	1	74	No limitations	N/A	Direct	Sparse	Very Low	0% (0, 10)			

Outcome	Regimen ¹¹	# of Studies ¹²	Total N of Patients on Treatment	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings			
								Certainty of Evidence for Outcome	Description of Findings	Importance of Outcome	
Change in CKD category	DCV/ASV	0						ND	Insufficient evidence	High	
	GLE/PIB	1	17	No limitations	N/A	Direct	Sparse	Very Low			Variable
	GZR/EBR	0						ND			
	PrO±D	1	12	No limitations	N/A	Direct	Sparse	Very Low	Incident dialysis 0% (0, 43)		
	SOF	0						ND			
	SOF/DCV	0						ND			
	SOF/LDV	0						ND			
	SOF/SIM	0						ND			
	SOF/VEL	0						ND			
eGFR	DCV/ASV	0						ND	Insufficient evidence		
	GLE/PIB	0						ND			
	GZR/EBR	0						ND			
	PrO±D	2	48	No limitations	Consistent	Direct	Imprecise	Very Low	Change NS		
	SOF	1	17	No limitations	N/A	Direct	Imprecise	Very Low	Change NS		
	SOF/DCV	1	11	No limitations	N/A	Direct	Imprecise	Very Low	Change NS		
	SOF/LDV	1	18	No limitations	N/A	Direct	Imprecise	Very Low	Change NS		
	SOF/SIM	0						ND			
	SOF/VEL	1	67	No limitations	N/A	Direct	Sparse	Very Low	Change NS		
Balance of Potential Benefits and Harms: DAAs yield very high rates of SVR12 with rare adverse events (although evidence on adverse events is sparse). Some regimens may have poorer SVR12, but there are no randomized or other comparisons of DAA regimens in comparable patients.								Certainty of Overall Evidence: High (for DAAs in general)			

Abbreviations: AE: adverse events, ASV: asunaprevir, CKD: chronic kidney disease (category), DAA: direct-acting antivirals, DCV: daclatasvir, EBR: elbasvir, GFR: glomerular filtration rate, GLE: glecaprevir, GZR: grazoprevir, LDV: ledipasvir, N/A: not applicable, ND: no data, NS: nonsignificant, PIB: pibrentasvir, PrO±D: paritaprevir/ritonavir/ombitasvir ± dasabuvir, SIM: simeprevir, SOF: sofosbuvir, SVR12: sustained virologic response at 12 weeks post-treatment, VEL: velpatasvir.

¹ Notation of inclusion of ribavirin omitted from this table.

² Single groups, mostly retrospective.

³ Reporting bias (larger study did not report outcome).

⁴ Reporting bias (many studies did not report outcome).

⁵ Reporting bias (study with half available patients did not report outcome).

⁶ Reporting bias (study with 90% of patients did not report outcome).

⁷ Reporting bias (larger study did not report outcome).

⁸ Reporting bias (many studies did not report outcome).

⁹ Reporting bias (study with half available patients did not report outcome).

¹⁰ Reporting bias (study with 90% of patients did not report outcome).

¹¹ Notation of inclusion of ribavirin omitted from this table.

¹² Single groups, mostly retrospective.

Table S6. Evidence Profile: Treatment with direct-acting antiviral regimens in CKD G5D (dialysis) patients

Outcome	Regimen ¹	# of Studies ²	Total N of Patients on Treatment	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings			
								Certainty of Evidence for Outcome	Description of Findings	Importance of Outcome	
Death, ~6-12 mo	DCV/ASV	0								Reported death rates low (0.9-6.4%) but very sparse, imprecise estimates. Reporting bias likely inflating estimates. No reported deaths related to DAA or HCV. No evidence of differences among regimens.	Critical
	GLE/PIB	2	109	Serious limitations ³	Consistent	Direct	Imprecise	Very low	0.9% (0.1, 6.2)		
	GZR/EBR	0									
	PrO±D	2	60	Serious limitations ⁴	N/A	Direct	Sparse	Very low	1.7% (0.2, 11)		
	SOF	0									
	SOF/DCV	1	31	Serious limitations ⁵	N/A	Direct	Sparse	Very low	6.4% (1.6, 22)		
	SOF/LDV	0									
	SOF/SIM	0									
	SOF/VEL	1	59	Serious limitations ⁶	N/A	Direct	Sparse	Very low	3.4% (0.8, 13)		
SVR12	DCV/ASV	9	341	Some limitations ⁷	Some inconsistency	Direct	None	Low	93.6% (89.5, 96.8)	Very high SVR12 for all treatments. Mostly ≥94%. No direct evidence of differences among regimens.	High
	GLE/PIB	11	529	Some limitations ⁸	Consistent	Direct	None	Moderate	96.9% (95.1, 98.3)		
	GZR/EBR	11	962	Some limitations ⁹	Consistent	Direct	None	Moderate	96.5% (94.9, 97.8)		
	PrO±D	16	582	Some limitations ¹⁰	Consistent	Direct	None	Moderate	96.8% (95.2, 98.1)		
	SOF	3	123	No limitations	Inconsistent	Direct	None	Low	91.9% (74.5, 99.8)		
	SOF/DCV	8	278	No limitations	Some inconsistency	Direct	None	Moderate	93.7% (88.9, 97.2)		
	SOF/LDV	7	220	Some limitations ¹¹	Consistent	Direct	None	Moderate	95.9% (92.8, 98.1)		
	SOF/SIM	1	12	No limitations	N/A	Direct	Sparse	Very Low	83.3% (52.3, 95.8)		
	SOF/VEL	8	629	No limitations	Consistent	Direct	None	High	93.0% (93.0, 97.3)		

Outcome	Regimen ¹²	# of Studies ¹³	Total N of Patients on Treatment	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings			
								Certainty of Evidence for Outcome	Description of Findings		Importance of Outcome
Serious AE due to DAA	DCV/ASV	8	274	Some limitations ¹⁴	Consistent	Direct	None	Moderate	0.4% (0.1, 2.5)	Rare. No evidence of differences among regimens.	High
	GLE/PIB	9	435	Some limitations ¹⁵	Consistent	Direct	None	Moderate	0.5% (0.1, 1.8)		
	GZR/EBR	6	163	Serious limitations ¹⁶	Consistent	Direct	Incomplete reporting	Low	0.6% (0.1, 4.2)		
	PrO±D	13	406	Some limitations ¹⁷	Consistent	Direct	None	Moderate	0.2% (0.03, 1.7)		
	SOF	2	63	Serious limitations ¹⁸	Consistent	Direct	Imprecise	Very Low	0% (0, 11.5)		
	SOF/DCV	4	112	Serious limitations ¹⁹	Consistent	Direct	Imprecise	Very Low	0% (0, 6.8)		
	SOF/LDV	6	208	No limitations	Consistent	Direct	Some imprecision	Moderate	0% (0, 3.7)		
	SOF/SIM	1	12	No limitations	N/A	Direct	Sparse	Very Low	0% (0, 43)		
	SOF/VEL	6	408	No limitations	Consistent	Direct	None	High	0% (0, 1.9)		
Discontinue due to AE	DCV/ASV	9	341	No limitations	Consistent	Direct	None	High	3.8% (2.0, 6.0)	Rare. Mostly due to minor AE. No evidence of differences among regimens.	High
	GLE/PIB	8	352	Some limitations ²⁰	Consistent	Direct	None	Moderate	1.6% (0.6, 3.1)		
	GZR/EBR	6	166	Serious limitations ²¹	Consistent	Direct	Incomplete reporting	Low	2.5% (0.7, 5.4)		
	PrO±D	14	446	Some limitations ²²	Consistent	Direct	None	Moderate	1.8% (0.8, 3.3)		
	SOF	3	123	No limitations	Consistent	Direct	Imprecise	Very Low	0% (0, 6.2)		
	SOF/DCV	8	247	No limitations	Consistent	Direct	None	High	0.4% (0.1, 2.8)		
	SOF/LDV	7	220	No limitations	Consistent	Direct	Some imprecision	Low	0% (0, 3.5)		
	SOF/SIM	1	12	No limitations	N/A	Direct	Sparse	Very Low	0% (0, 43)		
	SOF/VEL	6	407	Serious limitations ²³	Consistent	Direct	Some imprecision	Low	0% (0, 3.2)		
Quality of life	GLE/PIB	1	77	Serious limitations ²⁴	N/A	Indirect ²⁵	Sparse	Very Low	1/3 with clinical improvement in SF-12 PCS and MCS	Insufficient evidence	High
	SOF/DCV	1	41	Serious limitations ²⁶	N/A	Indirect ²⁷	Sparse	Very Low	SF-12 improvement 3-4 points		
Balance of Potential Benefits and Harms: DAA's yield very high rates of SVR12 with low rates of discontinuation due to adverse events or serious adverse events attributable to DAAs. Some regimens may have poorer SVR12, but there are no randomized or other comparisons of DAA regimens in comparable patients.								Certainty of Overall Evidence: High (for DAAs in general)			

Abbreviations. AE: adverse events, ASV: asunaprevir, DAA: direct acting antivirals, DCV: daclatasvir, EBR: elbasvir, GLE: glecaprevir, Gt: genotype, GZR: grazoprevir, HCV: hepatitis C virus, LDV: ledipasvir, MCS: Mental Component Summary, N/A: not applicable, PCS: Physical Component Summary, PIB:

pibrentasvir, PrO±D: paritaprevir/ritonavir/ombitasvir ± dasabuvir, SF-12: Short Form 12 item questionnaire, SIM: simeprevir, SOF: sofosbuvir, SVR12: sustained virologic response at 12 weeks after end of treatment, VEL: velpatasvir

¹ Notation of inclusion of ribavirin omitted from this table.

² Single groups, mostly retrospective.

³ Reporting bias (many studies did not report outcome).

⁴ Reporting bias (many studies did not report outcome).

⁵ Reporting bias (many studies did not report outcome).

⁶ Reporting bias (many studies did not report outcome).

⁷ Some per protocol and analyses with missing data.

⁸ Some per protocol and unclear analyses.

⁹ Some per protocol and unclear analyses.

¹⁰ Some per protocol analyses.

¹¹ Some per protocol analyses.

¹² Notation of inclusion of ribavirin omitted from this table.

¹³ Single groups, mostly retrospective.

¹⁴ Reporting bias (large study did not report outcome).

¹⁵ Reporting bias (large study did not report outcome).

¹⁶ Reporting bias (many studies did not report outcome).

¹⁷ Reporting bias (large studies did not report outcome).

¹⁸ Reporting bias (large study with half of available patients did not report outcome).

¹⁹ Reporting bias (many studies did not report outcome).

²⁰ Reporting bias (large studies did not report outcome).

²¹ Reporting bias (many studies did not report outcome).

²² Reporting bias (large studies did not report outcome).

²³ Reporting bias (large study with half of available patients did not report outcome).

²⁴ Inadequate reporting of quality of life outcome.

²⁵ No comparison with untreated group.

²⁶ Inadequate reporting from conference abstract; unclear overlap with prior study.

²⁷ No comparison with untreated group.

Table S7. Evidence Profile: Treatment with direct-acting antiviral regimens in kidney transplant recipients

Outcome	Regimen ¹	# of Studies ²	Total N of Patients on Treatment	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
								Certainty of Evidence for Outcome	Description of Findings	Importance of Outcome
Death, Long-term	Any specific regimen	0						ND	Death rates may be much lower with DAA treatment than without.	Critical
	DAA vs. no DAA	3	86 vs. 63	Serious limitations ³	Consistent	Direct	None	Low Unadj OR 0.16 (0.04, 0.61)		
Allograft loss	DCV/ASV	0						ND	Allograft loss rates low (≤1%) but very sparse, imprecise estimates. Reporting bias may be inflating estimates, but follow-up duration mostly short (SVR12 or end of treatment). No evidence of differences among regimens. Allograft loss rate with DAA vs. no DAA unclear.	Critical
	GLE/PIB	1	20	No limitations	N/A	Direct	Sparse	Very Low 0% (0, 30)		
	GZR/EBR	1	11	No limitations	N/A	Direct	Sparse	Very Low 0.1% (1.3, 44)		
	PrO±D	0						ND		
	SOF	1	10	Serious limitations ⁴	N/A	Direct	Sparse	Very Low 0% (0, 48)		
	SOF/DCV	2	141	Serious limitations ⁵	Consistent	Direct	Imprecise	Very Low 0% (0, 5.4)		
	SOF/LDV	3	84	Serious limitations ⁶	Consistent	Direct	None	Low 1.2% (0.2, 8.0)		
	SOF/SIM	0						ND		
	SOF/VEL	0						ND		
	DAA vs. no DAA	3	86 vs. 63	Serious limitations ⁷	Consistent	Direct	Imprecise	Very Low Unadj OR 0.50 (0.09, 2.73)		
SVR12	DCV/ASV	0						ND	Very high SVR12 for evaluated treatments. Mostly 100%. No evidence of differences among regimens.	High
	GLE/PIB	1	20	No limitations	N/A	Direct	Sparse	Very Low 100% (70, 100)		
	GZR/EBR	2	21	No limitations	N/A	Direct	Imprecise	Very Low 100% (71, 100)		
	PrO±D	2	33	No limitations	Consistent	Direct	Imprecise	Very Low 100% (80, 100)		
	SOF	6	117	No limitations	Consistent	Direct	Imprecise	Moderate 94.8% (88.2, 98.8)		
	SOF/DCV	6	290	No limitations	Consistent	Direct	None	High 99.7% (97.6, 100)		
	SOF/LDV	10	300	No limitations	Consistent	Direct	None	High 97.3 (94.9, 99.0)		
	SOF/SIM	0						ND		
Serious AE due to DAA	SOF/VEL	1	10	No limitations	Consistent	Direct	Sparse	Very Low 100% (52, 100)	Rare. No evidence of differences among regimens.	High
	DCV/ASV	0						ND		
	GLE/PIB	0						ND		
	GZR/EBR	2	21	No limitations	N/A	Direct	Sparse	Very Low 0% (0, 29)		
	PrO±D	2	33	No limitations	Consistent	Direct	Imprecise	Very Low 0% (0, 20)		
	SOF	4	91	Serious limitations ⁸	Consistent	Direct	Imprecise	Very Low 2.9% (0.5, 7.2)		
	SOF/DCV	5	166	Some limitations ⁹	Consistent	Direct	Imprecise	Very Low 0% (0, 4.6)		
	SOF/LDV	5	170	Serious limitations ¹⁰	Consistent	Direct	None	Low 2.6% (0.7, 5.7)		
	SOF/SIM	0						ND		
	SOF/VEL	1	10	No limitations	N/A	Direct	Sparse	Very Low 0% (0, 48)		

Outcome	Regimen ¹¹	# of Studies ¹²	Total N of Patients on Treatment	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
								Certainty of Evidence for Outcome	Description of Findings	Importance of Outcome
Discontinue due to AE	DCV/ASV	0						ND	Rare. No evidence of differences among regimens.	High
	GLE/PIB	0						ND		
	GZR/EBR	2	21	No limitations	N/A	Direct	Sparse	Very Low 4.8% (0.7, 27)		
	PrO±D	2	33	No limitations	Consistent	Direct	Imprecise	Very Low 0% (0, 20)		
	SOF	4	91	Serious limitations ¹³	Consistent	Direct	Imprecise	Very Low 2.9% (0.5, 7.2)		
	SOF/DCV	5	186	Some limitations ¹⁴	Consistent	Direct	Imprecise	Very Low 0% (0, 4.2)		
	SOF/LDV	7	224	Some limitations ¹⁵	Consistent	Direct	None	Moderate 1.7% (0.4, 3.7)		
	SOF/SIM	0						ND		
	SOF/VEL	1	10	No limitations	N/A	Direct	Sparse	Very Low 0% (0, 48)		
Acute rejection	DCV/ASV	0						ND	Reported acute rejection rates, treated with SOF and DCV or LDV may be about 3% to 6%. No evidence of differences among regimens.	Moderate
	GLE/PIB	1	20	No limitations	N/A	Direct	Sparse	Very Low 0% (0, 30)		
	GZR/EBR	0						ND		
	PrO±D	0						ND		
	SOF	1	10	Serious limitations ¹⁶	N/A	Direct	Sparse	Very Low 0% (0, 48)		
	SOF/DCV	3	246	Some limitations ¹⁷	Consistent	Direct	None	Moderate 3.4% (1.5, 6.1)		
	SOF/LDV	4	109	Some limitations ¹⁸	Consistent	Direct	None	Moderate 6.2% (2.3, 12)		
	SOF/SIM	0						ND		
	SOF/VEL	0						ND		
Balance of Potential Benefits and Harms: DAAs yield near 100% rates of SVR12 with rarely reported discontinuation due to adverse events or serious adverse events attributable to DAAs. Long-term death rates may be lower with DAA treatment than without.								Certainty of Overall Evidence: High (for DAAs in general)		

Abbreviations: ASV: asunaprevir, DAA: direct-acting antiviral, DCV: daclatasvir, EBR: elbasvir, GLE: glecaprevir, Gt: genotype, GZR: grazoprevir, LDV: ledipasvir, N/A: not applicable, ND: no data, PIB: pibrentasvir, PrO±D: paritaprevir/ritonavir/ombitasvir±dasabuvir, SIM: simeprevir, SOF: sofosbuvir, SVR12: sustained virologic response at 12 weeks post-treatment, Unadj OR: unadjusted odds ratio, VEL: velpatasvir.

¹ Notation of inclusion of ribavirin omitted from this table.

² Single groups, mostly retrospective.

³ No adjustment for potential confounders.

-
- ⁴ Reporting bias (many studies did not report outcome).
- ⁵ Reporting bias (study with half available patients did not report outcome).
- ⁶ Reporting bias (many studies did not report outcome).
- ⁷ No adjustment for potential confounders.
- ⁸ Reporting bias (study with half available patients did not report outcome).
- ⁹ Reporting bias (larger study did not report outcome).
- ¹⁰ Reporting bias (many studies did not report outcome).
- ¹¹ Notation of inclusion of ribavirin omitted from this table.
- ¹² Single groups, mostly retrospective.
- ¹³ Reporting bias (study with half available patients did not report outcome).
- ¹⁴ Reporting bias (larger study did not report outcome).
- ¹⁵ Reporting bias (larger study did not report outcome).
- ¹⁶ Reporting bias (many studies did not report outcome).
- ¹⁷ Reporting bias (larger study did not report outcome).
- ¹⁸ Reporting bias (larger study did not report outcome).

Table S8. Summary Table: DAAs in CKD G4-G5ND (non-dialysis) patients, part 1 (SVR12 and adverse events)

Regimen (SOF Dose, mg/d)	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12 Analysis Type	DAA-Related Serious AE ¹	D/C DAA Due to AE ²
DCV/ASV	Mawatari 2017 28078469 Japan (1)	24 wk	NR	NR	10/10 (100%) ³ ITT	NR	NR
DCV/ASV Summary					100% (52, 100) all ITT		
GLE/PIB	Atsukawa 2019A 30873651 Japan (2)	8 wk (65%) ⁴	Gt 1b 20% Gt 2 46% Gt 3 19% ⁵	NR	32/32 (100%) ITT	0/32 (0%)	2/32 (6.3%)
GLE/PIB	Liu C-H 2020 31981264 Taiwan (3)	8 wk (most) ⁶	Gt 1a 3% Gt 1b 44% Gt 2 47% Gt 3 3% Gt 6 3% ⁷	31% ⁸ (multiple ⁹)	35/35 (100%) ITT	0/35 (0%)	0/35 (0%)
GLE/PIB	Nozaki 2020 32128704 Japan (4)	8 wk (most) ¹⁰	NR	NR	63/65 (96.9%) ITT	NR	NR
GLE/PIB Summary					98.5% (94.1, 99.6)¹¹ 130/132 ITT	0% (0, 11)¹² 0/67	3.0% (0.7, 11)¹³ 2/67

¹ Pooled.

² Pooled, unless otherwise noted.

³ Not fully clear that all were non-dialysis.

⁴ 12 weeks if cirrhosis, genotype 3, or prior DAA treatment failure.

⁵ Mixed genotypes 1/141; 20/141 not tested.

⁶ 12 weeks if cirrhosis or 16 weeks if genotype 3 and prior treatment (numbers unclear).

⁷ Excludes n=3 with CKD 5ND.

⁸ Excludes n=3 with CKD 5ND.

⁹ TE, biopsy, clinical, imaging, FIB-4.

¹⁰ 12 weeks if cirrhosis, genotype 3, or prior DAA treatment failure (numbers not reported)

Regimen (SOF Dose, mg/d)	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12 Analysis Type	DAA- Related Serious AE ¹	D/C DAA Due to AE ²
GZR/EBR	Atsukawa 2019B 30144366 Japan (5)	12 wk	Gt 1b 100%	NR	14/14 (100%) ITT	0/14 (0%)	0/14 (0%)
GZR/EBR	Bruchfeld 2017 28576451 US (6)	12 wk	Gt 1a 52% ¹⁴ Gt 1b 48%	6% (TE)	50/51 (98.0%) ¹⁵ Per protocol ¹⁶	NR	NR
GZR/EBR	Choi 2020 31862503 US (7)	12 wk	Gt 1a 63% Gt 1b 33%	42% (ICD 9/10 code)	714/740 (96.5%) ITT	NR	NR
GZR/EBR	Cheng P-N 2021 32499107 Taiwan (8)	12 wk	Gt 1 100%	NR	31/31 (100%) mITT ¹⁷	NR	NR
GZR/EBR	Jang 2021 32539296 S Korea (9)	12 wk	Gt 1 100%	NR	21/21 (100%) ITT	NR	NR
GZR/EBR Summary					96.7% (95.4, 97.8)¹⁸ 830/857 mostly ITT	0% (0, 39) 0/14	0% (0, 39) 0/14

¹¹ 3 studies. Pooled.

¹² 2 studies. Pooled.

¹³ 2 studies. Pooled.

¹⁴ Includes dialysis patients.

¹⁵ Combined immediate and deferred treatment groups from randomized controlled trial. One patient in delayed treatment cohort had SVR4 on placebo; the patient's CKD category was not reported.

¹⁶ Excluding patients who died, were lost to follow-up, withdrew, or were noncompliant (reported as modified intention-to-treat).

¹⁷ Patients who received at least 4 weeks of treatment.

¹⁸ 5 studies. I² 0% (no heterogeneity)

Regimen (SOF Dose, mg/d)	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12 Analysis Type	DAA-Related Serious AE ¹	D/C DAA Due to AE ²
PrO±RBV	Elmowafy 2021 33111161 Egypt (10)	12 wk	NR	0% (TE)	SVR24 39/50 (78.0%) ITT	NR	NR
PrOD	Iliescu 2020 31948406 Romania (11)	12 wk	Gt 1b 100%	NR	18/18 (100%) ITT	0/18 (0%)	0/18 (0%)
PrO/RBV	Mekky 2019 30166253 Egypt (12)	12 wk	Gt 4 100%	23% (TE)	32/35 (91.4%) ITT	0/35 (0%)	0/35 (0%)
PrO±D Summary					89.4% (75.7, 97.8)¹⁹ 89/103 all ITT	0% (0, 13) 0/53	0% (0, 13) 0/53
SOF/RBV (200)	Lawitz 2020A 32531259 US, New Zealand (13)	24 wk	Gt 1a 70% Gt 1b 20% Gt 3 3a 10%	0% (not defined)	4/10 (40%) ITT	0/10 (0%)	2/10 (20%)
SOF/RBV (400)		24 wk	Gt 1a 60% Gt 1b 20% Gt 3a 20%	40% (not defined)	6/10 (60%) ITT	0/10 (0%)	2/10 (20%)
SOF/RBV (400)	Manoj 2018 29676846 India (14)	24 wk	Gt 1a 65% ²⁰ Gt 1b 4% Gt 3a 27% Gt 3b 4%	15% ²¹ (clinical definition)	21/21 (100%) ITT	0/21 (0%)	0/21 (0%)
SOF Summary					71.7% (29.1, 98.6)²² 31/41 all ITT	0% (0, 17) 0/41	11% (1.2, 28)²³ 4/41

¹⁹ 3 studies. REML. I² 70% (large heterogeneity). Combination of SVR12 and SVR24.

²⁰ Includes 5 on HD.

²¹ Includes 5 on HD.

²² 2 studies (3 cohorts). REML. I² 87% (large heterogeneity).

²³ REML. I² 51% (moderate heterogeneity).

Regimen (SOF Dose, mg/d)	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12 Analysis Type	DAA- Related Serious AE ¹	D/C DAA Due to AE ²
SOF/DCV (200)	Taneja 2018 29484572 India (15)	12 wk (most) ²⁴	Gt 1 65% Gt 2 1% Gt 3 34%	32% (TE), decompensated 9%	11/11 (100%) ITT	0/11 (0%)	0/11 (0%)
SOF/DCV (200)	Goel 2021 33097949 India (16)	8 wk	Gt 1 22% Gt 3 37% Gt 4 7% ²⁵	NR	25/27 (92.6%) ITT	0/27 (0%)	NR
SOF/DCV (400)	Manoj 2018 29676846 India (14)	12 wk	Gt 3 100%	37% ²⁶ (clinical definition)	14/14 (100%) ITT	0/14 (0%)	0/14 (0%)
SOF/DCV ±RBV (200)	Eletreby 2020 31858694 Egypt (17)	NR	NR	18.5% (Child B, implied) ²⁷	506/519 (97.5%) ITT	NR	NR
SOF/DCV Summary					97.1% (95.7, 98.3)²⁸ 556/571 all ITT	0% (0, 14) 0/52	0% (0, 25) 0/25
SOF/LDV (400)	Manoj 2018 29676846 India (14)	12 wk	Gt 1 100%	23% ²⁹ (clinical definition)	25/25 (100%) ITT	0/25 (0%)	0/25 (0%)
SOF/LDV (400)	Lawitz 2020A 32531259 US, New Zealand (13)	12 wk	Gt 1a 78% Gt 1b 22%	11% (not defined)	18/18 (100%) ITT	0/18 (0%)	0/18 (0%)
SOF/LDV Summary					100% (84, 100)³⁰ 43/43 all ITT	0% (0, 16)³¹ 0/43	0% (0, 16)³² 0/43

²⁴ 24 weeks if genotype 3 and cirrhosis (number not reported).

²⁵ Not tested 33%.

²⁶ Includes 5 on HD.

²⁷ Across all DAAs.

²⁸ 4 studies. REML. I² 0% (no heterogeneity).

²⁹ Includes 1 on HD.

³⁰ 2 studies. Pooled.

Regimen (SOF Dose, mg/d)	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12 Analysis Type	DAA- Related Serious AE ¹	D/C DAA Due to AE ²
SOF/SIM (200)	Eletreby 2020 31858694 Egypt (17)	NR	NR	18.5% (Child B, implied) ³³	38/41 (92.7%) ITT	NR	NR
SOF/SIM Summary					92.7% (79.6, 97.6) 38/41 all ITT		
SOF/VEL (400)	Cheng P-N 2022 34967920 Taiwan (18)	12 wk	NR	NR	25/25 (100%) ITT	NR	NR
SOF/VEL (400)	Liu C-H 2022 33408122 Taiwan (19)	12 wk	Gt 1a 3% ³⁴ Gt 1b 55% Gt 2 33% Gt 6 4%	14% (TE), 5% (Child B,C) ³⁵	70/74 (94.6%) ITT	0/74 (0%)	0/74 (0%)
SOF/VEL Summary					96.0% (89.7, 98.5)³⁶ 95/99 all ITT	0% (0, 9.9)	0% (0, 9.9)

Abbreviations: AE: adverse events, ASV: asunaprevir, CKD: chronic kidney disease (category), D/C: discontinued, DAA: direct-acting antivirals, DCV: daclatasvir, EBR: elbasvir, GLE: glecaprevir, Gt: genotype, GZR: grazoprevir, ICD: International Classification of Diseases, ITT: intention-to-treat (or all fully analyzed), LDV: ledipasvir, mITT: modified ITT, NR: not reported, PIB: pibrentasvir, PMID: PubMed identifier, PrO/D: paritaprevir/ritonavir/ombitasvir/dasabuvir, RBV: ribavirin, SIM: simeprevir, SOF: sofosbuvir, SVR12: sustained virologic response at 12 weeks post-treatment, TE: transient elastography, VEL: velpatasvir, wk: weeks.

³¹ 2 studies. Pooled.

³² 2 studies. Pooled.

³³ Across all DAAs.

³⁴ Across both dialysis and non-dialysis populations (n=191)

³⁵ Across both dialysis and non-dialysis populations (n=191)

³⁶ 2 studies. Pooled.

Table S9. Summary Table: DAAs in CKD G4-G5 (non-dialysis) patients, part 2 (kidney outcomes)

Regimen (SOF Dose, mg/qD)	Study, PMID Country (Reference)	Duration	Genotype	Liver Cirrhosis (Definition)	CKD Category	eGFR Chg (95% CI), P value [Baseline]
GLE/PIB	Lawitz 2020B ³⁷ 31821716 Multiple ³⁸ (20)	8 wk (83%) ³⁹	Gt 1 55% ⁴⁰ Gt 2 27% Gt 3 15% Gt 4 4%	14% ⁴¹ (TE)	At EOT: CKD 3b (improve) 2/17 (12%) CKD 4 (no change) 13/17 (76%) CKD 5ND (worsen) 2/17 (12%) CKD 5D (worsen) 0%	NR
PrO+RBV (75/50/12.5 ⁴²)	Said 2019 ⁴³ 30791838 Egypt (21)	12 wk	Gt 4 100%	NR	NR	At SVR4: Chg median 3, P=0.48 [22]
PrO±D±RBV	Muñoz-Gómez 2017 ⁴⁴ 27976490 Spain (22)	12 wk (most) ⁴⁵	NR	NR	At SVR12: Incident dialysis 0/12	At EOT: Chg median -1, NS [21]

³⁷ Study did not report SVR12 or adverse event data specifically for CKD 4-5ND population.

³⁸ Canada, Germany, Greece, Italy, Poland, South Korea, Spain, Sweden, US.

³⁹ 8 weeks (65%) if noncirrhotic except both prior treatment and genotype 3, 12 weeks (13%) if cirrhotic except genotype 3, 16 weeks (4%) if genotype 3 except treatment-naïve/noncirrhotic. Percentages include n=7 with CKD 3b.

⁴⁰ Including CKD 3b (n=7).

⁴¹ Including CKD 3b (n=7).

⁴² PrO dosages.

⁴³ Study did not report SVR12 or adverse event data specifically for CKD 4-5ND population.

⁴⁴ Study did not report SVR12 or adverse event data specifically for CKD 4-5ND population.

⁴⁵ 24 weeks if genotype 1a w/compensated cirrhosis (number not reported).

Regimen (SOF Dose, mg/qD)	Study, PMID Country (Reference)	Duration	Genotype	Liver Cirrhosis (Definition)	CKD Category	eGFR Chg (95% CI), P value [Baseline]
SOF/RBV (200)	Lawitz 2020A 32531259 US, New Zealand (13)	24 wk	Gt 1a 70% Gt 1b 20% Gt 3a 10%	0% (not defined)	NR	At SVR12: −3.0 (−7.1, 1.1), P=0.15 ⁴⁶ [21.8]
SOF/RBV (400)		24 wk	Gt 1a 60% Gt 1b 20% Gt 3a 20%	40% (not defined)	NR	At SVR12: −3.0 (−8.9, 2.9), P=0.32 ⁴⁷ [26.2]
SOF/DCV (200)	Taneja 2018 29484572 India (15)	12 wk (most) ⁴⁸	Gt 1 65% Gt 2 1% Gt 3 34%	32% (TE), decompensated 9%	NR	At EOT: −0.4 (−4.3, 3.4), P=0.82 [24.8]
SOF/LDV (400)	Lawitz 2020A 32531259 US, New Zealand (13)	12 wk	Gt 1a 78% Gt 1b 22%	11% (not defined)	NR	At SVR12: −1.0 (−3.5, 1.5), P=0.43 ⁴⁹ [24.9]
SOF/VEL (400)	Liu C-H 2022 33408122 Taiwan (19)	12 wk	Gt 1a 3% ⁵⁰ Gt 1b 55% Gt 2 33% Gt 6 4%	14% (TE), 5% (Child B,C) ⁵¹	NR	CKD G4: 1.6 (−0.1, 3.3), P=0.06 CKD G5ND: −0.3 (−1.6, 1.0), P=0.65

⁴⁶ Estimated.

⁴⁷ Estimated

⁴⁸ 24 weeks if genotype 3 and cirrhosis (number not reported).

⁴⁹ Estimated.

⁵⁰ Across both dialysis and non-dialysis populations (n=191)

⁵¹ Across both dialysis and non-dialysis populations (n=191)

Regimen (SOF Dose, mg/qD)	Study, PMID Country (Reference)	Duration	Genotype	Liver Cirrhosis (Definition)	CKD Category	eGFR Chg (95% CI), P value [Baseline]
DAAs, various ⁵²	D'Ambrosio 2020 31813755 Italy (23)	12 wk (52%) ⁵³	Gt 1 61% Gt 2 17% Gt 3 9% Gt 4 13%	43% (TE)	At SVR12: CKD category improvement: 12/22 (55%) CKD category no change: 7/22 (32%) CKD category worsening: 3/22 (13%) CKD 1: 0% CKD 2: 1/22 (5%) CKD 3a: 2/22 (9%) CKD 3b: 9/22 (41%) CKD 4: 7/22 (32%) CKD 5: 3/22 (13%)	At SVR12: Chg median 6, P=0.016 [24]

Abbreviations: Chg: change, CI: confidence interval, CKD: chronic kidney disease (category), DAA: direct-acting antiviral, D/C: discontinued, DAA: direct-acting antivirals, DCV: daclatasvir, eGFR: estimated glomerular filtration rate, EOT: end of treatment, GLE: glecaprevir, Gt: genotype, LDV: ledipasvir, NR: not reported, NS: nonsignificant, PIB: pibrentasvir, PMID: PubMed identifier, Pro/D: paritaprevir/ritonavir/ombitasvir/dasabuvir, qD: per day, RBV: ribavirin, SOF: sofosbuvir, SVR4/12: sustained virologic response at 4/12 weeks post-treatment, TE: transient elastography, VEL: velpatasvir, wk: weeks.

⁵² SOF/RBV ± PegIFN (n=7, 30%), SOF/SIM ± RBV (n=2, 9%), SOF/DCV ± RBV (n=4, 17%), SOF/LDV ± RBV (n=5, 22%), ProD ± RBV (n=4, 17%), Pro/RBV (n=1, 5%).

⁵³ Implied that the remainder had <12 weeks treatment

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Table S10. Summary Table: DAAs in CKD G5D (dialysis¹) population, part 1 (SVR12 and adverse events)

Regimen ²	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12 ³	DAA-Related Serious AE ⁴ <i>Transfusion</i> ⁵	D/C DAA Due to AE ⁶
DCV/ASV	Fujii 2018 29480939 Japan (1)	24 wk	Gt 1 100%	NR	64/67 (95.5%) Per protocol	NR	1/67 (1.5%)
DCV/ASV	Kawakami 2016 27346670 Japan (2)	12 wk	Gt 1 100%	17% (NR)	18/18 (100%) ITT	0/18 (0%)	0/18 (0%)
DCV/ASV	Lee 2019 ⁷ 30400729 S Korea (3)	24 wk	Gt 1b 100%	19% (NR)	16/21 (76.1%) ITT	0/21 (0%)	3/21 (14%)
DCV/ASV	Miyazaki 2016 27098678 Japan (4)	24 wk	Gt 1b 100%	NR	10/10 (100%) ITT	0/10 (0%)	0/10 (0%)
DCV/ASV	Otsuka 2017 30483552 Japan (5)	24 wk	Gt 1b 100%	22% or 26% (serum markers) ⁸	21/23 (91.3%) ITT	0/23 (0%)	0/23 (0%)
DCV/ASV	Suda 2016 26768604 Japan (6)	24 wk	Gt 1a 5% Gt 1b 91% Unknown 5%	19% (TE or imaging/serum markers)	20/21 (95.2%) missing data ⁹	1/21 (4.5%)	1/21 (4.5%)

¹ 100% hemodialysis populations, unless otherwise noted (for peritoneal dialysis).

² Sofosbuvir doses were 400 mg daily unless otherwise noted. All other regimens used standard doses.

³ REML meta-analysis of double arcsine transformed proportion, unless otherwise noted.

⁴ Pooled.

⁵ Unreliable estimates. Rarely explicitly reported, possibly suggesting no transfusions in most studies. Mostly unclearly reported whether need for transfusion related to ribavirin treatment.

⁶ REML meta-analysis of double arcsine transformed proportion, unless otherwise noted.

⁷ n=4 on peritoneal dialysis.

⁸ 5 or 6/23, unclear if 1 patient with elevated APRI also had abnormal FIB-4.

⁹ Missing data on 13 patients.

Regimen ²	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12 ³	DAA-Related Serious AE ⁴ <i>Transfusion</i> ⁵	D/C DAA Due to AE ⁶
DCV/ASV	Suda 2018 28560477 Japan (7)	24 wk	Gt 1a 1% Gt 1b 99%	32% (TE)	118/123 (95.9%) ITT	0/123 (0%)	4/123 (3.3%)
DCV/ASV	Toyoda 2016 26872889 Japan (8)	24 wk	Gt 1b 100%	39% (NR)	28/28 (100%) ITT	0/28 (0%)	1/28 (3.6%)
DCV/ASV	Uojima 2017 Ren Replace Ther Japan (9)	24 wk	Gt 1b 100%	30% (NR)	25/30 (83.3%) ITT	0/30 (0%)	3/30 (10%)
DCV/ASV Summary					93.6% (89.5, 96.8)¹⁰ 320/341 mostly ITT	0.4% (0.1, 2.5) 1/274¹¹	3.8% (2.0, 6.0) 13/341¹²
GLE/PIB	Atsukawa 2019 30873651 Japan (10)	8 wk (65%) ¹³	Gt 1b 20% ¹⁴ Gt 2 46% Gt 3 19% Mixed 1% Unknown 14%	29% (serum markers ± imaging) ¹⁵	99/100 (100%) ITT	0/100 (0%)	1/100 (1%)
GLE/PIB	Lawitz 2020 31821716 Multiple ¹⁶ (11)	8 wk (~83%) ¹⁷	Gt 1 55% ¹⁸ Gt 2 27% Gt 3 15% Gt 4 4%	14% (TE) ¹⁹	NR	0/77 (0%)	NR

¹⁰ 9 studies. I² 40% (moderate heterogeneity).

¹¹ 8 studies.

¹² 9 studies. I² 0% (no heterogeneity).

¹³ 12 weeks (n=35) if cirrhosis, genotype 3, or prior DAA treatment failure.

¹⁴ Including n=9 CKD 5ND.

¹⁵ Including n=9 CKD 5ND.

¹⁶ Canada, Germany, Greece, Italy, Poland, South Korea, Spain, Sweden, US.

¹⁷ 12 weeks (~13%) if cirrhotic except genotype 3, 16 weeks (~4%) if genotype 3 except treatment-naïve/noncirrhotic. Percentages include n=7 with CKD 3b.

¹⁸ Including CKD 4-5ND.

¹⁹ Including CKD 4-5ND.

Regimen ²	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12 ³	DAA-Related Serious AE ⁴ <i>Transfusion</i> ⁵	D/C DAA Due to AE ⁶
GLE/PIB	Liu C-H 2020 31981264 Taiwan (12)	8 wk (most) ²⁰	Gt 1a 5% Gt 1b 32% Gt 2 58% Gt 6 4% % Gt 1b & 2 1% ²¹	33% ²² (multiple ²³)	72/73 (98.6%) ITT	0/73 (0%)	0/73 (0%)
GLE/PIB	Miyasaka-2022- 35024454 Japan (13)	8 (33%) or 12 wk (67%) ²⁴	Gt 1 62% Gt 2 38%) ²⁵	67% (NR)	18/18 (100%) ITT	NR	NR
GLE/PIB	Morishita 2020 31883211 Japan (14)	8 wk (62%) ²⁶	Gt 1b 33% Gt 2 67%	14% (imaging, serum markers)	24/24 (100%) Per protocol	0/24 (0%)	0/24 (0%)
GLE/PIB	Nozaki 2020 32128704 Japan (15)	8 wk (most) ²⁷	NR	NR	125/132 (94.7%) ITT	NR	NR
GLE/PIB	Ogawa 2019 30849206 Japan (16)	8 or 12 wk ²⁸	Gt 1 or 2 100%	NR	23/23 (100%) ITT	NR	0/23 (0%)
GLE/PIB	Persico 2019 Gastro Hep Italy (17)	8 (58%) or 12 wk (42%) ²⁹	Gt 1a 11% Gt 1b 31% Gt 2 36% Gt 3 19% Gt 4 3%	28% (TE)	35/36 (97.2%) ITT	1/36 (2.8%)	0/36 (0%)

²⁰ 12 weeks if cirrhosis or 16 weeks if genotype 3 and prior treatment (numbers unclear).

²¹ Includes n=3 with CKD 5ND.

²² Includes n=3 with CKD 5ND.

²³ TE, biopsy, clinical, imaging, FIB-4.

²⁴ 8 weeks if noncirrhotic, treatment naïve. 12 weeks if cirrhosis (or prior treatment failure)

²⁵ For all (n=230) with any stage of CKD.

²⁶ 12 weeks if cirrhosis or prior DAA treatment failure (n=9)

²⁷ 12 weeks if cirrhosis, genotype 3, or prior DAA treatment failure (numbers not reported)

²⁸ No further details.

Regimen ²	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12 ³	DAA-Related Serious AE ⁴ <i>Transfusion</i> ⁵	D/C DAA Due to AE ⁶
GLE/PIB	Stein 2020 ³⁰ 32956186 Germany (18)	8 wk (85%) ³¹	Gt 1a 15% ³² Gt 1b 27% Gt 1 undefined 3% Gt 2 9% Gt 3 36% Gt 4 6%	12% (TE, imaging, or clinical) ³³	21/23 (91.3%) Unclear ³⁴	0/25 (0%)	0/25 (0%)
GLE/PIB	Suda 2019 30778716 Japan (19)	8 (52%) or 12 wk (48%) ³⁵	Gt 2 100%	30% (serum markers)	26/27 (96.3%) ITT	1/27 (3.7%)	2/27 (7.4%)
GLE/PIB	Yen 2020 32790715 Taiwan (20)	8 wk (68%) ³⁶	Gt 1 55% Gt 2 39% Gt 3 2% Misc 5%	32% (biopsy, imaging, endoscopy)	42/44 (95.5%) ITT	0/44 (0%)	1/44 (2.2%)
GLE/PIB	Yu M-L 2021 33303567 Taiwan (21)	NR	NR	NR	27/29 (93.1%) ITT	0/29 (0%)	NR
GLE/PIB Summary					96.9% (95.1, 98.3)³⁷ 512/529 mostly ITT	0.5% (0.1, 1.8) 2/435³⁸	1.6% (0.6, 3.1) 4/352³⁹

²⁹ Reasons for different durations not reported.

³⁰ Includes patients on peritoneal dialysis (number not reported).

³¹ 12 weeks (n=2), 16 weeks (n=1), reasons not reported.

³² Include CKD 4-ND (n=8).

³³ Include CKD 4-ND (n=8).

³⁴ 3/70 omitted from intention-to-treat analysis, but not acknowledged or accounted for.

³⁵ 12 week if cirrhosis or failed to respond to previous DAA treatment

³⁶ 12 weeks (n=14) if cirrhosis.

³⁷ 11 studies. I² 10% (small heterogeneity).

³⁸ Pooled. 9 studies.

³⁹ 8 studies. I² 0% (no heterogeneity).

Regimen ²	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12 ³	DAA-Related Serious AE ⁴ <i>Transfusion</i> ⁵	D/C DAA Due to AE ⁶
GZR/EBR	Atsukawa 2017 28457003 Japan (22)	12 wk	Gt 1b 100%	32% (imaging)	30/31 (96.8%) ITT	1/31 (3.2%)	1/31 (3.2%)
GZR/EBR	Bayu 2020 APASL 360 Indonesia (23)	12 wk	NR	NR	37/38 (97%) ITT	NR	NR
GZR/EBR	Bruchfeld 2017 28576451 US (24)	12 wk	NR	NR	162/164 (98.8%) ⁴⁰ Per protocol ⁴¹	NR	NR
GZR/EBR	Choi 2020 31862503 US (25)	12 wk	Gt 1a 63% ⁴² Gt 1b 33%	42% (ICD-9/10 code) ⁴³	541/563 (96.1%) ITT	NR	NR
GZR/EBR	Ji Q 2022 34599755 China (26)	12 wk	Gt 1b 100%	0% (NR)	11/11 (100%) ITT	0/11 (0%)	0/11 (0%)
GZR/EBR	Li C 2020 33235113 China (27)	12 wk	NR	NR	15/15 Per protocol ⁴⁴	0/16 (0%)	1/16 (6.3%)
GZR/EBR	Liu C-H 2020 32513953 Taiwan (28)	12 wk	Gt 1b 100%	10% (TE)	38/40 (95%) ITT	0/40 (0%)	1/40 (2.5%)
GZR/EBR	Ogawa 2018 30300717 Japan (29)	12 wk	Gt 1 100%	NR	19/21 (90.5%) ITT	NR	NR

⁴⁰ Combined immediate and deferred treatment groups from randomized controlled trial. One patient in delayed treatment cohort had SVR4 on placebo; the patient's CKD category was not reported.

⁴¹ Excluding patients who died, were lost to follow-up, withdrew, or were noncompliant (reported as modified intention-to-treat).

⁴² Including CKD 4-5ND population.

⁴³ Including CKD 4-5ND population.

⁴⁴ 1 patient who discontinued due to adverse event did not have SVR12 evaluated.

Regimen ²	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12 ³	DAA-Related Serious AE ⁴ <i>Transfusion</i> ⁵	D/C DAA Due to AE ⁶
GZR/EBR±RBV	Stein 2020 ⁴⁵ 32956186 Germany (18)	12 wk (98%) ⁴⁶	Gt 1a 23% ⁴⁷ Gt 1b 72% Gt 4 5%	14% (TE, imaging, or clinical) ⁴⁸	39/42 (92.9%) Unclear ⁴⁹	0/45 (0%)	0/45 (0%)
GZR/EBR	Suda 2019 30019127 Japan (30)	12 wk	Gt 1b 100%	31% (TE)	22/23 (95.7%) ITT	0/23 (0%)	0/23 (0%)
GZR/EBR	Suryamin 2020 APASL 1182 Indonesia (31)	12 wk	NR	NR	14/14 (100%) ITT	NR	NR
GZR/EBR Summary					96.5% (94.9, 97.8)⁵⁰ 928/962 mostly ITT	0.6% (0.1, 4.2) 1/163⁵¹	2.5% (0.7, 5.4) 3/166⁵²
PrOD±RBV	Abad 2017 28166520 Spain (32)	12 wk (most) ⁵³	Gt 1a 29% Gt 1b 71%	21% (NR) ⁵⁴	31/31 (100%) ITT	0/31 (0%) <i>Transfusion 0/31 (0%), no RBV</i>	0/31 (0%)
PrO±RBV	Elmowafy 2021 33111161 Egypt (33)	12 wk	Gt 1a 8% Gt 4 92%	2% (imaging), 0 (TE)	40/40 ⁵⁵ (100%) ITT	NR	0/40 (0%)

⁴⁵ Includes patients on peritoneal dialysis (number not reported).

⁴⁶ 16 weeks (n=2), reason not reported

⁴⁷ Include CKD 4-5ND (n=15).

⁴⁸ Include CKD 4-5ND (n=15).

⁴⁹ 3/70 omitted from intention-to-treat analysis, but not acknowledged or accounted for.

⁵⁰ 11 studies. I² 12% (small heterogeneity).

⁵¹ Pooled. 6 studies.

⁵² 6 studies. I² 0% (no heterogeneity).

⁵³ 24 wk if genotype 1a or cirrhosis (numbers not reported).

⁵⁴ Including n=4 on other treatment (genotype 4).

⁵⁵ SVR24 = 38/40 (95%)

Regimen ²	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12 ³	DAA-Related Serious AE ⁴ <i>Transfusion</i> ⁵	D/C DAA Due to AE ⁶
PrOD±RBV ⁵⁶	Etik 2019 30719954 Turkey (34)	12 wk	Gt 1a 28% Gt 1b 72%	NR	17/18 (94.4%) ITT	0/18 (0%)	0/18 (0%)
PrOD	Iliescu 2020 31948406 Romania (35)	12 wk	Gt 1b 100%	17% (TE)	48/48 (100%) ITT	0/48 (0%)	0/48 (0%)
PrOD	Liu C-H 2019 30931537 Taiwan (36)	12 wk	Gt 1b 100%	0% (biopsy or TE)	46/46 (100%) ITT	0/46 (0%)	0/46 (0%)
PrO±D±RBV	Londoño 2019 ⁵⁷ 31550267 Spain (37)	12 or 24 wk ⁵⁸	Gt 1a 16% Gt 1b 76% Gt 1 unknown 1% Gt 4 7%	30% (TE)	93/100 (93%) ITT	NR	NR
PrO/RBV	El-Raey 2019 SP138 Egypt (38)	12 wk	NR	NR	SVR36 36/36 (100%) Per protocol	NR Transfusion 6/53 (11%), on RBV	NR
PrO/RBV	Mekky 2019 30166253 Egypt (39)	12 wk	Gt 4 100%	11% (TE)	72/75 (96%) ITT	0/75 (0%)	0/75 (0%)
PrO	Morisawa 2017 28621007 Japan (40)	12 wk	Gt 1b 100%	NR	8/10 (80%) ITT	0/10 (0%)	2/10 (20%)
PrOD±RBV	Pockros 2016 26976799 US (41)	12 wk	Gt 1 65% ⁵⁹ Gt 1b 35%	0% (biopsy, TE, serum markers)	12/14 (85.7%) ⁶⁰ ITT	0/14 (0%) <i>Transfusion 0/14 (0%), ~10 on RBV</i>	0/14 (0%)

⁵⁶ N=1 on SOF/LDV.

⁵⁷ Reported as n=12 (12%) on peritoneal dialysis and 92% were on hemodialysis. Discrepancy not explained.

⁵⁸ Per "SmPC" indications (not defined). Numbers not reported.

⁵⁹ Includes 6 with CKD 4.

⁶⁰ 1 SVR12 failure had relatively low adherence, 1 died unrelated to HCV. Unclear if all truly on dialysis.

Regimen ²	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12 ³	DAA-Related Serious AE ⁴ <i>Transfusion</i> ⁵	D/C DAA Due to AE ⁶
PrOD	Ponziani 2017 28258770 Italy (42)	12 wk	Gt 1a 10% Gt 1b 80% Gt 4 10%	70% (TE) ⁶¹	10/10 (100%) ITT	1/10 (10%)	0/10 (0%)
PrO±D±RBV	Sanai 2018 29288514 Saudi Arabia, Canada (43)	12 wk (96%) ⁶²	Gt 1a 37% Gt 1b 13% Gt 1 unknown 3% Gt 4 48%	21% (TE)	65/67 (97.0%) ⁶³ ITT	0/67 (0%) <i>Transfusion</i> 3/54 (5.6%), on RBV ⁶⁴	2/67 (2.9%)
PrOD±RBV	Sperl 2018 29669332 Czech Republic (44)	12 wk	Gt 1a 9% ⁶⁵ Gt 1b 87% Unknown 4%	26% (NR) ⁶⁶	19/19 (100%) ITT	0/19 (0%) <i>Transfusion</i> 0/19 (0%), ~6 on RBV	0/19 (0%)
PrOD±RBV	Tatar 2019 31994628 Turkey (45)	12 wk	Gt 1a 45% Gt 1b 39% Gt 1 undefined 15%	NR	33/33 (100%) Per protocol ⁶⁷	0/33 (0%)	0/33 (0%)
PrOD±RBV	Torun 2019 30762283 Turkey (46)	12 wk	Gt 1a 30% Gt 1b 70%	0% (NR)	10/10 (100%) ITT	0/10 (0%)	0/10 (0%)
PrOD±RBV	Yaraş 2019 30666967 Turkey (47)	12 wk	Gt 1a 12% Gt 1b 64% Gt 1 undefined 24%	0% (NR)	25/25 (100%) ITT	0/25 (0%)	0/25 (0%)
PrO±D Summary					96.8% (95.2, 98.1)⁶⁸ 565/582 mostly ITT	0.2% (0.03, 1.7) 1/406⁶⁹	1.8% (0.8, 3.3) 4/446⁷⁰

⁶¹ 30% with F3.

⁶² 24 weeks (4%), reasons not reported.

⁶³ Includes n=2 with CKD 4-5ND

⁶⁴ 0/13 without RBV.

⁶⁵ Includes n=4 with CKD 4.

⁶⁶ Includes n=4 with CKD 4.

⁶⁷ 3 patients excluded due to death, missed visits, and abandoning treatment.

Regimen ²	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12 ³	DAA-Related Serious AE ⁴ <i>Transfusion</i> ⁵	D/C DAA Due to AE ⁶
SOF(400 QOD) ⁷¹ /RBV	Agarwal 2017 29270489 India (48)	12 wk	Gt 1 65% ⁷² Gt 2 2% Gt 3 29% Gt 4 3% Gt 6 2%	0% (endoscopy)	39/41 (95.1%) ITT	0/41 (0%) <i>Transfusion</i> 3/41 (7.3%) <i>on RBV</i>	0/41 (0%)
SOF/RBV	Akhil 2018 28339162 India (49)	12 wk	Gt 1 64% Gt 3 27% Gt 4 9%	NR	16/22 (72.7%) ⁷³ ITT	0/22 (0%) <i>Transfusion</i> 0/22 (0%), <i>on RBV</i>	0/22 (0%)
SOF/RBV/IFN	Mandhwani 2020 32308935 Pakistan (50)	12 wk	Gt 1 50% ⁷⁴ Gt 2 1% Gt 3 43% Gt 4 1% Mixed Gt 5%	0% (clinical, imaging)	59/60 (98.3%) ITT	NR <i>Transfusion</i> 20/60 (33%) <i>on RBV</i>	0/60 (0%)
SOF/RBV Summary					91.9% (74.5, 99.8)⁷⁵ 114/123 all ITT	0% (0, 11.5) 0/63⁷⁶	0% (0, 6.2) 0/123⁷⁷
SOF (QOD) ⁷⁸ /DCV	Agarwal 2017 29270489 India (48)	12 wk	Gt 1 65% ⁷⁹ Gt 2 2% Gt 3 29% Gt 4 3% Gt 6 2%	0% (endoscopy)	20/21 (95.2%) ITT	0/21 (0%)	0/21 (0%) <i>Transfusion</i> 0/21 (0%), <i>no RBV</i>

⁶⁸ 16 studies. I² 4% (small heterogeneity).

⁶⁹ 13 studies.

⁷⁰ 14 studies. I² 0% (no heterogeneity).

⁷¹ n=39/41.

⁷² Across interventions.

⁷³ Includes 2 lost to follow-up pre-SVR12

⁷⁴ Across interventions.

⁷⁵ 3 studies. I² 85% (large heterogeneity).

⁷⁶ 2 studies.

⁷⁷ Pooled. 2 studies.

Regimen ²	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12 ³	DAA-Related Serious AE ⁴ <i>Transfusion</i> ⁵	D/C DAA Due to AE ⁶
SOF/DCV	Butt 2019 31720170 Pakistan (51)	12 wk	Gt 1 32% Gt 3 68%	0% (clinical, history, and serum markers)	SVR40 27/31 (87.1%) ITT	NR	NR
SOF (400 qD)/DCV	Cheema 2019 31779583 Pakistan (52)	12 wk (most) ⁸⁰	Gt 1b 100%	22% (Various ⁸¹)	15/18 (83.3%) ⁸² ITT	NR	0/18 (0%)
SOF (400 TIW)/DCV					17/18 (94.4%) ⁸³ ITT	NR	1/18 (5.6%)
SOF/DCV/RBV	Mandhwani 2020 32308935 Pakistan (50)	12 wk	Gt 1 50% ⁸⁴ Gt 2 1% Gt 3 43% Gt 4 1% Mixed Gt 5%	0% (clinical, imaging)	70/73 (95.9%) ITT	NR <i>Transfusion</i> 11/73 (15%), on RBV	0/73 (0%)
SOF/DCV	Mehta 2018 29430587 India (53)	12 wk	Gt 1a 54% Gt 1b 46%	NR	12/13 (92.3%) ITT	NR	0/13 (0%)
SOF (400 QOD)/DCV					9/13 (69.2%) ITT	NR	0/13 (0%)
SOF (200 qD)/DCV	Mostafi 2020 Ukr JND Bangladesh (54)	12 wk	NR	~23% (NR)	26/26 (100%) ITT	0/26 (0%)	0/26 (0%)
SOF/DCV	Singh 2018 30113115 India (55)	12 wk (most) ⁸⁵	Gt 3 100%	26% ⁸⁶ (TE) ⁸⁷	~11/~11 (100%) ⁸⁸ ITT estimated	0/~11 (0%) ⁸⁹	0/~11 (0%) ⁹⁰

⁷⁸ 400 mg every other day in n=6/21

⁷⁹ Across interventions.

⁸⁰ 24 weeks if cirrhosis (numbers not reported).

⁸¹ Based on Child-Pugh score and abdominal imaging, TE, and esophagogastroduodenoscopy.

⁸² SVR24 15/18 (83.3%)

⁸³ SVR24 14/18 (77.%)

⁸⁴ Across interventions.

⁸⁵ 24 weeks if cirrhosis (number not reported).

Regimen ²	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12 ³	DAA-Related Serious AE ⁴ <i>Transfusion</i> ⁵	D/C DAA Due to AE ⁶
SOF (200 qD)/DCV	Taneja 2018 29484572 India (56)	12 wk (most) ⁹¹	Gt 1 65% Gt 2 1% Gt 3 34%	32% (TE) ⁹²	54/54 (100%) ITT	0/54 (0%)	0/54 (0%)
SOF/DCV Summary					93.7% (88.9, 97.2)⁹³ 261/278 all ITT	0% (0, 6.8) 0/112⁹⁴	0.4% (0.1, 2.8) 1/247⁹⁵

⁸⁶ Includes n=8 CKD 4-5ND.

⁸⁷ 15% decompensated.

⁸⁸ N's estimated due to incomplete reporting for hemodialysis population specifically; 2 patients across both treatments were reinfected with a new genotype prior to SVR12; thus, viremic. However, counted as achieving SVR12 since original genotype was cleared.

⁸⁹ N's estimated due to incomplete reporting for hemodialysis population specifically; 2 patients across both treatments were reinfected with a new genotype prior to SVR12; thus, viremic. However, counted as achieving SVR12 since original genotype was cleared.

⁹⁰ N's estimated due to incomplete reporting for hemodialysis population specifically; 2 patients across both treatments were reinfected with a new genotype prior to SVR12; thus, viremic. However, counted as achieving SVR12 since original genotype was cleared.

⁹¹ 24 weeks if genotype 3 and cirrhosis (number not reported).

⁹² 9% decompensated.

⁹³ 8 studies (10 cohorts). I² 47% (moderate heterogeneity).

⁹⁴ Pooled. 4 studies.

⁹⁵ Pooled. 7 studies (9 cohorts).

Regimen ²	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12 ³	DAA-Related Serious AE ⁴ <i>Transfusion</i> ⁵	D/C DAA Due to AE ⁶
SOF (NR)/LDV	Asanbek kyzy 2019 SP641 Kyrgyzstan (57)	12 wk	NR	NR	SVR24: 11/11 (100%) ITT	0/11 (0%)	0/11 (0%)
SOF/LDV	Chuang 2021 ⁹⁶ 34465694 Multiple ⁹⁷ (58)	8 wk	Gt 1 100% Gt 1a 16%	0% (NR)	42/45 (93.3%) ITT	0/45 (0%)	0/45 (0%)
		12 wk	Gt 1 26% Gt 1a 3% Gt 2 61% Gt 5 3% Gt 6 6% Unknown 3%	0% (NR)	31/31 (100%) ITT	0/31 (0%)	0/31 (0%)
		24 wk	Gt 1 79% Gt 1a 21% Gt 2 11% Gt 4 11%	100% (NR)	16/19 (84.2%) ITT	0/19 (0%)	0/19 (0%)
SOF/LDV	Debnath 2020 32294734 India (59)	12 wk	Gt 1 92% ⁹⁸ Gt 5 8%	0% (TE)	13/13 (100%) Per protocol ⁹⁹	0/13 (0%) <i>Transfusion</i> 0/13 (0%), <i>No RBV</i>	0/13 (0%)
SOF/LDV	Gohel 2020 32507712 India (60)	12 wk	Gt 1 93% ¹⁰⁰ Gt 3 7%	0% (NR)	40/40 (100%) ITT	0/40 (0%)	0/40 (0%)
SOF/LDV	Mehta 2018 29430587 India (53)	12 wk	Gt 1a 17% Gt 1b 83%	NR	12/12 (100%) ITT	NR	0/12 (0%)
SOF/LDV	Singh 2018 30113115 India (55)	12 wk (most) ¹⁰¹	Gt 1 94% Gt 4 6%	26% ¹⁰² (TE) ¹⁰³	~28/~28 (100%) ¹⁰⁴ ITT estimated	0/~28 (0%) ¹⁰⁵	0/~28 (0%) ¹⁰⁶

⁹⁶ 8/95 on peritoneal dialysis (n=1 8 weeks, n=3 12 weeks, n=4 24 weeks).

⁹⁷ Belgium, Germany, Italy, Taiwan, United States

⁹⁸ Including n=5 on other regimens.

⁹⁹ Excludes n=2 patients who died within 4 weeks of treatment initiation, but not reported which treatment they were on.

¹⁰⁰ Includes n=3 on different regimen

Regimen ²	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12 ³	DAA-Related Serious AE ⁴ <i>Transfusion</i> ⁵	D/C DAA Due to AE ⁶
SOF (QOD)/LDV	Surendra 2018 28972699 India (61)	12 wk	Gt 1a 63% Gt 1b 37%	0% (TE)	19/21 (90.5%) ¹⁰⁷ ITT	0/21 (0%) <i>Transfusion 0/21 (0%), no RBV</i>	0/21 (0%)
SOF/LDV Summary					95.9% (92.8, 98.1)¹⁰⁸ 212/220 mostly ITT	0% (0, 3.7) 0/208¹⁰⁹	0% (0, 3.5) 0/220¹¹⁰
SOF (200 qD)/SIM	Bhamidimarri 2015 ¹¹¹ 26095179 US (62)	12 wk ¹¹²	Gt 1a 67% Gt 1b 33%	60% (biopsy) ¹¹³	10/12 (83.3%) ITT	0/12 (0%)	0/12 (0%)
SOF/SIM Summary					83.3% (52.3, 95.8) all ITT	0% (0, 43)	0% (0, 43)

¹⁰¹ 24 weeks if cirrhosis (number not reported).

¹⁰² Includes n=8 CKD 4-5ND.

¹⁰³ 15% decompensated.

¹⁰⁴ N's estimated due to incomplete reporting for hemodialysis population specifically; 2 patients across both treatments were reinfected with a new genotype prior to SVR12; thus, viremic. However, counted as achieving SVR12 since original genotype was cleared.

¹⁰⁵ N's estimated due to incomplete reporting for hemodialysis population specifically; 2 patients across both treatments were reinfected with a new genotype prior to SVR12; thus, viremic. However, counted as achieving SVR12 since original genotype was cleared.

¹⁰⁶ N's estimated due to incomplete reporting for hemodialysis population specifically; 2 patients across both treatments were reinfected with a new genotype prior to SVR12; thus, viremic. However, counted as achieving SVR12 since original genotype was cleared.

¹⁰⁷ 2 died pre-SVR12 due to inadequate hemodialysis

¹⁰⁸ 7 studies (1 with 3 arms). I² 5% (small heterogeneity).

¹⁰⁹ 6 studies (1 with 3 arms).

¹¹⁰ Pooled. 7 studies (1 with 3 arms).

¹¹¹ N=1 on peritoneal dialysis.

¹¹² 24 wk if cirrhosis (n=1)

¹¹³ Including n=3 CKD 5ND.

Regimen ²	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12 ³	DAA-Related Serious AE ⁴ <i>Transfusion</i> ⁵	D/C DAA Due to AE ⁶
SOF/VEL	Borgia 2019 ¹¹⁴ 31195062 Multiple ¹¹⁵ (63)	12 wk	Gt 1a 25% Gt 1b 19% Gt 1 undefined1% Gt 2 12% Gt 3 32% Gt 4 7% Gt 6 3%	29% (TE, biopsy, serum markers)	56/59 (94.9%) ITT	0/59 (0%)	0/59 (0%)
SOF/VEL	Cheng P-N 2022 34967920 Taiwan (64)	12 wk	NR	NR	122/126 (96.8%) ITT	NR	NR
SOF/VEL	Gaur 2020 32405174 India (65)	NR	Gt 1 68% Gt 3 32%	10% (TE)	30/31 (96.8%) ITT	0/31 (0%) <i>Transfusion 2/31</i> (6.5%) <i>no RBV</i>	0/31 (0%)
SOF/VEL	Hussain 2021 APASL 2021 Pakistan (66)	12 wk	NR	NR	25/28 (89.3%) ITT	NR	NR
SOF/VEL	Liu C-H 2022 ¹¹⁶ 33408122 Taiwan (67)	12 wk	Gt 1a 3% ¹¹⁷ Gt 1b 55% Gt 2 33% Gt 6 4%	14% (TE), 5% (Child B,C) ¹¹⁸	111/117 (94.9%) ITT	0/117 (0%)	0/117 (0%)
SOF/VEL	Mostafi 2020 Ukr JND Bangladesh (54)	12 wk	NR	~23% (NR)	44/44 (100%) ITT	0/44 (0%)	0/44 (0%)
SOF/VEL	Taneja 2020 33025685 India (68)	12 wk	Gt 1 79% Gt 3 15% Gt 4 5%	20% (TE) ¹¹⁹	49/51 (96.1%) ITT	0/51 (0%)	0/51 (0%)

¹¹⁴ N=5 (8%) on peritoneal dialysis.

¹¹⁵ Canada, UK, Spain, Israel, New Zealand, Australia.

¹¹⁶ 3/117 on peritoneal dialysis.

¹¹⁷ Across both D and ND populations (n=191)

¹¹⁸ Across both D and ND populations (n=191)

¹¹⁹ n=1 decompensated.

Regimen ²	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12 ³	DAA-Related Serious AE ⁴ <i>Transfusion</i> ⁵	D/C DAA Due to AE ⁶
SOF (NR)/VEL	Yu M-L 2021 33303567 Taiwan (21)	12 wk	Gt 1 44% Gt 2 50%% Gt 6 1%	35% (TE and clinical)	95/106 (89.6%) ITT	0/106 (0%)	5/105 (4.8%) ¹²⁰
SOF/VEL Summary					95.4% (93.0, 97.3) ¹²¹ 598/629 all ITT	0% (0, 1.9) 0/408 ¹²²	0% (0, 3.2) 5/407 ¹²³

Abbreviations. AE: adverse events, ASV: asunaprevir, CKD 4-5ND: chronic kidney disease category 4 or 5-nondialysis, D/C: discontinued, DAA: direct acting antivirals, DCV: daclatasvir, EBR: elbasvir, GLE: glecaprevir, Gt: genotype, GZR: grazoprevir, ICD: International Classification of Diseases, IFN: interferon, LDV: ledipasvir, NR: not reported, PIB: pibrentasvir, PMID: PubMed identifier, PrOD: combination paritaprevir/ritonavir/ombitasvir/dasabuvir, qD: every day, QOD: every other day, RBV: ribavirin, REML: random effects maximum likelihood (meta-analysis), SIM: simeprevir, SOF: sofosbuvir, SVR12/24/36/52: sustained virologic response at 12/24/36/52 weeks after end of treatment, TE: transient elastography, TIW: three times a week, VEL: velpatasvir, wk: weeks.

¹²⁰ One patient was categorized and reported in a separate group, without clear reporting about adverse events.

¹²¹ 8 studies. I^2 35% (small to moderate heterogeneity).

¹²² Pooled. 6 studies.

¹²³ 6 studies. I^2 29% (small to moderate heterogeneity).

Table S11. Summary Table: DAAs in CKD G5D (dialysis¹²⁴) population, part 2 (Death)¹²⁵

Regimen ¹²⁶	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	Follow-Up	Death ¹²⁷ % (95% CI)
GLE/PIB	Liu C-H 2020 31981264 Taiwan (12)	8 wk (most) ¹²⁸	Gt 1a 5% Gt 1b 32% Gt 2 58% Gt 6 4% % Gt 1b & 2 1% ¹²⁹	33% ¹³⁰ (multiple ¹³¹)	40 wk	0/73 0% (0, 10.1)
GLE/PIB	Persico 2019 Gastro Hep Italy (17)	8 (58%) or 12 wk (42%) ¹³²	Gt 1a 11% Gt 1b 31% Gt 2 36% Gt 3 19% Gt 4 3%	28% (TE)	1 yr	1/36 ¹³³ 2.8% (0.4, 17)
PrOD	Liu C-H 2019 30931537 Taiwan (36)	12 wk	Gt 1b 100%	0% (biopsy or TE)	SVR24	0/46 0% (0, 15)
PrOD±RBV	Pockros 2016 26976799 US (41)	12 wk	Gt 1 65% ¹³⁴ Gt 1b 35%	0% (biopsy, TE, serum markers)	SVR24	1/14 ¹³⁵ 7.1% (1.0, 37)

¹²⁴ 100% hemodialysis populations, unless otherwise noted (for peritoneal dialysis).

¹²⁵ The studies not included in this table either did not follow patients beyond SVR12 or did not explicitly report deaths. Only explicitly reported deaths (or survival) included. Therefore, estimates are likely to be inflated (if all studies were included).

¹²⁶ Sofosbuvir doses all were 400 mg daily. All other regimens used standard doses.

¹²⁷ Restricted to follow-up of about ≥6 month (omitting end of treatment and SVR12 timepoint data)

¹²⁸ 12 weeks if cirrhosis or 16 weeks if genotype 3 and prior treatment (numbers unclear).

¹²⁹ Includes n=3 with CKD 5ND.

¹³⁰ Includes n=3 with CKD 5ND.

¹³¹ TE, biopsy, clinical, imaging, FIB-4.

¹³² Reasons for different durations not reported.

¹³³ Car accident.

¹³⁴ Includes 6 with CKD 4.

¹³⁵ At SVR2 due to congestive heart failure and lower gastrointestinal bleeding. Not deemed related to treatment.

Regimen ¹²⁶	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	Follow-Up	Death ¹²⁷ % (95% CI)
SOF/DCV	Butt 2019 31720170 Pakistan (51)	12 wk	Gt 1 32% Gt 3 68%	0% (clinical, history, and serum markers)	1 yr	2/31 ¹³⁶ 6.4% (1.6, 22)
SOF/VEL	Borgia 2019 ¹³⁷ 31195062 Multiple ¹³⁸ (63)	12 wk	Gt 1a 25% Gt 1b 19% Gt 1 undefined 1% Gt 2 12% Gt 3 32% Gt 4 7% Gt 6 3%	29% (TE, biopsy, serum markers)	≥SVR16	2/59 ¹³⁹ 3.4% (0.8, 13)

Abbreviations. CI: confidence interval, CKD 4: chronic kidney disease category 4, DAA: direct acting antivirals, DCV: daclatasvir, ESRD: end-stage renal disease, GLE: glecaprevir, Gt: genotype, GZR: grazoprevir, HCV = hepatitis C virus, PIB: pibrentasvir, PMID: PubMed identifier, PrOD: combination paritaprevir/ritonavir/ombitasvir/dasabuvir, qD: every day, RBV: ribavirin, SOF: sofosbuvir, SVR2/12/24: (time of) sustained virologic response at 2/12/24 weeks after end of treatment, TE: transient elastography, wk: weeks, yr: year.

¹³⁶ Both due to "natural progression of ESRD."

¹³⁷ N=5 (8%) on peritoneal dialysis.

¹³⁸ Canada, UK, Spain, Israel, New Zealand, Australia.

¹³⁹ Neither related to HCV, DAA, or CKD (anxiety/suicide, lung cancer).

Table S12. Summary Table: DAAs in CKD G5D (dialysis) population, part 3 (Quality of Life)

Regimen ¹⁴⁰	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	Follow-Up	Quality of Life
GLE/PIB	Lawitz 2020 31821716 Multiple ¹⁴¹ (11)	8 wk (~83%) ¹⁴²	Gt 1 55% ¹⁴³ Gt 2 27% Gt 3 15% Gt 4 4%	14% (TE) ¹⁴⁴	1 yr	“Clinical meaningful improvement”: SF-12 PCS: 27/77 (35.1%) SF-12 MCS: 29/77 (37.8%)
SOF (200) / DCV	Singhal 2019 ¹⁴⁵ AASLD 1618 India (69)	12 wk	NR	NR	EOT	SF-12 PCS: Mean Δ 3.4 (1.1, 5.7) SF-12 MCS: Mean Δ 4.0 (1.6, 6.4)

Abbreviations. CKD 4-5ND: chronic kidney disease category 4 or 5-nondialysis, DAA: direct acting antivirals, EOT: end of treatment, GLE: glecaprevir, Gt: genotype, MCS: Mental Component Summary, PCS: Physical Component Summary, PIB: pibrentasvir, PMID: PubMed identifier, SF-12: Short Form 12 item questionnaire, E: transient elastography, wk: weeks, yr: year.

¹⁴⁰ Regimens used standard doses.

¹⁴¹ Canada, Germany, Greece, Italy, Poland, South Korea, Spain, Sweden, US.

¹⁴² 12 weeks (~13%) if cirrhotic except genotype 3, 16 weeks (~4%) if genotype 3 except treatment-naïve/noncirrhotic. Percentages include n=7 with CKD 3b.

¹⁴³ Including CKD 4-5ND.

¹⁴⁴ Including CKD 4-5ND.

¹⁴⁵ Probably substudy of Taneja 2018 PMID 29484572.

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Table S13. Summary Table: DAAs in kidney transplant recipients, part 1 (SVR12 and adverse events)

Regimen ¹	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12 ²	DAA-Related Serious AE ³ <i>Transfusion</i> ⁴	D/C DAA Due to AE ⁵
GLE/PIB	Reau 2018 29672891 US (1)	12 wk	Gt 1a 30% Gt 1b 55% Gt 3 10% Gt 4 5%	0% (TE)	20/20 (100%) ITT	NR	NR
GLE/PIB Summary					100% (70, 100) all ITT		
GZR/EBR	Eisenberger 2019 30656217 Germany (2)	12 wk (most) ⁶	Gt 1a 18% Gt 1b 73% Gt 4 9%	NR	11/11 (100%) ITT	0/11 (0%)	0/11 (0%)
GZR/EBR	Lai 2022 34902265 Taiwan (3)	12 wk	Gt 1b 100%	40% (F2)	10/10 (100%) ITT	0/10 (0%)	1/10 (10%)
GZR/EBR Summary					100% (71, 100)⁷ 21/21 all ITT	0% (0, 29)⁸ 0/21	4.8% (0.7, 27)⁹ 1/21
PrO±D±RBV ¹⁰	Daniş 2019 31418413 Turkey (4)	12 wk (most) ¹¹	Gt 1a 48% Gt 1b 48%	10% (not defined)	21/21 (100%) ITT	0/21 (0%) <i>Transfusion</i> 3/21 (14.3%) ¹²	0/21 (0%)

¹ Sofosbuvir doses are noted. All other regimens used standard doses.

² Pooled, unless otherwise noted.

³ Pooled.

⁴ Unreliable estimates. Rarely explicitly reported, possibly suggesting no transfusions in most studies. Mostly unclearly reported whether need for transfusion related to ribavirin treatment.

⁵ Pooled, unless otherwise noted.

⁶ 16 weeks (n=1 patient with high HCV mRNA at baseline).

⁷ Pooled. 2 studies.

⁸ Pooled. 2 studies.

⁹ Pooled. 2 studies.

¹⁰ Dasabuvir for genotype 1 (n=20), ribavirin for genotypes 1a and 4 (n=10).

¹¹ 24 weeks (n=1 patient with cirrhosis).

¹² Not reported whether on RBV or not.

Regimen ¹	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12 ²	DAA-Related Serious AE ³ <i>Transfusion</i> ⁴	D/C DAA Due to AE ⁵
PrOD	Iliescu 2020 31948406 Romania (5)	12 wk	Gt 1b 100%	0% (TE)	12/12 (100%) ITT	0/12 (0%)	0/12 (0%)
PrO±D Summary					100% (80, 100)¹³ 33/33 all ITT	0% (0, 20) 0/33 <i>Transfusion 14% (5, 36)</i>	0% (0, 20) 0/33
SOF/RBV (400)	Hanif 2017 28260436 Pakistan (6)	24 wk	Gt 1 57% Gt 3 30% Gt 4 3% Mixed 11%	11% (Decompensated)	37/37 (100%) ITT	0/37	0/37
SOF/RBV (400)	Kirushnan 2016 Indian J Transpl India (7)	12 wk	Gt 1 65% Gt 2 5% Gt 3 30% Gt 4 5%	0% (Clinical)	10/13 (76.9%) Available data ¹⁴	NR	NR
SOF/RBV (400) ¹⁵	Taneja 2018 28703905 India (8)	12 wk	Gt 1 79% Gt 3 14% Gt 4 7%	14% (TE, LSM)	12/14 (85.7%) ¹⁶ ITT	2/14 (14.3%) <i>Transfusion 0/12 (0%)</i>	2/14 (14.3%)
SOF/RBV (400)	Prasad 2018 29962673 India (9)	12 wk	Gt 1 27% ¹⁷ Gt 2 4.5% Gt 3 64% Gt 4 4.5%	45% (TE) ¹⁸	14/14 (100%) ITT	NR	NR
SOF/RBV (400)	Reddy 2018 29942507 India (10)	12 wk	Gt 1 70% Gt 2 10% Gt 3 10% Gt 4 10%	NR	10/10 (100%) ITT	0/10 (0%)	0/10 (0%)

¹³ Pooled. 2 studies.

¹⁴ Implied that all 20 completed treatment, but SVR12 data available for only 13.

¹⁵ In n=1, SOF dose 200 mg daily.

¹⁶ 1 patient included in both SOF/RBV and (after rapid virologic response failure) SOF/LDV arms

¹⁷ Including n=8 on other regimens.

¹⁸ Including n=8 on other regimens.

Regimen ¹	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12 ²	DAA-Related Serious AE ³ <i>Transfusion</i> ⁴	D/C DAA Due to AE ⁵
SOF/RBV (400)	Sharma 2018 29796311 India (11)	24 wk	Gt 1 33% ¹⁹ Gt 3 67%	10% (TE) ²⁰	29/29 (100%) ITT	0/30 (0%) <i>Transfusion or EPO</i> 0/30 (0%)	0/30 (0%)
SOF Summary					94.8% (88.2, 98.8)²¹ 112/117 mostly ITT	2.9% (0.5, 7.2)²² 2/91 <i>Transfusion 0% (0, 17)</i>	2.9% (0.5, 7.2)²³ 2/91
SOF/DCV (400)	D'Ambrosio 2019 30904073 Italy (12)	12 wk (86%) ²⁴	Gt 2 71% Gt 3 29%	14% (not defined)	14/14 (100%) ITT	0/14 (0%)	0/14 (0%)
SOF/DCV (400)	Duerr 2019 30717681 Germany (13)	12 wk	Gt 1a 6% Gt 1b 94%	0% (biopsy)	15/16 (93.8%) ITT	0/16 (0%)	0/16 (0%)
SOF/DCV±RBV (400)	El Maghrabi 2019 31531807 Egypt (14)	24 wk	Gt 1 13% ²⁵ Gt 4 87%	3% (U/S) ²⁶ , 0% (TE)	105/105 (100%) ITT	0/105 (0%)	NR
SOF/DCV±RBV (400)	Elmowafy 2020 33111161 Egypt (15)	24 wk	Gt 1 10% Gt 4 90%	2% (U/S), 0% (TE)	125/125 (100%) ITT	NR	0/125 (0%)
SOF/DCV (400)	Huang 2019 30369001 China (16)	12 wk (89%) ²⁷	Gt 1 84% Others 16%	16% (FIB4 >3.25)	19/19 (100%) ITT	0/19 (0%)	0/19 (0%)

¹⁹ Including n=15 on other regimens.

²⁰ Including n=15 on other regimens.

²¹ 6 studies. REML MA, I² 41% (moderate heterogeneity)

²² 4 studies. REML MA, I² 2% (no heterogeneity)

²³ 4 studies. REML MA, I² 2% (no heterogeneity)

²⁴ 24 weeks (n=2), reason not reported.

²⁵ Including n=9 who received other regimens.

²⁶ Including n=9 who received other regimens.

²⁷ 24 weeks for genotypes 1a or 4, cirrhosis, or prior treatment (n=2).

Regimen ¹	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12 ²	DAA-Related Serious AE ³ <i>Transfusion</i> ⁴	D/C DAA Due to AE ⁵
SOF/DCV±RBV (400) ²⁸	Taneja 2018 28703905 India (8)	12 wk (most) ²⁹	Gt 1 25% Gt 2 8% Gt 3 67% Gt 4 0%	17% (TE, LSM)	12/12 (100%) ITT	0/12 (0%)	0/12 (0%)
SOF/DCV Summary					99.7% (97.6, 100)³⁰ 290/291 all ITT	0% (0, 4.6)³¹ 0/166	0% (0, 4.2)³² 0/186
SOF/LDV (400)	Colombo 2017 27842383 ³³ Italy, France, Austria, Germany (17)	12 wk	Gt 1a 12% Gt 1b 74% Gt 1, no subtype 4% Gt 4 11%	14% (multiple) ³⁴	57/57 (100%) ITT	1/57 (1.8%)	0/57 (0%)
		24 wk	Gt 1a 18% Gt 1b 75% Gt 4 7%	16% (multiple) ³⁵	57/57 (100%) ITT	2/57 (3.5%)	1/57 (1.8%)
SOF/LDV (400)	Eisenberger 2017 27495770 Germany (18)	12 wk (80%) ³⁶	Gt 1a 27% Gt 1b 67% Gt 4 7%	NR	15/15 (100%) ITT	NR	NR
SOF/LDV (400)	Weigert 2018 29661427 Portugal (19)	12 wk (most) ³⁷	Gt 1a 22%) ³⁸ Gt 1b 56% Gt 3 13% Gt 4 9%	13% (TE) ³⁹	14/14 (100%) ITT	NR	NR

²⁸ In n=3, SOF dose 200 mg daily.

²⁹ 24 weeks if cirrhosis or detectable RNA at week 4 (n not reported).

³⁰ Pooled. 6 studies.

³¹ Pooled. 5 studies.

³² Pooled. 5 studies.

³³ RCT of 12 vs. 24 wk.

³⁴ TE, Ishak score ≥ 5 by biopsy, FibroScan >12.5 kPa, or FibroTest score >0.75 plus APRI >2.

³⁵ TE, Ishak score ≥ 5 by biopsy, FibroScan >12.5 kPa, or FibroTest score >0.75 plus APRI >2.

³⁶ 8 weeks (n=3), unclear reason.

³⁷ 24 weeks for F4 fibrosis (number not reported).

Regimen ¹	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12 ²	DAA-Related Serious AE ³ <i>Transfusion</i> ⁴	D/C DAA Due to AE ⁵
SOF/LDV +RBV (400)	Musialik 2019 30972854 Poland (20)	12 wk (74%) ⁴⁰	Gt 1b 90% Gt 4 10%	5% (TE) ⁴¹	31/31 (100%) Per protocol ⁴²	NR	0/31 (0%)
SOF/LDV +RBV (400)	Akin 2018 29899985 Turkey (21)	12 or 24 wk ⁴³	Gt 1a 25% Gt 1b 75%	17% (not defined)	12/12 (100%) ITT	0/12 (0%) Transfusion 0/12 (0%)	0/12 (0%)
SOF/LDV +RBV (400)	Bhamidimarri 2017 28332729 US (22)	12 wk (91%) ⁴⁴	Gt 1a 74% Gt 1b 26%	0% (TE)	22/23 (95.7%) ITT	NR	0/23 (0%)
SOF/LDV +RBV (400)	Chascsa 2018 ⁴⁵ 29758123 US (23)	12 wk (77%) ⁴⁶	Gt 1 82% ⁴⁷ Gt 1a 54% Gt 1b 29% Gt 2 4% Gt 3 11%	36% (not defined) ⁴⁸	22/22 (100%) ITT	0/22 (0%)	0/22 (0%)
SOF/LDV +RBV (400)	Saxena 2017 28504842 US (24)	12 or 24 wk ⁴⁹	Gt 1 90% ⁵⁰ Gt 1a 48% Gt 1b 37% Gt 2 2% Gt 3 3% Gt 4 3% Gt 6 2%	0% (TE)	42/47 (89.4%) mITT ⁵¹	NR	NR

³⁸ Including n=9 who received other regimens.

³⁹ Including n=9 who received other regimens.

⁴⁰ 24 weeks for first 8 patients treated.

⁴¹ Including n=9 who received other regimens.

⁴² 1 dropout excluded from analysis.

⁴³ 24 weeks if cirrhosis, previous treatment failure and for specific genotypes (implied) (number not reported).

⁴⁴ 8 weeks (n=1), 24 weeks (n=1); reasons not reported.

⁴⁵ Study specific to D+/R+ patients.

⁴⁶ 24 weeks (n=5), reasons not reported.

⁴⁷ Including n=6 who received other regimens.

⁴⁸ Including n=6 who received other regimens.

Regimen ¹	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12 ²	DAA-Related Serious AE ³ <i>Transfusion</i> ⁴	D/C DAA Due to AE ⁵
SOF/LDV +RBV (400)	Taneja 2018 28703905 India (8)	12 wk (most) ⁵²	Gt 1 86% Gt 4 14%	5% (TE, LSM)	22/22 (100%) ⁵³ ITT	0/22 (0%)	0/22 (0%)
SOF/LDV Summary					97.3% (94.9, 99.0)⁵⁴ 294/300 almost all ITT	2.6% (0.7, 5.7)⁵⁵ 3/170	1.7% (0.4, 3.7)⁵⁶ 1/224
SOF/VEL (400)	Greco 2019 SP786 ⁵⁷ Italy (25)	12 wk	Gt 1 60% Gt 2 40%	0% (not defined)	10/10 (100%) ITT	0/10 (0%)	0/10 (0%)
SOF/VEL Summary					100% (52, 100) all ITT	0% (0, 48)	0% (0, 48)

Abbreviations: AE: adverse event, APRI: aspartate aminotransferase to platelet ratio index, D/C = discontinuation, DAA: direct-acting antiviral, DCV: daclatasvir, EBR: elbasvir, EPO: erythropoietin, FIB4: fibrosis 4 (score), GLE: glecaprevir, Gt: genotype, GZR: grazoprevir, ITT: intention-to-treat analysis (or all participants analyzed), LDV: ledipasvir, LSM: liver stiffness measurement, mITT: modified ITT, NR: not reported, PIB: pibrentasvir, PMID: PubMed identifier, PrOD: paritaprevir/ritonavir/ombitasvir/dasabuvir, RBV: ribavirin, REML MA: restricted maximum likelihood meta-analysis, SOF: sofosbuvir, SVR12: sustained virologic response at 12 weeks post-treatment, TE: transient elastography, U/S: ultrasound, VEL: velpatasvir, wk: weeks.

⁴⁹ Numbers and reasons not reported.

⁵⁰ Including n=11 on other regimens.

⁵¹ Omitted 1 who discontinued DAA for administrative reasons.

⁵² 24 weeks if cirrhosis or detectable RNA at week 4 (n not reported).

⁵³ 1 patient included in both SOF/RBV and (after rapid virologic response failure) SOF/LDV arms

⁵⁴ 10 study arms. REML MA, I² 18% (small heterogeneity)

⁵⁵ 5 study arms. REML MA, I² 0% (no heterogeneity)

⁵⁶ 7 study arms. REML MA, I² 0% (no heterogeneity)

⁵⁷ European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) 2019 conference abstract.

Table S14. Summary Table: DAAs in kidney transplant recipients, part 2 (allograft outcomes and death)

Regimen	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	Timing	Acute Rejection	Allograft Loss	Patient Death (≥12 Months)
GLE/PIB	Reau 2018 29672891 US (1)	12 wk	Gt 1a 30% Gt 1b 55% Gt 3 10% Gt 4 5%	0% (TE)	SVR12	0/20 (0%)	0/20 (0%)	NR
GLE/PIB Summary						0% (0, 30)	0% (0, 30)	
GZR/EBR	Eisenberger 2019 30656217 Germany (2)	12 wk (91%) ⁵⁸	Gt 1a 18% Gt 1b 73% Gt 4 9%	NR	SVR12	NR	1/11 (9.1%) ⁵⁹	NR
GZR/EBR Summary							9.1% (1.3, 44)	
SOF/RBV	Reddy 2018 29942507 India (10)	12 wk	Gt 1 70% Gt 2 10% Gt 3 10% Gt 4 10%	NR	1 yr	0/10 (0%)	0/10 (0%)	NR
SOF Summary						0% (0, 48)	0% (0, 48)	
SOF/DCV (400)	Duerr 2019 30717681 Germany (13)	12 wk	Gt 1a 6% Gt 1b 94%	0% (biopsy)	24 wk	0/16 (0%)	0/16 (0%)	NR
SOF/DCV±RBV (400)	El Maghrabi 2019 31531807 Egypt (14)	24 wk	Gt 1 13% ⁶⁰ Gt 4 87%	3% (U/S) ⁶¹ , 0% (TE)	EOT	4/105 (3.8%)	NR	NR

⁵⁸ 16 weeks (n=1 patient with high HCV mRNA at baseline).

⁵⁹ Not associated with DAA, but with progressive diabetic nephropathy.

⁶⁰ Including n=9 who received other regimens.

⁶¹ Including n=9 who received other regimens.

Regimen	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	Timing	Acute Rejection	Allograft Loss	Patient Death (≥12 Months)
SOF/DCV±RBV (400)	Elmowafy 2020 33111161 Egypt (15)	24 wk	Gt 1 10% Gt 4 90%	2% (U/S), 0 (TE)	EOT	4/125 (3.2%)	0/125 ⁶²	NR
SOF/DCV Summary						3.4% (1.5, 6.1)⁶³ 8/246	0% (0, 5.4)⁶⁴ 0/141	
SOF/LDV (400)	Colombo 2017 27842383 ⁶⁵ Italy, France, Austria, Germany (17)	12 wk	Gt 1 4% Gt 1a 12% Gt 1b 74% Gt 4 11%	14% (multiple) ⁶⁶	SVR12	NR	NR	NR
SOF/LDV (400)		24 wk	Gt 1a 18% Gt 1b 75% Gt 4 7%	16% (multiple) ⁶⁷	SVR12	NR	NR	NR
SOF/LDV (400)	Eisenberger 2017 27495770 Germany (18)	12 wk (80%) ⁶⁸	Gt 1a 27% Gt 1b 67% Gt 4 7%	NR	SVR12	0/15 (0%)	0/15 (0%)	NR
SOF/LDV±RBV (400)	Chascsa 2018 29758123 US (23)	12 wk (77%) ⁶⁹	Gt 1 82% ⁷⁰ Gt 1a 54% Gt 1b 29% Gt 2 4% Gt 3 11%	36% (not defined) ⁷¹	Median 413 d	1/22 (4.5%) ⁷²	0/22 (0%)	NR

⁶² Incident dialysis.

⁶³ 3 studies. REML MA. I² 0% (no heterogeneity)

⁶⁴ Pooled. 2 studies.

⁶⁵ RCT of 12 vs. 24 weeks.

⁶⁶ TE, Ishak score ≥ 5 by biopsy, FibroScan >12.5 kPa, or FibroTest score >0.75 plus APRI >2.

⁶⁷ TE, Ishak score ≥ 5 by biopsy, FibroScan >12.5 kPa, or FibroTest score >0.75 plus APRI >2.

⁶⁸ 8 weeks (n=3), unclear reason.

⁶⁹ 24 weeks (n=5), reasons not reported.

⁷⁰ Including n=6 who received other regimens.

Regimen	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	Timing	Acute Rejection	Allograft Loss	Patient Death (≥12 Months)
SOF/LDV±RBV (400)	Saxena 2017 28504842 US (24)	12 or 24 wk ⁷³	Gt 1 90% ⁷⁴ Gt 1a 48% Gt 1b 37% Gt 2 2% Gt 3 3% Gt 4 3% Gt 6 2%	0% (TE)	EOT	2/47 (4.3%)	1/47 (2.1%)	NR
SOF/LDV±RBV ⁷⁵ (400)	Bhamidimarri 2017 28332729 US (22)	12 wk (91%) ⁷⁶	Gt 1a 72% Gt 1b 24% Gt 2b 4%	0% (TE)	EOT	4/25 (16%) ⁷⁷	NR	NR
SOF/LDV Summary						6.2% (2.3, 12.0)⁷⁸ 7/109	1.2% (0.2, 8.0)⁷⁹ 1/84	

⁷¹ Including n=6 who received other regimens.

⁷² During first week of treatment.

⁷³ Numbers and reasons not reported.

⁷⁴ Including n=11 on other regimens.

⁷⁵ Also SOF/DCV (n=1), SOF/SIM (n=1).

⁷⁶ 8 weeks (n=1), 24 weeks (n=1); reasons not reported.

⁷⁷ All resolved.

⁷⁸ 4 studies. REML MA. I² 12% (small heterogeneity).

⁷⁹ 3 studies. Pooled.

Regimen	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	Timing	Acute Rejection	Allograft Loss	Patient Death (≥12 Months)
DAA, various ⁸⁰	Chevallier 2020 32636068 France (26)	12 wk (80%) ⁸¹	Gt 1 68% ⁸² Gt 2 7% Gt 3 2% Gt 4 18% Gt 5 5% Unknown 0%	9% (TE)	Mean 951 d (SD 189)	NR	5/44 (11.4%) ⁸³ OR 2.69 (0.30, 24.6)	0/44 (0%) OR~0.06 (<0.01, 1.27)
No DAA (Retrospective NRCS)			Gt 1 50% Gt 2 14% Gt 3 5% Gt 4 5% Gt 5 0% Unknown 27%	9% (TE)		NR	1/22 (4.5%) ⁸⁴	3/22 (13.6%) ⁸⁵
DAA, various ⁸⁶	Gendia 2019 30580473 Italy (27)	NR	Gt 1a 15% Gt 1b 54% Gt 2 31% Gt 3 0% Gt 4 0%	NR	Mean 7.4 y (3.7)	NR	1/13 (7.7%) OR 0.38 (0.03, 4.81)	0/13 (0%) OR~0.06 (<0.01, 1.31)
No DAA (Retrospective NRCS)			Gt 1a 18% Gt 1b 55% Gt 2 9% Gt 3 9% Gt 4 9%	NR	Mean 4.9 y (4.1)	NR	2/11 (18.2%)	4/11 (36%)

⁸⁰ SOF/LDV±RBV (n=23), SOF/DCV (n=14), GZR/EBR (n=4), SOF/SIM (n=1), SOF/RBV (n=1), PrO (n=1).

⁸¹ 4 weeks (n=2), 8 weeks (n=1), 24 weeks (n=6), reasons not reported.

⁸² P values vs. no DAA: genotype 1 P=0.07, genotype 2 P=0.18, genotype 3 P=0.30, genotype 4 P=0.06, genotype 5 P=0.15, Unknown P=0.0001.

⁸³ 4 of 5 had pre-DAA GFR <30; 5th GFR 50.

⁸⁴ Baseline GFR not reported.

⁸⁵ 1 hepatocellular carcinoma, 2 septic shock.

⁸⁶ SOF/RBV (n=6), SOF/LDV (n=4), SOF/DCV (n=2), SOF/VEL (n=1).

Regimen	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	Timing	Acute Rejection	Allograft Loss	Patient Death (≥12 Months)
DAA, various ⁸⁷	Goetsch 2020 33089036 US (28)	NR	NR	NR	>2 y	NR	2/29 (6.9%) OR 0.17 (0.03, 0.89)	2/29 (6.9%) OR 0.30 (0.05, 1.61)
No DAA (Retrospective NRCS)			NR	NR	>2 y	NR	9/30 (30%)	6/30 (20%)
DAA vs. no DAA Summary							Unadj OR 0.50 (0.09, 2.73)⁸⁸	Unadj OR 0.16 (0.04, 0.61)⁸⁹
DAA, various ⁹⁰	Weigert 2018 29661427 Portugal (19)	12 (61%) or 24 (39%) wk ⁹¹	Gt 1a 22% Gt 1b 56% Gt 3 13% Gt 4 9%	13% (TE)	1 yr	NR	NR	2/23 (9%)

Abbreviations: adjHR: adjusted hazard ratio, APRI: aspartate aminotransferase to platelet ratio index, DAA: direct-acting antiviral, DCV: daclatasvir, EBR: elbasvir, EOT: end of treatment, GFR: glomerular filtration rate, GLE: glecaprevir, Gt: genotype, GZR: grazoprevir, LDV: ledipasvir, mo: months, NR: not reported, NRCS: nonrandomized comparative study, OR: odds ratio (unadjusted), PIB: pibrentasvir, PMID: PubMed identifier, PrOD: paritaprevir/ritonavir/ombitasvir/dasabuvir, RBV: ribavirin, REML MA: restricted maximum likelihood meta-analysis, SIM: simeprevir, SOF: sofosbuvir, SVR12: sustained virologic response at 12 weeks post-treatment, TE: transient elastography, U/S: ultrasound, Unadj: unadjusted, VOX: voxipaprevir, wk: weeks.

⁸⁷ SOF/LDV+-RBV (n=22), SOF/SIM (n=2), SOF/RBV (n=1), SOF/VEL (n=1), SOF/VEL/VOX (n=1), GLE/PIB (n=1).

⁸⁸ 3 studies. REML MA. I² 48% (moderate heterogeneity).

⁸⁹ 3 studies. REML MA. I² 0% (no heterogeneity).

⁹⁰ SOF/LDV (n=15), SOF/RBV (n=4), SOF/DCV (n=2), GZR/ELB (n=2).

⁹¹ 24 weeks for F4 fibrosis.

Table S15. Summary Table: DAAs in kidney transplant recipients, part 3 (eGFR and proteinuria)

Regimen	Study, PMID Country (Reference)	Duration	Genotype	Liver Cirrhosis (Definition)	Follow- up	eGFR Chg (95% CI), P value [Baseline]	Proteinuria Chg (95% CI), P value [Baseline]
GZR/EBR	Eisenberger 2019 30656217 Germany (2)	12 wk (most) ⁹²	Gt 1a 18% Gt 1b 73% Gt 4 9%	NR	SVR12	ΔMedian -2, NS [29]	ΔMedian ~-240 mg/g Cr, NS [~740]
PrOD	Iliescu 2020 31948406 Romania (5)	12 wk	Gt 1b 100%	0% (TE)	Mean 2.6 yr	NR	Decrease (NR), P=0.013 [NR]
SOF/RBV (400)	Hanif 2017 28260436 Pakistan (6)	24 wk	Gt 1 57% Gt 3 30% Gt 4 3% Mixed 11%	11% (Decompensated)	EOT (24 wk)	Mean Δ 17.0 (11.7, 22.5), P=0.04 [63.7]	NR
SOF/RBV (400) ⁹³	Taneja 2018 28703905 India (8)	12 wk (most)	Gt 1 79% Gt 3 14% Gt 4 7%	14% (TE, LSM)	EOT	ΔMedians -1.0, P=0.14 [72.8]	NR
SOF/DCV (400)	Duerr 2019 30717681 Germany (13)	12 wk	Gt 1a 6% Gt 1b 94%	0% (biopsy)	SVR12	NR	-165 mg/g Cr (-692, 363) P=0.75 [606]
SOF/DCV (400)	Huang 2019 30369001 China (16)	12 wk (89%) ⁹⁴	Gt 1 84% Others 16%	16% (FIB4 >3.25)	SVR12	NR P=0.07 [57.2]	-0.6 g/g Cr(-1.1, 0) P=0.048 [0.95] 8/12 >10% improvement 2/12 >10% worsening
SOF/DCV (400)	Michels 2020 32294735 Brazil ⁹⁵ (29)	NR	NR	48% (TE) ⁹⁶	12 or 24 wk ⁹⁷	Mean Δ -1.4 (-6.0, 3.2), P=0.55 [51.4]	NR

⁹² 16 weeks (n=1 patient with high HCV mRNA at baseline).

⁹³ In n=1, SOF dose 200 mg daily.

⁹⁴ 24 weeks for cirrhosis or prior treatment (n=2).

⁹⁵ This study did not report DAA or kidney outcomes specifically for the transplant population.

⁹⁶ Of whole population (n=241) including hemodialysis and other CKD.

⁹⁷ Unclear.

Regimen	Study, PMID Country (Reference)	Duration	Genotype	Liver Cirrhosis (Definition)	Follow-up	eGFR Chg (95% CI), P value [Baseline]	Proteinuria Chg (95% CI), P value [Baseline]
SOF/DCV (400)	D'Ambrosio 2019 30904073 Italy (12)	12 wk (86%) ⁹⁸	Gt 2 71% Gt 3 29%	14% (not defined)	48 wk	ΔMedians 3, P=0.57 [54]	NR
SOF/DCV±RBV (400)	Elmowafy 2020 33111161 Egypt (15)	24 wk	Gt 1 10% Gt 4 90%	2% (U/S), 0% (TE)	SVR12	Mean Δ -2.0 (NR), P NR [61.5]	NR
SOF/DCV±RBV (400) ⁹⁹	Taneja 2018 28703905 India (8)	12 wk (most) ¹⁰⁰	Gt 1 25% Gt 2 8% Gt 3 67% Gt 4 0%	17% (TE, LSM)	EOT	ΔMedians -2.0, P=0.51 [65.5]	NR
SOF/LDV (400)	Colombo 2017 27842383 ¹⁰¹ Italy, France, Austria, Germany (17)	12 wk	Gt 1a 12% Gt 1b 74% Gt 1, no subtype 4% Gt 4 11%	14% (multiple) ¹⁰²	SVR12	ΔMedians 0, P NR [50]	NR
SOF/LDV (400)		24 wk	Gt 1a 18% Gt 1b 75% Gt 4 7%	16% (multiple) ¹⁰³	EOT	ΔMedians -5, P NR [60]	NR
SOF/LDV (400)	Eisenberger 2017 27495770 Germany (18)	12 wk (80%) ¹⁰⁴	Gt 1a 27% Gt 1b 67% Gt 4 7%	NR	EOT	ΔMedians -9, P NR [78]	NR
SOF/LDV±RBV (400)	Akin 2018 29899985 Turkey (21)	12 or 24 wk ¹⁰⁵	Gt 1a 25% Gt 1b 75%	17% (not defined)	SVR12	Mean Δ 4.1 (-2.1, 10.3), P=0.20 [68.6]	NR

⁹⁸ 24 weeks (n=2), reason not reported.

⁹⁹ In n=3, SOF dose 200 mg daily.

¹⁰⁰ 24 weeks if cirrhosis or detectable RNA at week 4 (n not reported).

¹⁰¹ Randomized controlled trial of 12 vs. 24 weeks.

¹⁰² TE, Ishak score ≥ 5 by biopsy, FibroScan >12.5 kPa, or FibroTest score >0.75 plus APRI >2.

¹⁰³ TE, Ishak score ≥ 5 by biopsy, FibroScan >12.5 kPa, or FibroTest score >0.75 plus APRI >2.

¹⁰⁴ 8 weeks (n=3), unclear reasons.

¹⁰⁵ Numbers not reported. Implied 24 weeks if cirrhosis, previous treatment failure and for specific genotypes.

Regimen	Study, PMID Country (Reference)	Duration	Genotype	Liver Cirrhosis (Definition)	Follow-up	eGFR Chg (95% CI), P value [Baseline]	Proteinuria Chg (95% CI), P value [Baseline]
SOF/LDV+RBV (400)	Taneja 2018 28703905 India (8)	12 wk (most) ¹⁰⁶	Gt 1 86% Gt 4 14%	5% (TE, LSM)	EOT	ΔMedians -12.2, P=0.30 [65.9]	NR
SOF±LDV+RBV (400)	Musialik 2019 30972854 Poland (20)	12 wk (most) ¹⁰⁷	Gt 1b 90% Gt 4 10%	5% (TE) ¹⁰⁸	EOT	Mean Δ -2 (-4.9, 0.9), P=0.17 [55]	NR
SOF/VEL (400)	Greco 2019 SP786 ¹⁰⁹ Italy (25)	12 wk	Gt 1 60% Gt 2 40%	0% (not defined)	EOT	Mean Δ 3 (NR), P NR [54] ¹¹⁰	Mean Δ -20 mg/24 hr (NR), P NR [430] ¹¹¹
SOF-based regimens ¹¹² (400)	Prasad 2018 29962673 India (9)	12 wk	Gt 1 27% Gt 2 4.5% Gt 3 64% Gt 4 4.5%	45% (TE)	EOT	Mean Δ -0.5 (-7.0, 6.0), NS [60.6]	NR
DAAAs, various ¹¹³	El Maghrabi 2019 31531807 Egypt (14)	24 wk	Gt 1 13% Gt 4 87%	3% (U/S), 0% (TE)	SVR12	Mean Δ -1.9 (-10.7, 6.9), P=0.67 [64.3]	NR
DAAAs, various ¹¹⁴	Chevallier 2020 32636068 France (26)	12 wk (most) ¹¹⁵	Gt 1 68% Gt 2 7% Gt 3 2% Gt 4 18% Gt 5 5%	9% (TE)	EOT	Mean Δ 11 (-1, 23), P=0.075 [47]	NR

Abbreviations: APRI: aspartate aminotransferase to platelet ratio index, Chg: change, CI: confidence interval, DAA: direct-acting antiviral, DCV: daclatasvir, EBR: elbasvir, eGFR: estimated glomerular filtration rate, EOT: end of treatment, Gt: genotype, GZR: grazoprevir, ILDV: ledipasvir, LSM: liver stiffness measurement,

¹⁰⁶ 24 weeks if cirrhosis or detectable RNA at week 4 (n not reported).

¹⁰⁷ 24 weeks if genotype 2 or 3 and first several treated for genotype 1b or 4 (numbers not reported for this regimen).

¹⁰⁸ Including n=9 who received other regimens.

¹⁰⁹ European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) 2019 conference abstract.

¹¹⁰ Reported as P<0.01, but this is likely one-sided P for "not worsening."

¹¹¹ Reported as P<0.01, but this is likely one-sided P for "not worsening."

¹¹² SOF/RBV (n=14), SOF/DCV/RBV (n=5), SOF/LDV (n=3).

¹¹³ SOF/DCV+-RBV (n=105), SOF/RBV (n=4), PrO/RBV (n=5).

¹¹⁴ SOF/LDV±RBV (n=23), SOF/DCV (n=14), GZR/EBR (n=4), SOF/SIM (n=1), SOF/RBV (n=1), PrO (n=1).

¹¹⁵ 4 weeks (n=2), 8 weeks (n=1), 24 weeks (n=6), reasons not reported.

Mean Δ : mean change in value (final minus pre-treatment), NR: not reported, NS, nonsignificant, P: P value, PMID: PubMed identifier, PrOD: paritaprevir/ritonavir/ombitasvir/dasabuvir, RBV: ribavirin, SIM: simeprevir, SOF: sofosbuvir, SVR12: sustained virologic response at 12 weeks post-treatment, TE: transient elastography, U/S: ultrasound, VEL: velpatasvir, wk: weeks, yr: years, Δ Median: difference between final and pre-treatment median values (not median change).

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Table S16: Summary Table
Isolation of HCV patients receiving hemodialysis
Categorical outcomes

PMID	Author	Year	Country	Type of article	Study design	Sample size	CKD stage	Blood transfusions	HD vintage	Outcome	Definition	Arm
19147995	Agarwal SK., Dash SC., Gupta S., Pandey RM.	2009	India	Peer-reviewed publication	Pre-post design	1285	CKD HD	6.6 (3.9)	nd	HCV seroconversion	nd	Isolation for HCV+, 2003-2006 No isolation for HCV+, 1995-1998
7753458	Blumberg A., Zehnder C., Burckhardt JJ.	1995	Switzerland	Peer-reviewed publication	Pre-post design	131	CKD HD	nd	2 weeks-284 months	HCV seroconversion	nd	Isolation for HCV+ No isolation for HCV+
16903625	Karkar A., Abdelrahman M., Ghacha R., Malik TQ.	2006	Saudi Arabia	Peer-reviewed publication	Pre-post design	265	CKD HD	nd	4-21 years	HCV seroconversion	nd	Isolation for HCV+
												No isolation for HCV+
										HCV (antibody) positivity	nd	Isolation for HCV+
												No isolation for HCV+
										HCV seroconversion	nd	
16685138	Gallego E., López A., Pérez J., Llamas F., Lorenzo I., López E., Illescas ML., Andrés E., Olivas E., Gómez-Roldan C.	2006	Spain	Peer-reviewed publication	Pre-post design	282	CKD HD	nd	nd			Strict/complete isolation for HCV+ Isolation for HCV+
										HCV (antibody) positivity	nd	Strict/complete isolation for HCV+
												Isolation for HCV+
17382087	Shebeb AM., Kotkat AM., Abd El Reheim SM., Farghaly AG., Fetohy EM.	2006	Egypt	Peer-reviewed publication	nRCS, unclear	101	CKD HD	nd	2.3 (1.4)	HCV seroconversion	nd	Intervention program + no isolation No intervention program + isolation No intervention program + no isolation Intervention program + no isolation No intervention program + no isolation Intervention program + no isolation No intervention program + isolation No intervention program + no isolation
15469615	Shamshirsaz AA., Kamgar M., Bekheirnia MR., Ayazi F., Hashemi SR., Bouzari N., Habibzadeh MR., Pourzahedgilani N., Broumand V., Shamshirsaz AH., Moradi M., Borghei M., Haghighi NN., Broumand B.	2004	Iran	Peer-reviewed publication	RCT	442	CKD HD	24%	21.6 month	HCV (RNA) positivity	incidence of HC dedicated HD machine	nondedicated HD machine dedicated HD machine nondedicated HD machine

Table S16: Summary Table
Isolation of HCV patients receiving hemodialysis
Categorical outcomes

PMID	Author	Year	Definition	Timepoint	Frequency/Rate	Relative effect	p-value	Quality
19147995	Agarwal SK., Dash SC., Gupta S., Pandey RM.	2009	separate room, separate machine shared room, shared machine	3 years	2.7% 36.2%	nd	<0.001	Fair
7753458	Blumberg A., Zehnder C., Burckhardt JJ.	1995	separate machine, same room nd	1992+ nd	7/<131 (unclear) 0/nd (unclear)	nd	nd	Poor
16903625	Karkar A., Abdelrahman M., Ghacha R., Malik TQ.	2006	separate rooms, separate machines	2005	0/265 (0%)	nd	nd	Poor
				2004	0/265 (0%)	nd	nd	
				2003	nd/265 (0.2%)	nd	nd	
				2002	1/265 (0.3%)	nd	nd	
			nd	2001	7/265 (2.6%)	nd	nd	
				2000	6/265 (2.3%)	nd	nd	
				1999	6/265 (2.1%)	nd	nd	
				1998	7/265 (2.7%)	nd	nd	
			separate rooms, separate machines	2005	77/265 (29%)	nd	nd	
				2004	85/265 (32%)	nd	nd	
				2003	90/265 (34%)	nd	nd	
				2002	117/265 (44%)	nd	nd	
			nd	2001	151/265 (57%)	nd	nd	
				2000	130/265 (49%)	nd	nd	
				1999	148/265 (56%)	nd	nd	
				1998	154/265 (58%)	nd	nd	
				1996-2003	0/171 (0%)	nd	nd	
16685138	Gallego E., López A., Pérez J., Llamas F., Lorenzo I., López E., Illescas ML., Andrés E., Olivas E., Gómez-Roldan C.	2006	separate room, separate staff, separate machine separate machines, shared room separate room, separate staff, separate machine	1993 2003 2003	2/144 (1.4%) 10/161 (6.2%) 14/175 (8.0%)	nd nd nd	nd nd nd	Fair
				2001	13/183 (7.1%)	nd	nd	
				2000	17/172 (10%)	nd	nd	
				1999	18/150 (12%)	nd	nd	
				1998	23/161 (14.3%)	nd	nd	
				1997	26/169 (15.4%)	nd	nd	
				1996	31/171 (18.1%)	nd	nd	
			separate machines, shared room	1995	34/157 (21.7%)	nd	nd	
				1994	38/146 (26.0%)	nd	nd	
				1993	37/144 (25.7%)	nd	nd	
				1992	37/121 (30.6%)	nd	nd	
17382087	Shebeb AM., Kotkat AM., Abd El Reheim SM., Farghaly AG., Fetohy EM.	2006	Health Education Program (HEP)	6 month	1/10 (10%)	nd	nd	Poor
			isolation of seropositive patients nd		11/45 (24%) 2/19 (11%)	nd nd	nd nd	
			Health Education Program (HEP)	6-12 month	1/18	nd	nd	
			isolation of seropositive patients nd		3/32 5/24	nd nd	nd nd	
			Health Education Program (HEP)	6-18 months	0/15	nd	nd	
			isolation of seropositive patients nd		3/30 2/12	OR 0.65 (0.23, 1.80) nd	nd nd	
15469615	Shamshirsaz AA., Kamgar M., Bekheirnia MR., Ayazi F., Hashemi SR., Bouzari N., Habibzadeh MR., Pourzahedgilani N., Broumand V., Shamshirsaz AH., Moradi M., Borghei M., Haghighi NN., Broumand B.	2004	The only difference between two groups of HD centre 9 months		4/254 (1.6%)	nd	0.05	
					9/192 (4.7%)	nd		Good
			The only difference between two groups of HD centre 18 months		2/160 (1.3%) 7/121 (5.8%)	nd nd	<0.05	

Table S17: Evidence profile: Isolation of HCV patients receiving hemodialysis

Outcome	# of Studies and Study Design	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence, including Applicability	Other Considerations	Summary of Findings		
							Quality of Evidence for Outcome	Description of Findings	Importance of Outcome
HCV seroconversion	4 Pre-post design, 1 nRCS	2064	Important Limitations* (-2)	No Important Inconsistencies† (0)	Some uncertainty about directness of evidence‡ (-1)	None	Very Low	Large reductions in rates of seroconversion in most studies, to 0% in 2 studies	High
HCV positivity	1 RCT 2 Pre-post design 1 cohort	1072	RCT: none Observational: Important Limitations* (-2)	No Important Inconsistencies§ (0)	Some uncertainty about directness of evidence‡ (-1)	None	Low	Significantly lower event rate with dedicated HD machines (1.3% vs. 5.8%) 1 study with reduction post-isolation, but rate was already falling annually without isolation 2 studies with rate falling by about half	Moderate
Total N		2543							
Balance of Potential Benefits and Harms: Introduction of isolation associated with reduction in HCV seroconversion and HCV positivity; however, unclear if this was the primary cause of the improvement.							Quality of Overall Evidence: Very Low		

Studies included in EP: 19147995,7753458, 16903625, 16685138, 17382087, 15469615

Abbreviations: HCV = hepatitis C virus, HD = hemodialysis, nRCS = nonrandomized comparative study, RCT = randomized controlled trial.

Annotations:

* Some studies did not incorporate or report the comparability of the baseline characteristics and co-interventions between groups in the study design and/or data analysis. Some studies did not report the compliance with the interventions. Mostly based on pre-post studies, where other factors may have changed also.

† HCV seroconversion rate was higher in the non-isolation group in most studies, while was slightly higher in the NRCS. There was great heterogeneity in measures for isolation.

‡ Mostly limited to developing countries (Iran, Egypt, India, Macedonia, Saudi Arabia, Turkey; also Spain and Switzerland).

§ HCV (antibody) positive rate was consistently higher in the non-isolation group, although it might reflect the decreased prevalence in the general population in the pre-post design.

Table S18: Summary table
Transplantation vs. waitlist among patients with HCV infection
Categorical outcomes

PMID	Author	Year	Type of article	Study design	Database	Sample size	CKD stage	Kidney function	HCV+	HCV genotype	Outcome	Definition	Arm
21546575	Roth D, Gaynor JJ, Reddy R, Ciancio G, Sageshima J, Kupin W, Guerra G, Chen L, Burke GW	2011	Peer-reviewed publication	nRCS	United Network Organ Sharing	175	nd	nd	nd	nd	Patient survival	relative risk of the impact of kidney transplantation on the HR of death	KTx
													No KTx (candidates)
													KTx
													No KTx (candidates)
													KTx
													No KTx (candidates)
													KTx
													No KTx (candidates)
25340605	Scalea JR, Barth RN, Munivenkatappa R, Philosophe B, Cooper M, Whitlow V, LaMattina JC	2015	Peer-reviewed publication	nRCS	nd	1679	nd	nd	nd	nd	Graft survival	hazards ratio of multivariate analysis of variables associated with graft failure	Longer waitlist time
													Shorter waitlist time
													KTx
15636622	Bloom RD, Sayer G, Kosunarty F, Constantinescu S, Abt, Reddy KR	2005	Peer-reviewed publication	nRCS	nd	315	nd	nd	100%	nd	Patient survival	Kaplan Meier	KTx
													No KTx (candidates)
9100052	Knoll GA, Tankersley MR, Lee JY, Julian BA, Curtis JJ	1997	Peer-reviewed publication	nRCS	United Network for Organ Sharing	58	nd	nd	100%	nd	Patient survival	Kaplan Meier	KTx
													No KTx (candidates)
9573555	Pereira BJ, Natov SN, Bouthot BA, Murthy BV, Ruthazer R, Schmid CH, Levey AS	1998	Peer-reviewed publication	nRCS	New England Organ Bank	287	nd	nd	100%	nd	Patient survival	relative risk of death	KTx
													No KTx (candidates)
													KTx
													No KTx (candidates)
													KTx
													No KTx (candidates)

Table S18: Summary table
Transplantation vs. waitlist among patients with HCV infection
Categorical outcomes

PMID	Author	Year	Timepoint	Frequency/Rate	Relative effect	p-value	Adjusted for
21546575	Roth D, Gaynor JJ, Reddy R, Ciano G, Sageshima J, Kupin W, Guerra G, Chen L, Burke GW	2011	0-6 mo post-tpx	nd	2.51 (1.12, 5.66)	0.03	simultaneous panceas-kidney transplant listing, age55 years, and white race
			>6-≤84 mo post-tpx	nd	0.32 (0.17, 0.62)	0.0007	simultaneous panceas-kidney transplant listing, age55 years, and white race
			>84 mo post tpx	nd	0.74 (0.19, 2.92)	0.66	simultaneous panceas-kidney transplant listing, age55 years, and white race
			0-6 mo post-tpx	nd	26.62 (5.01, 141.3)	0.0001	simultaneous panceas-kidney transplant listing
			>6 months post -tpx	nd	1.69 (0.31, 9.14)	0.54	simultaneous panceas-kidney transplant listing
			overall post-tpx effect	nd	0.20 (0.08, 0.47)	0.0002	simultaneous panceas-kidney transplant listing, age55 years, and white race
25340605	Scalea JR, Barth RN, Munivenkatappa R, Philosophe B, Cooper M, Whitlow V, LaMattina JC	2015	7.8 years	nd	1.05 (1.01, 1.10)	0.02	DGF, Donor age, R-D-, R+D+, R+D-, Retransplant, Pretransplant, History of receipient DM, Recipient race
15636622	Bloom RD, Sayer G, Kosunarty F, Constantinescu S, Abt, Reddy KR	2005	96 months	~80%	nd	0.003	nd
				~50%			
9100052	Knoll GA, Tankersley MR, Lee JY, Julian BA, Curtis JJ	1997	48 months	~85%	nd	0.043	nd
9573555	Pereira BJ, Natov SN, Bouthot BA, Murthy BV, Ruthazer R, Schmid CH, Levey AS	1998		~70%			
			0-3 months post-tx	nd	4.75 (2.76, 8.17)	nd	nd
			4-6 months post-tx	nd	1.76 (0.75, 4.13)	nd	nd
			7-47 months post-tx	nd	0.31 (0.18, 0.54)	nd	nd
			>48 months post-tx	nd	0.84 (0.51, 1.37)	nd	nd

Table S19: Evidence profile: Transplantation vs. waitlist among patients with HCV infection

Outcome	# of Studies and Study Design	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence, including Applicability	Other Considerations	Summary of Findings		
							Quality of Evidence for Outcome	Description of Findings	Importance of Outcome
Death	4 retrospective	835	Serious limitations (-1)*	No important inconsistencies (0)	Direct (0)	None (0)	Moderate	Better long-term survival with kidney transplant	Critical
Graft loss	1 retrospective	1679	No limitations (0)	N/A	Indirect (-1)	Sparse (-1)	Low	Better graft survival with short waitlist time than long waitlist time.	Critical
Total N		2514							
Balance of Potential Benefits and Harms: Kidney transplantation results in improved patient and graft survival than remaining on the waitlist.							Quality of Overall Evidence: Moderate		

Studies included in EP: 21546575, 25340605, 15636622, 9100052, 9573555

Annotations:

* Mostly unadjusted analyses.

† Study comparison was of short vs. long waitlist time.

**Table S20: Summary table
HCV infection as predictor of
death among kidney transplant
recipients**

PMID	Author Fontaine	Year 2013	Type of article Abstract	Country France	Study design Retrospective Case Control	Registry Name Cristal database	Population KTx	Sample Size, Total 25,830	CKD stage, baseline CKD 5T	Kidney function, baseline	HCV genotypes	Follow-up Time 15 y	Predictor HCV+ HBV+ and HCV+	Predictor Definition nd coinfection	Predictor units 983	# w/Predictor or mean (95%) 76	Outcome Mortality
23400903	Soliman	2013	Peer-reviewed	Egypt	Retrospective cohort study	nd	KTx, HCV genotype 4	411	CKD 5T	nd	genotype 4 100%	8 years	HCV + HCV -	HCV Ab + one year after transplantation HCV Ab - one year after transplantation	137 274		Mortality
25098499	Xia	2014	Peer-reviewed	US	Retrospective cohort study	Donor kidney mate analysis	KTx	7036	CKD 5T			10 years max	HCV + (D-/R+) HCV - (D-/R-)		3518 3518		Mortality
	Heo	2015	Abstract	US	Retrospective cohort study	OPTN	KTx	35,557	CKD 5T			10 years max	HCV + HCV -		2024 33533		Mortality
222994610	Ridruejo	2010	Peer-reviewed	Argentina	Retrospective cohort study	none	KTx	542	CKD 5T			Long-term (unclear)	HCV + HCV -		180 362		Mortality

**Table S20: Summary table
HCV infection as predictor of
death among kidney transplant
recipients**

PMID	Author	Year	Outcome	Definition	Cases (# w/Outcome)	Rate	Adjustments (reject if none)	Metric (HR, OR, RR, beta, change)	Estimate (95% CI)	Comparison	P_value	Risk of Bias
	Fontaine	2013			64 59	nd nd	"confounding factors"	HR HR	1.8 (1.6, 2.2) 3.2 (1.9, 5.2)	vs. HCV- vs. not coinfectd	<0.0001 <0.0001	LOW
23400903	Soliman	2013	nd		43 101	31% 37%	Univariate. Excluded from multivariate model (with age, diabetes, sex, HD time, HTN, CMV, proteinuria)	HR	1.01 (0.97, 1.06) Univariate; Excluded from multivariate model.	vs. HCV -	0.5	HIGH
25098499	Xia	2014			nd nd	nd nd	recipient risk factors	HR	1.24 (1.06, 1.45)	vs HCV- (matched to donor kidney mate)	nd	LOW
	Heo	2015			nd	nd	not reported	HR	1.60 (1.40, 1.82)	vs. HCV -	nd	LOW
22994610	Ridruejo	2010			46 48	26% 13%	age >49 y, HBsAg, cadaveric donor, pancreas transplant, IS triple therapy	HR	1.64 (1.05, 2.55)	vs. HCV -	0.027	LOW

**Table S20: Summary Table
HCV infection as predictor of
graft loss among kidney
transplant recipients**

PMID	Author	Year	Type of article	Country	Study design	Registry Name	Population	Sample Size, Total	CKD stage, baseline	Kidney function, baseline	HCV genotypes	Follow-up Time	Predictor	Predictor Definition	Predictor units
	Fontaine	2013	Abstract	France	Retrospective Case Control	Cristal database	KTx	25,830				15 y	HCV+ HBV+ and HCV+		
16244496	Mitwalli	2006	Peer-reviewed	Saudi Arabia	Retrospective cohort study	nd	KTx	448	CKD 5T	nd	nd	5.85 (2.7)	HCV + HCV -	2nd and 3rd generation ELISA tests for HCV Ab, Ampiclor HCV amplification kit for HCV RNA	
26900309	Molmenti	2015	Peer-reviewed publication	US	Retrospective cohort study	UNOS	KTx	88,284	CKD 5T	nd, all received KTx	nd	nd	HCV + HCV - HCV + HCV -		
25098499	Xia	2014	Peer reviewed	US	Retrospective cohort study	Donor kidney mate analysis	KTx	7036	CKD 5T			10 years max	HCV + (D-/R+) HCV - (D-/R-)		
	Heo	2015	Abstract	US	Retrospective cohort study	OPTN	KTx	35,557	CKD 5T			10 years max	HCV + HCV -		
	Kassis	2014	Abstract	US	Retrospective cohort study	UNOS/OPTN	KTx	61,775	CKD 5T			14 years max	HCV + HCV -		
22994610	Ridruejo	2010	Peer-reviewed	Argentina	Retrospective cohort study	none	KTx	542	CKD 5T			6 months	HCV + HCV -		

**Table S20: Summary Table
HCV infection as predictor of
graft loss among kidney
transplant recipients**

PMID	Author	Year	# w/ Predictor or mean (95%)	Outcome	Outcome Definition	Cases (# w/ Outcome)	Rate	Adjustments (reject if none)	Metric (HR, OR, RR, beta, change)	Estimate (95% CI)	Comparison	P_value	Risk of Bias	
	Fontaine	2013	983	Graft loss		53	nd	"confounding factors"		HR	1.3 (1.2, 1.6)	vs. HCV-	<0.0001	LOW
			76			54	nd							
16244496	Mitwalli	2006	286	Graft failure	nd	119	41.6%	age, sex, type of donor, hypertension	HR	4.37 (1.81, 4.77)	vs. HCV -	nd	LOW	
			162			106	65.4%							
26900309	Molmenti	2015	799	graft failure (live donor recipient)	nd	nd	nd	donor age, donor BMI, donor gender, donor ethnicity, HLA mismatch level, donor preoperative creatinine, and donor hepatitis C antibodyrecipient drug-treated hypertension and Hep B SAg	HR	1.56 (1.33, 1.83)	vs. HCV-	<0.05	LOW	
			23,544	graft failure (deceased donor recipient)		nd	nd	donor age, donor BMI, donor gender, donor ethnicity, HLA mismatch level, donor terminal laboratory creatinine, donor hepatitis C antibody, donor history of diabetes, donor history of hypertension, donor cause of death, and donor cardiac arrest postbrain death, recipient drug-treated hypertension and hepatitis B surface antigen						
			4076		nd	nd	nd		HR	1.44 (1.34, 1.54)	vs. HCV-	<0.05		
			49241			nd	nd							
25098499	Xia	2014	3518	Graft loss		nd	nd	recipient risk factors	HR	1.24 (1.04, 1.47)	vs HCV- (matched to donor kidney mate)	nd	LOW	
			3518			nd	nd							
	Heo	2015	2024	Graft failure		nd	nd	not reported	HR	1.32 (1.15, 1.52)	vs. HCV -	nd	LOW	
			33533											
	Kassis	2014	3334	Graft failure		nd	nd	not reported	HR	1.34 (1.31, 1.37)	vs. HCV-	<0.001		
			58441											
22994610	Ridruejo	2010	180	Graft failure		36	20%	age >49 y, cadaveric donor, IS triple therapy	HR	2.65 (1.19, 3.23)	vs. HCV -	0.008	LOW	
			362			31	9%							

Table S21: Evidence profile: HCV infection as predictor of death and graft loss among kidney transplant recipients

Outcome	# of Studies and Study Design	Total N of Participants	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence, including Applicability	Other Considerations	Summary of Findings		
							Quality of Evidence for Outcome	Description of Findings	Importance of Outcome
Death	5 retrospective cohorts	Cohorts: 411-35,557	No limitations (0)	No important inconsistencies (0)	Direct (0)	None	High	4 of 5 studies found significant association between HCV+ status and mortality among KTx recipients (HR 1.01-1.8). The study with a nonsignificant finding was restricted to HCV genotype 4 (in Egypt). 1 study found that HCV/HBV coinfection was associated with a higher death rate (HR 3.2).	Critical
Graft Loss	7 retrospective cohorts	Cohorts: 448-61,775	No limitations (0)	No important inconsistencies (0)	Direct (0)	None	High	All 7 studies found statistically significant associations between HCV+ status and increased risk of graft loss (ES 1.3-4.37). 1 study found similarly increased risk in patients with live or deceased donor kidneys. 1 study found that HCV/HBV coinfection was associated with a higher rate of graft loss (HR 1.8).	Critical
Total N	8 retrospective cohorts	Cohorts: 411-61,775							
Association of HCV+ status and CKD: Kidney transplant recipients with HCV infection are at higher risk of death and graft loss than similar patients without HCV.							Quality of Overall Evidence: High		

Studies included in EP: 23400903, 16244496, 26900309, 25098499, 22994610, AASLD-850 2013, ATC Abstracts 2015, Kassis 2014

Abbreviations: CKD: chronic kidney disease; DAA: direct-acting antivirals; GFR: glomerular filtration rate; RCT: randomized controlled trial; SVR: sustained virological response

Table S22. Summary Table: DAA treatment in HCV-infected donor to HCV-uninfected recipient kidney transplantation

Study Year PMID ¹ (Reference)	Design (Txp Years)	N Kidney: + → - [- → -]	F/up Time	Waitlist Time ²	Time to DAA, Days	DAA Regimen (N) [Duration]	SVR12	DAA- Related SAE	Hepatic Events	Allograft Survival	Allograft GFR, mL/min/1.73 m ²	Death	DGF	Acute Rejection	QoL
<i>Prospective studies (with protocol)</i>															
Chen R 2021 34489392 China (1)	Prosp (2019-21)	26 [0]	24 wk		0 ³	SOF/VEL (n=26) [12 wk]	26/26 (100%) ITT	0/26 (0%)	0/26 (0%) ⁴	26/26 (100%)	Md 74.1 (IQR 37.0-102.4)	0/26 (0%)	6/26 (23%)	3/26 (12%)	NR
Concepcion 2021 34514116 (2)	Prosp (2018-19)	50 [50 ⁵]	180 d	NR	Md 26 (IQR 21, 37)	GLE/PIB (n=30) SOF/LDV (n=13) SOF/VEL (n=7) [12 wk]	49/50 (98% ⁶)	0/50 (0%)	0/50 (0%) [vs. 0/50 (0%)] ⁷	49/50 (98%) ⁸ [vs. 50/50 (100%)]	Mn 58.9 (16.5) [vs. 61.9 (23.5)], P=0.47	0/50 (0%) [vs. 1/50 (2%)]	2/50 (4%) [vs. 6/49 (12%)], P=0.27	5/50 (10%) [vs. 4/49 (8%)], P=1.0	NR
Daloul 2021 34169833 (3)	Prosp (2019-20)	30 [0]	Md 17 mo (IQR 12, 21)		Md 26 (IQR 20, 34)	SOF/VEL (n=24) GLE/PIB (n=5) SOF/LDV (n=1) [12 wk]	28/30 (93.3% ⁹)	0/30 (0%)	NR	30/30 (100%)	Md 46 (IQR 40, 63)	0/30 (0%)	4/30 (13%)	4/30 (13%)	NR
Durand 2018 29507971 (4)	Prosp (2015~17)	10 [0]	24 wk		0 ¹⁰	GZR/EBR (n=7), GZR/EBR/SOF ¹¹ (n=3) [12 wk]	10/10 (100%) ITT	0/10 (0%)	Acute hepatitis 1/10 (10%)	10/10 (100%)	Md 63.5 (IQR 47.8-69.9)	0/10 (0% ¹²)	4/10 (40%)	0/10 (0%)	NR
Durand 2021 32894697 (5)	Prosp (2018-19)	10 [0]	12 mo		0 ¹³	GLE/PIB (n=10) [4 wk]	10/10 (100%) ITT	0/10 (0%)	NR	9/10 (90%) ¹⁴	Md 54.5 (IQR 30-79)	0/10 (0%)	NR	1/10 (10%)	NR

¹ All conducted in the United States, except as indicated.

² For comparative studies only (+ → - vs. - → -)

³ 2 hour prior to transplantation surgery, per protocol.

⁴ Liver function stable in all.

⁵ Matched by age, gender, race, presence of diabetes, kidney donor profile index, and calculated panel-reactive antibody.

⁶ One SVR12 failure (sofosbuvir/ledipasvir) retreated with 12 wk sofosbuvir/velpatasvir/voxilaprevir with SVR12.

⁷ No cases of fibrosing cholestatic hepatitis.

⁸ One allograft loss at day 151 due to acute rejection.

⁹ One SVR12 failure (sofosbuvir/velpatasvir) who was noncompliant retreated with 12 wk sofosbuvir/velpatasvir/voxilaprevir with SVR12. One SVR12 failure (sofosbuvir/velpatasvir) with 12 wk sofosbuvir/velpatasvir/voxilaprevir/ribavirin and was found to have NS5A-Y93H mutation and is continuing treatment with ribavirin.

¹⁰ On call to operating room, per protocol.

¹¹ Added for genotypes 2 or 3.

¹² Implied.

¹³ Before organ perfusion.

¹⁴ One allograft loss at day 261 unrelated to HCV or DAA treatment.

Study Year PMID ¹ (Reference)	Design (Txp Years)	N Kidney: + → - [- → -]	F/up Time	Waitlist Time ²	Time to DAA, Days	DAA Regimen (N) [Duration]	SVR12	DAA- Related SAE	Hepatic Events	Allograft Survival	Allograft GFR, mL/min/1.73 m ²	Death	DGF	Acute Rejection	QoL
Feld 2020 32389183 Canada (6)	Prosp (2019)	10 [0]	36 wk		0 ¹⁵	GLE/PIB/ ezetimibe (n=10) [8 d]	10/10 (100%) ITT	1/10 (10%) ¹⁶	0/10 (0%) ¹⁷	10/10 (100%)	Md 74 (IQR 65- 92)	0/10 (0%)	NR	0/10 (0%) ¹⁸	NR
Gupta 2020/ 2021 34212479 / 31652392 (7, 8) vs. D-/R- ¹⁹	Prosp (2017-20)	102 [102 ²⁰]	4.5 yr [1.3 yr]	1.8 y [vs. 4.4 y] P<0.001	0 ²¹	SOF/VEL ± Ez ²² [2 d (n=10); 12 wk if viremia]	No viremia 7/10 (70%) After full course 8/10 (80%) ²³	NR	0/102 (0%) ²³	99/102 (97%) [vs. 69/71 (97%)] ²⁴	Mn 57 (SD 23) [vs. 56 (22)] ²⁵	2/102 (2%) [vs. 4/71 (6%)] ²⁶	44/102 (43%) [vs. 54/102 (53%)] ²⁷	8/102 (8%) [vs. 5/71 (7%)] ²⁸	NR
						[4 d (n=42); 12 wk if viremia]	No viremia 38/42 (90%) After full course 41/42 (98%) ²⁹								
						[7 d (n=50); 12 wk if viremia]	No viremia 48/50 (96%) After full course 50/50 (100%)								
Reese 2018 / Mazur 2019 30083748 / 30779252 (9, 10)	Prosp (2016-17)	20 [100 ³¹]	12 mo	NR	3±1 ³²	GZR/EBR (n=17) [12 wk], GZR/EBR/RBV (n=3, NSSA) [16 wk]	20/20 (100%) ITT	0/20 (0%)	0/40 (0%) ³³ [vs. NR]	20/20 (100%) [vs. NR]	Md 72.8 (IQR 58.6-74.4, N=10) [Md 57.7 (IQR 46.0-68.6) Median difference 13.6 (IQR 7.9-19.2), N=50, P<0.001]	0/20 (0%) [vs. NR]	5/20 (25%) [vs. 45/100 (45%), P=0.076]	0/20 (0%) [vs. NR]	Stable ³⁴

¹⁵ 6–12 hours before transplant.

¹⁶ Prolongation of hospital admission for transiently elevated liver enzymes (peak ALT 650 U/L on postoperative day 11 (possibly related to the therapy). No discontinuation due to adverse events.

¹⁷ Acute liver failure or fibrosing cholestatic hepatitis.

¹⁸ Implied.

¹⁹ Gupta 2021 34212479 reported the comparison of D+/R- vs. D-/R- combining patients reported in this study (7 day regimen) with patients reported in Gupta 2020 31652392 (2-4 day regimen), plus two patients (and matched controls) who had a 4 day regimen.

²⁰ Matched by multiple factors.

²¹ 6 hours prior to transplant.

²² Patient requiring full 12-week course had different DAA regimens.

²³ No abnormal liver function except transient transaminitis that resolved with DAA therapy.

²⁴ 1 year. 31 D-/R- did not yet have 1 year follow-up. P=0.71 between groups.

²⁵ 6 months. P=0.84 between regimens.

²⁶ 1 year. 31 D-/R- did not yet have 1 year follow-up. P=0.38 between groups.

²⁷ P=0.21 between regimens.

²⁸ 1 year. 31 D-/R- did not yet have 1 year follow-up. P=0.92 between groups.

²⁹ 2 patients required a second 12-week course, with cure.

³⁰ 1 patient required a second 12-week course, with cure.

³¹ Matched by Kidney Donor Profile Index (KDPI) score.

Study Year PMID ¹ (Reference)	Design (Txp Years)	N Kidney: + → - [- → -]	F/up Time	Waitlist Time ²	Time to DAA, Days	DAA Regimen (N) [Duration]	SVR12	DAA- Related SAE	Hepatic Events	Allograft Survival	Allograft GFR, mL/min/1.73 m ²	Death	DGF	Acute Rejection	QoL
Sise 2020/2021 32843477 / 35155863 (11, 12)	Prosp (2019)	30 [0]	12 mo		2-5 ³⁵	GLE/PIB (n=30) [8 wk]	30/30 (100%) ITT	0/30 (0%)	0/30 (0%) ³⁶	30/30 (100%)	Md 60 (IQR 51- 81)	2/30 (6.7%) ³⁷	7/30 (23%)	3/30 (10%)	NR
Terrault 2020 32926749 (13)	Prosp (2018-19)	11 [0]	36 wk		Md 16.5 (IQR 9.8, 24.5)	SOF/VEL (n=10) ³⁸ [12 wk]	11/11 (100%) ITT	0/10 (0%)	0/10 (0%) ³⁹	10/10 (100%) ⁴⁰	NR	0/11 (0%) ⁴¹	2/10 (20%) ⁴²	0/10 (0%) ⁴³	NR
<i>Retrospective studies</i>															
Graham 2020 32072689 (14)	Retro (2018-19)	30 [30 ⁴⁴]	6 mo	1355 d (1230) [vs. 1162 d (1027)] P=0.51	Md 9 (Rn 5- 41)	GLE/PIB (n=29) ⁴⁵ [12 wk]	30/30 (100%) ITT	0/30 (0%)	0/30 (0%) ⁴⁶ [vs. NR]	30/30 (100%) [vs. 29/20 (97%)]	Mn 55.5 (SD 18) [vs. 48.6 (SD 15), P=0.12] ⁴⁷	0/30 (0%) [vs. 0/30 (0%)]	8/30 (27%) [vs. 18/30 (60%), P=0.01]	2/30 (6.6%) [vs. 2/30 (6.6)%]	NR
Hudson 2021 34132438 (15)	Retro (2019-20)	22 [0]	12 mo		Md 41 (SD 13)	GLE/PIB (n=15), SOF/VEL (n=7) [12 wk]	22/22 (100%) ITT	0/22 (0%)	0/22 (0%) ⁴⁸	NR	NR	0/22 (0%)	NR	0/22 (0%)	NR
Jandovitz 2020 33259125 (16)	Retro (2018)	25 [0]	12 mo		Md >20 ⁴⁹	SOF/LDV (n=14), SOF/VEL (n=8), GLE/PIB (n=3) [12 wk]	24/25 (96%) ⁵⁰ ITT	NR	NR	24/25 (96%) ⁵¹	NR	NR	16/25 (64%)	NR	NR

³² Per protocol.

³³ 5 with transient minor elevated transaminase. Unclear description of the additional 20 patients.

³⁴ SF-36 stabilized higher than baseline by post-op week 16.

³⁵ Per protocol.

³⁶ No "clinically significant liver disease".

³⁷ Neither related to HCV or DAA treatment.

³⁸ 1 patient did not have viremia, not treated with DAA.

³⁹ 3 with elevated transaminases, 2 unrelated to HCV or DAA treatment; 3rd with mild increased transaminase that normalized by SVR12. 1 patient who was not treated with DAA was omitted from analysis.

⁴⁰ Implied. 1 patient who was not treated with DAA was omitted from analysis.

⁴¹ Implied.

⁴² 1 patient who was not treated with DAA was omitted from analysis.

⁴³ 1 patient who was not treated with DAA was omitted from analysis.

⁴⁴ Age-matched.

⁴⁵ Also n=1 SOF/VEL.

⁴⁶ No major liver function adverse events.

⁴⁷ Difference somewhat greater at 1 and 3 months, favoring HCV-donor.

⁴⁸ Abnormal liver function or fibrosing cholestatic hepatitis.

⁴⁹ After viremia detected (mean 7 days post-transplant) and genotype established, median 13 days (range 8-22).

⁵⁰ The 1 patient who did not achieve SVR12 was successfully retreated with sofosbuvir/velpatasvir/voxilaprevir.

⁵¹ 1 allograft loss due to renal artery aneurysm 55 days post-transplant.

Study Year PMID ¹ (Reference)	Design (Txp Years)	N Kidney: + → - [- → -]	F/up Time	Waitlist Time ²	Time to DAA, Days	DAA Regimen (N) [Duration]	SVR12	DAA- Related SAE	Hepatic Events	Allograft Survival	Allograft GFR, mL/min/1.73 m ²	Death	DGF	Acute Rejection	QoL
Kapila 2020 31659775 (17)	Retro (2018)	64 [0]	≤55 wk		Md 72 (Rn 9- 198)	GLE/PIB (n=33), SOF/LDV (n=24), No DAA (n=4) ⁵² [12 wk ⁵³]	44/45 (97.8%) ⁵⁴ Incomplete	NR	2/64 (3.1%) FCH ⁵⁵	NR	NR	1/64 (1.5%) ⁵⁶	NR	NR	NR
Molnar 2019/2021 31306549 / 33333148 (18, 19)	Retro (2018)	65 [59] ⁵⁷	12 mo	Dialysis vintage Median (IQR) 49 mo (33-69) [vs. 71 (50- 98)] P=0.006	Md 76 (IQR 68-88)	GLE/PIB (n=59), SOF/VEL (n=5) ⁵⁸ [12 wk ⁵⁹]	65/65 (100%) ITT	NR	1/65 (1.5%) [vs. NR] FCH ⁶⁰	65/65 (100%) [vs. 56/59 (95%)] ⁶¹	Mn 64 (SD 16) [Adjusted difference: -5.2 (-13.8, 3.5); P=0.2] ⁶²	1/65 (2%) [vs. 3/59 (5%), P=0.3] ⁶³	5/65 (7.7%) [vs. 7/59 (11.9%), P=0.4] ⁶⁴	3/54 (6%) [vs. 3/42 (7%), P=0.8] ⁶⁵	NR
Torabi 2021 32810315 (20)	Retro (2018-20)	52 [0]	12 mo		Md 11 (IQR 7- 17)	GLE/PIB (n=48), SOF/VEL (n=3) ⁶⁶ [12 wk]	39/39 (100%) ⁶⁷ Incomplete	NR	NR	50/52 (96.2%)	Mn 62.3 (SD ~23)	0/52 (0%)	13/52 (25%)	3/52 (5.8%)	NR

⁵² 4 (6%) did not receive DAA (3 no viremia, 1 had poor post-transplantation course); 1 treated with SOF/VEL. 2 were not accounted for.

⁵³ 1 treated for 16 weeks.

⁵⁴ Excluding 17 who had not yet reached SVR12. Including 1 who died with viremia who was not treated with DAA.

⁵⁵ With complete resolution.

⁵⁶ Died day 77 after complicated post-transplantation course. Did not receive DAA despite viremia. Cause of death unknown.

⁵⁷ Outcomes of 65 HCV-uninfected recipients of a kidney from an HCV-infected donor were compared with 59 HCV-uninfected recipients of a kidney from an HCV-uninfected kidney during the same time period (2018) .

⁵⁸ Also n=1 SOF/LDV.

⁵⁹ 5 patients treated for 16 weeks.

⁶⁰ With complete resolution.

⁶¹ Article reported allograft loss including death: 1/65 vs. 6/59, unadjusted P value 0.04.

⁶² Nominally favor D-/R-. Adjusted for recipients' age, sex, race, body mass index, calculated panel reactive antibody, comorbidities (diabetes, hypertension, peripheral vascular disease, coronary artery disease), donor optimal kidney donor profile index.

⁶³ Crude comparison (unadjusted).

⁶⁴ Crude comparison (unadjusted).

⁶⁵ Crude comparison (unadjusted). 28/124 (23%) missing (no biopsy).

⁶⁶ Also n=1 SOF/VEL/VOX.

⁶⁷ Excluding 13 who did not reach SVR12 follow-up time.

SUMMARY:

N=485 HCV + → – kidney allografts

Summary SVR12⁶⁸:

Prospective	293/299 (10 studies)	97.2% (95.1, 98.7)	[meta-analysis. I^2 = 0% (no heterogeneity)]
Retrospective	224/226 (6 studies)	98.4% (96.3, 99.6)	[meta-analysis. I^2 = 0% (no heterogeneity)]
Total	517/525 (16 studies)	97.7% (96.3, 98.8)	[meta-analysis. I^2 = 0% (no heterogeneity)]

Summary DAA SAE:

Prospective	1/196 (9 studies)	0.5% (0.1, 3.5)	[simple pooling] (likely an overestimate, SAE not reported for 100 patients)
Retrospective	0/52 (2 studies)	0% (0, 13.7)	[simple pooling] (likely an overestimate, SAE not reported for 226 patients)
Total	1/248 (11 studies)	0.4% (0.1, 2.8)	[simple pooling] (likely an overestimate, SAE not reported for 326 patients)

Summary FCH (assumes studies reporting any hepatic event included FCH):

Prospective	0/276 (8 studies)	0% (0, 2.8)	[simple pooling]
Retrospective	3/181 (4 studies)	2.1% (0.4, 4.7)	[meta-analysis. I^2 = 0% (no heterogeneity)]
Total	3/457 (12 studies)	0.7% (0.2, 2.1)	[simple pooling]

Summary allograft survival $\geq$ 1 year⁶⁹:

Prospective	188/192 (5 studies)	97.3% (94.6, 99.1)	[meta-analysis. I^2 = 0% (no heterogeneity)]
Retrospective	139/142 (3 studies)	97.8% (94.7, 99.6)	[meta-analysis. I^2 = 6% (no heterogeneity)]
Total	327/334 (8 studies)	97.6% (95.7, 98.9)	[meta-analysis. I^2 = 0% (no heterogeneity)]
vs. D-/R-	167 vs. 130 (2 studies)	OR 1.98 (0.27, 14.4)	[meta-analysis. I^2 not applicable]

Summary death $\geq$ 1 year⁷⁰:

Prospective	4/192 (5 studies)	2.9% (1.0, 5.9)	[meta-analysis. I^2 = 0% (no heterogeneity)]
Retrospective	4/303 (5 studies)	1.6% (0.5, 3.3)	[meta-analysis. I^2 = 0% (no heterogeneity)]
Total	8/495 (10 studies)	2.1% (1.0, 3.5)	[meta-analysis. I^2 = 0% (no heterogeneity)]
vs. D-/R-	167 vs. 130 (2 studies)	OR 0.32 (0.08, 1.26)	[meta-analysis. I^2 not applicable]

Summary DGF:

Prospective	74/278 (8 studies)	22.2% (12.5, 33.7), range 4.0-43%	[meta-analysis. I^2 = 75% (large heterogeneity)]
Retrospective	42/172 (4 studies)	28.3% (8.9, 53.5), range 7.7-64%	[meta-analysis. I^2 = 91% (large heterogeneity)]
Total	116/450 (12 studies)	24.2% (15.1, 34.6), range 4.0-64%	[meta-analysis. I^2 = 82% (large heterogeneity)]
vs. D-/R-	267 vs. 340 (5 studies)	OR 0.49 (0.31, 0.78)	[meta-analysis. I^2 = 12% (small heterogeneity)]

Summary acute rejection:

Prospective	24/298 (10 studies)	8.3% (5.5, 11.7)	[meta-analysis. I^2 = 0% (no heterogeneity)]
Retrospective	8/158 (4 studies)	5.2% (2.3, 9.2)	[meta-analysis. I^2 = 0% (no heterogeneity)]
Total	32/456 (14 studies)	7.2% (5.0, 9.2)	[meta-analysis. I^2 = 0% (no heterogeneity)]
vs. D-/R-	267 vs. 340 (5 studies)	OR 1.06 (0.51, 2.19)	[meta-analysis. I^2 = 0% (no heterogeneity)]

Abbreviations: +/-: HCV infected/uninfected individuals, ASN: American Society of Nephrology (conference), CI: confidence interval, D: donor, DAA: direct acting antiviral, DGF: delayed graft function, EBR: elbasvir, Ez: ezetimibe, F/up: follow-up, FCH: fibrosing cholestatic hepatitis, GFR: glomerular filtration rate, GLE: glecaprevir, GZR: grazoprevir, HCV: hepatitis C virus, IQR: interquartile range, LDV: ledipasvir, Md: median, Mn: mean, NR: not reported, NS5A: nonstructural protein 5A resistance-associated substitutions (mutation), PIB: pibrentasvir, PMID = PubMed identifier, Prosp: prospective study design, QoL: quality of life, R: recipient, RBV: ribavirin, Retro: retrospective study design, Rn: range (full), SAE: serious adverse events (related to DAAs), SD: standard deviation, SF-36: Short Form 36 item questionnaire, SOF: sofosbuvir, SVR12: sustained virologic response at 12 weeks post-treatment, Txp = transplantation, VEL: velpatasvir, VOX: voxipaprevir.

⁶⁸ Patients treated with short course DAA who became viremic and were treated with full-course DAA assessed at SVR12 after full course.

⁶⁹ Median 10 months to 4.5 years; thus, omitting Chen 2021, Concepcion 2021, Durand 2018, Feld 2020, Graham 2020, Terrault 2020.

⁷⁰ Median 10 months to 4.5 years; thus, omitting Chen 2021, Concepcion 2021, Durand 2018, Feld 2020, Graham 2020, Terrault 2020.

Table S23. Evidence Profile: DAA treatment for HCV donor-infected to HCV-uninfected recipients

Outcome	# of Studies ⁷¹	Total N of Patients on Treatment	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings			
							Certainty of Evidence for Outcome	Description of Findings		Importance of Outcome
Death, ≥~12 mo	10	495	Some limitations ⁷²	Consistent	Indirect ⁷³	None	Low	2.1% (1.0, 3.5)	High likelihood of survival to 1 year.	Critical
	2 vs. D-/R-	167 vs. 130	Some limitations ⁷⁴	Consistent	Direct	Imprecise	Very Low	OR 0.32 (0.08, 1.26)		
Allograft survival, ≥~12 mo	8	334	Some limitations ⁷⁵	Consistent	Indirect ⁷⁶	None	Low	97.6% (95.7, 98.9)	High likelihood of allograft survival to 1 year.	Critical
	2 vs. D-/R-	167 vs. 130	Some limitations ⁷⁷	Some inconsistency	Direct	Imprecise	Very Low	OR 1.98 (0.27, 14.4)		
SVR12	16	525	Some limitations ⁷⁸	Consistent	Direct	None	Moderate	97.7% (96.3, 98.8)	Very high SVR12	High
	11	248	Some limitations ⁷⁹	Consistent	Direct	None	Moderate	0.4% (0.1, 2.8)		
Serious adverse events									Low reported rate of SAE due to DAAs; likely is an overestimate	High
Fibrosing cholestatic hepatitis	12	447	Some limitations ⁸⁰	Consistent	Direct	None	Moderate	0.7% (0.2, 2.1)	Low reported rate of hepatic complications	High
Allograft GFR	12	435	No limitations	Consistent	Indirect ⁸¹	None	Moderate	Range mean/median 46-74 mL/min	Achieved eGFR mostly in CKD G2-G3a range.	High
	5 vs. D-/R-	267 vs. 341	Some limitations ⁸²	Inconsistent	Direct	None	Low	Inconsistent, but mostly no significant difference	Difference between D+/R-/ and D-/R- unclear.	
Delayed graft function	12	450	Some limitations ⁸³	Inconsistent	Indirect ⁸⁴	None	Low	24.2% (15.1, 34.6)	Estimate unclear. ~1/2 risk compared with D-/R-	Moderate
	5 vs. D-/R-	267 vs. 340	Some limitations ⁸⁵	Consistent	Direct	None	Moderate	Range 7.7-64% OR 0.49 (0.31, 0.78)		
Acute rejection	1514	456	No limitations	Consistent	Indirect ⁸⁶	None	Moderate	7.2% (5.0, 9.7)	Low reported rate	Moderate

⁷¹ Single group studies, except as noted.

⁷² Incomplete or unclear reporting.

⁷³ No comparator.

⁷⁴ Incomplete or unclear reporting.

⁷⁵ Incomplete or unclear reporting.

⁷⁶ No comparator.

⁷⁷ Unadjusted analysis.

⁷⁸ Some incomplete analyses (mostly preliminary analyses before all had reached SVR12, some missing data).

⁷⁹ Incomplete or unclear reporting.

⁸⁰ Incomplete or unclear reporting.

⁸¹ No comparator.

⁸² No or incomplete adjustment.

⁸³ Incomplete or unclear reporting.

⁸⁴ No comparator.

⁸⁵ No or incomplete adjustment.

Outcome	# of Studies ⁷¹	Total N of Patients on Treatment	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence for Outcome	Description of Findings	Importance of Outcome
	5 vs. D-/R-	236 vs. 192	Some limitations ⁸⁷	Consistent	Direct	Imprecise	Very Low	OR 1.06 (0.51, 2.19)	of acute rejection. Difference between D+/R-/ and D-/R- unclear.
Balance of Potential Benefits and Harms: Patient and allograft survival rates good with D+/R- transplantation but insufficient evidence for comparison with D-/R-. SVR rates high with DAA with low rates of serious adverse event rates. Moderate rates of delayed graft function and acute rejection and allograft GFR good, but insufficient evidence for comparison with D-/R-.							Certainty of Overall Evidence: Low		

Abbreviations: CKD: chronic kidney disease (category), D+/R-: donor HCV infected/recipient HCV uninfected, D-/R-: donor HCV uninfected/recipient HCV uninfected, DAA: direct-acting antiviral, GFR: glomerular filtration rate, HCV: hepatitis C virus, OR: odds ratio, SAE: serious adverse events, SVR12: sustained virologic response at 12 weeks post-treatment.

⁸⁶ No comparator.

⁸⁷ No or incomplete adjustment.

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Table S24. Summary Table: HCV-associated GN DAA treatment, categorical outcomes

Study, Country (Reference)	Population	Follow-Up	Treatment	Genotype	SVR12	Death	SCr Double or ESRD	Cryoglobulinemia
Affatato 2020 ERA-EDTA P0283 Italy (1)	Active cryoglobulinemic kidney disease NR by biopsy	6-48 mo	DAA, various ¹	1 83% 3 17%	NR	1/11 (9%) ² #	NR	CR 10/12 (83%) PR 1/12 (8%) Relapse after CR 3/10 (30%)
Cacoub 2019, 29857143 France, Italy, Egypt (2)	HCV-related cryoglobulinemic vasculitis (n=148), of which GN (n=25) NR by biopsy	15.3 mo	SOF/LDV n=23 SOF/DCV n=53 SOF/SIM n=18 SOF/RBV n=51 NR n=3	1 53% 2 13% 3 11% 4 19% 5 3% 6 0.7%	141/145 (97%) ³ Not ITT	4/148 (3%) ⁴	NR	All DAA (SVR12) ⁵ : CR 106/146 (73%) PR 33/146 (23%) No response 7/146 (5%) All DAA, GN (SVR12): CR NR/25 PR NR/25 No response 3/25 (12%) CR (15.3 mo), by DAA ⁶ SOF/LDV 87% adjOR 4.09 (1.19, 19.0) SOF/DCV 88% adjOR 2.28 (0.96, 5.63) SOF/SIM 72% adjOR 1.23 (0.40, 4.02) SOF/RBV 70% reference
Elnadry 2021 EASL 2021 Egypt (3)	HCV-related mixed cryoglobulinemia (n=80), of whom biopsy-proven kidney involvement (n=20)	30-36 mo	SOF/DCV±RBV 12 wk	NR	80/80 (100%) ITT	NR	NR	CR 43/80 (54%) PR 27/80 (34%)
Fayed 2022 35103020 Egypt, France, Italy (4)	HCV-related cryoglobulinemic vasculitis (n=913), of whom had kidney involvement (n=332) NR by biopsy	35 mo	DAA, various ⁷	1 10% 2 3% 3 2% 4 85% 5 1% 6 0.1%	911/913 (99.8%)	20/913 (2.2%) ⁸	NR	CR 814/888 (92%) PR 37/888 (4%) No response 31/888 (3%) Worsened 6/888 (0.7%)
Iliescu 2020 31948406 Romania (5)	HCV-related cryoglobulinemia with CKD G2 (n=13), G3 (n=39), G4 (n=3) NR by biopsy	SVR12	PrOD 12 wk	1b 100%	56/56 (100%) ITT	NR	0/56 ("significant worsening of kidney function during treatment")	CR 47/56 (84%) ⁹ PR 5/56 (9%) No response 4/56 (7%)

Study, Country (Reference)	Population	Follow-Up	Treatment	Genotype	SVR12	Death	SCr Double or ESRD	Cryoglobulinemia
Kondili 2021 34919289 Italy (6)	HCV-related cryoglobulinemic vasculitis (n=423 ¹⁰), of whom had kidney involvement by blood/urine measures (n=64)	3 yr	DAA, unspecified	NR	NR	NR	NR	End of treatment: FCR ¹¹ 51/423 (12%) CR ¹² 72/423 (17%) PR ¹³ 118/423 (28%) 12 mo post-SVR12: No response ¹⁴ 102/423 (24%) Across 3 yr ¹⁵ FCR 164/423 (39%) Relapse 18/137 ¹⁶ (13%)
Pérez de José 2021 33623683 Spain (7)	HCV-related MC ¹⁷ 65/138 (47%) by biopsy DAA 37% IFN+RBV 83% No treatment 53%	138 mo (median)	DAA, unspecified	1b 78%	98/100 (98%) ITT	4/100 (4%) HR 0.12 (0.04, 0.40)	6/100 (6%) HR 0.10 (0.04, 0.33)	NR
			IFN+RBV	1b 71%	10/23 ¹⁸ (43.5%)	9/24 (38%)	6/24 (25%)	NR
			No treatment	1b 60%	0/15 (0%)	10/15 (67%)	3/15 (20%)	NR

Abbreviations: adjOR: adjusted odds ratio, CKD G2/3/4: chronic kidney disease category G2/3/4, CR: complete remission, DAA: direct acting antiviral, DCV: daclatasvir, eGFR: estimated glomerular filtration rate, ERA-EDTA: European Renal Association – European Dialysis and Transplant Association, ESRD: end-stage renal disease, HCV: hepatitis C, HR: hazard ratio, IFN+RBV: interferon and ribavirin, LDV: ledipasvir, MC: mixed cryoglobulinemia, NR: not reported, PR: partial remission, PrOD: paritaprevir 150 mg qD/ritonavir 100 mg qD/ombitasvir 25 mg qD/dasabuvir 250 mg BID, RBV: ribavirin, SCr: serum creatinine, SIM: simeprevir, SOF: sofosbuvir, SVR12: sustained viral response 12 weeks after end of therapy (or this timepoint), wk: weeks.

¹ PrOD (n=5), SOF/DCV (n=3), SOF/SIM (n=3), No treatment (n=1; unable to omit patient from results). Durations not reported.

² 1 died at 9 months after the end of DAA of acute disease reactivation. Omits untreated patient omitted who did not die during follow-up.

³ 3 unexplained missing.

⁴ Median follow-up 15.3 months: hepatocellular carcinoma (n=2), alveolar pulmonary hemorrhage (n=1), acute respiratory failure (n=1).

⁵ 2 unexplained missing.

⁶ Adjusted for severity of vasculitis and type of mixed cryoglobulin.

⁷ Sofosbuvir 95%, Daclatasvir 50%, Simeprevir 31%, Ledipasvir 21%, Ribavirin 8%. 12 weeks 92%, 24 weeks 7%.

⁸ 11/115 (9.6%; mostly due to immunosuppression-related infections) of relapsers; 9/798 (1.1%; unrelated to vasculitis or immunosuppression) of non-relapsers.

⁹ Complete response included disappearance of purpuric lesions. All with partial response, prior to treatment had cutaneous lesions, nephrotic syndrome, paresthesia and (in 4/5) ulcerative lesions.

All with no response had nephrotic syndrome; renal function improved in all with no response.

¹⁰ Of 523 treated with DAA for cryoglobulinemic vasculitis who both achieved SVR12 and had available follow-up data.

¹¹ Full clinical response: all symptoms disappeared.

¹² Complete clinical response: all baseline clinical manifestations had improved.

¹³ Partial clinical response: improvement in at least half of the baseline symptoms.

¹⁴ No clinical response: improvement in less than half of the baseline symptoms.

¹⁵ At any time point during 3 years of follow-up.

¹⁶ 137 of 164 who achieved FCR had continuing follow-up. Relapse was transient in 6 of 9 who had subsequent follow-up and 3 of 9 had no response status after relapse.

¹⁷ Patients had HCV-related MC followed in a nephrology clinic. Implied, but not clearly stated, that all had kidney involvement, “defined by the presence of cryoglobulinaemic glomerulonephritis with a membranoproliferative pattern of injury on histological examination of kidney biopsy or by the presence of proteinuria or haematuria or an eGFR <60 mL/min/1.73 m² without an alternative cause for CKD in patients without kidney biopsy”. Across all patients, mean eGFR = 56 mL/min and mean proteinuria = 2.1 g/day.

¹⁸ Denominator based on reported percentage. One participant apparently missing.

Table S25. Summary Table: HCV-associated GN DAA treatment, continuous outcomes

Study, Country	Treatment	N	eGFR, mL/min, Mean (SD) [P Value]	Proteinuria, g/d, Mean [P Value Vs. T0]	Cryocrit, %, Mean (SD) [P Value Vs. T0]	c3, mg/dL, Mean (SD) [P Value Vs. T0]	c4, mg/dL, Mean (SD) [P Value Vs. T0]
Fayed 2022 35103020 Egypt, France, Italy (4)	DAA	913	NR	NR	NR	NR	Median [IQR] T0 8 [7-10] EOT 22 [16-26] [P NR]
Iliescu 2020 31948406 Romania (5)	PrOD	56	NR	"Decreased" (P 0.013)	NR	NR	NR
Pérez de José 2021 33623683 Spain (7)	DAA, unspecified	100	NS change	T0 2.4 EOT 1.3 [P 0.003] 138 mo* 0.9 [P <0.001]	T0 5.0 (4.4) EOT 1.7 (2.0) 138 mo* 0.7 (1.8) [P 0.001]	T0 32 (41) EOT 101 (30) [P <0.001] 138 mo* 100 (24) [P <0.001]	T0 5 (6) EOT 14 (18) [P <0.001] 138 mo* 20 (24) [P <0.001]
	IFN+RBV	34	NS change (implied)	NS change	NR	NS change	NS change
	No treatment	15	NS change (implied)	NS change (implied)	NR	NR	NR

Abbreviations: c3/4: complement component 3/4, DAA: direct acting antiviral, eGFR: estimated glomerular filtration rate, EOT: end of therapy, IFN+RBV: interferon and ribavirin, IQR: interquartile range, NR: not reported, NS: statistically nonsignificant, PrOD: Paritaprevir 150 mg qD/Ritonavir 100 mg qD/Ombitasvir 25 mg qD/Dasabuvir 250 mg BID, SD: standard deviation, T0: baseline (time 0).

* Median follow-up duration across all arms (138 months)

Table S26. Evidence Profile: Management of HCV-associated glomerulonephritis

Outcome	Treatment	# of Studies ¹⁹	Total N of Patients on Treatment	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings			
								Certainty of Evidence for Outcome	Description of Findings	Importance of Outcome	
Death, ≥12 mo	DAA, various	4	1172 (GN in 506)	Some limitations ²⁰	Consistent	Indirect (no comparator, most without GN)	None	Low	2.4% (1.6, 3.4)	Low rate. Indication of possible large effect of DAA.	Critical
	vs. No Tx	1	100 vs 15	No limitation ²¹	N/A	Direct	Sparse Very large effect	Very Low	OR 0.02 (0.005, 0.09)		
SCr double or ESRD	DAA, various	2	156	Some limitations ²²	Inconsistent	Indirect (no comparator)	None	Low	3.8% (1.7, 8.3)	Possible low rate. Indication of possible large effect of DAA.	Critical
	vs. No Tx	1	100 vs 15	No limitation ²³	N/A	Direct	Sparse Very large effect	Very Low	OR 0.06 (0.02, 0.12)		
Cryoglobulinemia, complete remission	DAA, various	6	1616 (GN in ~500)	Some limitations ²⁴	Serious inconsistency ²⁵	Indirect (no comparator, most without GN)	None	Very Low	70% (49, 88) Range 29-92%	High rate of complete remission	High
	DAA comparisons	1	146 (GN in 25)	Serious limitations ²⁶	N/A	Indirect (83% no GN)	Sparse	Very Low	adjOR (vs. SOF/RBV) SOF/LDV 4.1 (1.2, 19) SOF/DCV 2.3 (0.96, 5.6) SOF/SIM 1.2 (0.4, 4.0)		
	vs. No Tx	0							ND		
SVR12	DAA, various	5	1294 (GN in ~479)	Some limitations ²⁷	Consistent	Indirect (most without GN)	None	Low	99.0% (97.7, 99.8)	Very high SVR12	High
Serious adverse events	0								ND		High
eGFR	DAA vs. No Tx	1	100 vs. 15	Serious limitations ²⁸	N/A	Direct	Sparse, no analysis	Very Low	NS	NS change with DAA	Moderate
Proteinuria	DAA, various	2	156	Some limitations ²⁹	Consistent	Indirect (no comparator)	None		Significant decrease	Proteinuria reduced with DAA treatment	Moderate
	vs. No Tx	1	100 vs. 15	Some limitations ³⁰	N/A	Direct	Sparse, no analysis	Very Low	ND		
Cryocrit, c3, c4	DAA, various	2 (c4)	1013	Some limitations ³¹	Consistent	Indirect (no comparator, most without GN)	None	Low	Significant improvements	Measures improved with DAA treatment	Moderate
	DAA vs. No Tx	1	100 vs. 15	No limitation	N/A	Direct	Sparse, no analysis	Very Low	Significant improvements		
Balance of Potential Benefits and Harms: Very high rate of SVR12 and complete remission, with indication of large reduction in risks of death and SCr doubling or ESRD, with DAA								Certainty of Overall Evidence: Low			

Outcome	Treatment	# of Studies ¹⁹	Total N of Patients on Treatment	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
								Certainty of Evidence for Outcome	Description of Findings	Importance of Outcome
treatment. Unclear evidence regarding best DAA regimen. No direct evidence regarding adverse event rates with DAA treatment. Unclear evidence regarding intermediate markers of glomerulonephritis and cryoglobulinemia.										

Abbreviations: CKD: chronic kidney disease, CR: complete remission, DAA: direct acting antiviral, eGFR: estimated glomerular filtration rate, ERA-EDTA: ESRD: end-stage renal disease, HCV: hepatitis C, IFN+RBV: interferon and ribavirin, MC: mixed cryoglobulinemia, NR: not reported, PR: partial remission, ProD: paritaprevir 150 mg qD/ritonavir 100 mg qD/ombitasvir 25 mg qD/dasabuvir 250 mg BID, RBV: ribavirin, SCr: serum creatinine, SVR12: sustained viral response 12 weeks after end of therapy, wk: weeks

¹⁹ Single group studies, except as noted.

²⁰ Unclear, possibly incomplete reporting.

²¹ Unadjusted, but very large effect.

²² Unclear, possibly incomplete reporting.

²³ Unadjusted, but very large effect.

²⁴ Unclear, possibly incomplete reporting.

²⁵ $I^2 = 97\%$

²⁶ Unclear, possibly incomplete reporting; possibly insufficient adjustment for confounders.

²⁷ Unclear, possibly incomplete reporting.

²⁸ No actual data reported, unclear reporting.

²⁹ Unclear, possibly incomplete reporting.

³⁰ Unclear, possibly incomplete reporting.

³¹ Unclear, possibly incomplete reporting.

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