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

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SUMMARY TABLES AND EVIDENCE PROFILES

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Chapter 2: Treatment of HCV Infection in Patients with CKD

Summary Table 2.1: DAAs in CKD G4-G5 (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**		
EBR/GZR	Atsukawa 2019 30144366 Japan (2)	12 wk	Gt 1b 100%	NR	14/14 (100%) ITT	0/14 (0%)	0/14 (0%)
EBR/GZR	Bruchfeld 2017 28576451 US (3)	12 wk	Gt 1a 52%[4] Gt 1b 48%	6% (TE)	50/51 (98.0%)[5] Per protocol[6]	NR	NR
EBR/GZR	Choi 2020 31862503 US (4)	12 wk	Gt 1a 63% Gt 1b 33%	42% (ICD 9/10 code)	714/740 (96.5%) ITT	NR	NR
EBR/GZR	Cheng 2020 32499107 Taiwan (5)	12 wk	Gt 1 100%	NR	31/31 (100%) mITT[7]	NR	NR
EBR/GZR	Jang 2020 32539296 S Korea (6)	12 wk	Gt 1 100%	NR	21/21 (100%) ITT	NR	NR

[1] Pooled.

[2] Pooled, unless otherwise noted.

[3] Not fully clear that all were non-dialysis.

[4] Includes dialysis patients.

[5] 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.

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

[7] Patients who received at least 4 weeks of treatment.

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]
EBR/GZR Summary					**96.7% (95.4, 97.8)[8] 830/857 mostly ITT**	**0% (0, 39) 0/14**	**0% (0, 39) 0/14**
GLE/PIB	Atsukawa 2019 30873651 Japan (2)	8 wk (65%)[9]	Gt 1b 20% Gt 2 46% Gt 3 19%[10]	NR	32/32 (100%) ITT	0/32 (0%)	2/32 (6.3%)
GLE/PIB	Nozaki 2020 32128704 Japan (7)	8 wk (most)[11]	NR	NR	63/65 (96.9%) ITT	NR	NR
GLE/PIB Summary					**97.9% (92.1, 99.5)[12] 95/97 ITT**	**0% (0, 21) 0/32**	**6.3% (1.6, 22) 2/32**
PrO±RBV	Elmowafy 2020 33111161 Egypt (8)	12 wk	NR	0% (TE)	SVR 24 39/50 (78.0%) ITT	NR	NR
PrOD	Iliescu 2020 31948406 Romania (9)	12 wk	Gt 1b 100%	NR	18/18 (100%) ITT	0/18 (0%)	0/18 (0%)
PrO/RBV	Mekky 2019 30166253 Egypt (10)	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)[13] 89/103 all ITT**	**0% (0, 13) 0/53**	**0% (0, 13) 0/53**

[8] 5 studies. I^2 0% (no heterogeneity)

[9] 12 weeks if cirrhosis, genotype 3, or prior DAA treatment failure.

[10] Mixed genotypes 1/141; 20/141 not tested.

[11] 12 weeks if cirrhosis, genotype 3, or prior DAA treatment failure (numbers not reported)

[12] 2 studies. Pooled.

[13] REML. I^2 70% (large heterogeneity). Combination of SVR12 and SVR24.

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/RBV (200)	Lawitz 2020 32531259 US, New Zealand (11)	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)	Manoj 2018 29676846 India (12)	24 wk	Gt 1a 65%[14] Gt 1b 4% Gt 3a 27% Gt 3b 4%	15%[15] (clinical definition)	21/21 (100%) ITT	0/21 (0%)	0/21 (0%)
SOF/RBV (400)	Lawitz 2020 32531259 US, New Zealand (11)	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 Summary					**71.7% (29.1, 98.6)[16] 31/41 all ITT**	**0% (0, 17) 0/41**	**11% (1.2, 28)[17] 4/41**
SOF/DCV (200)	Taneja 2018 29484572 India (13)	12 wk (most)[18]	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 2020 33097949 India (14)	8 wk	Gt 1 22% Gt 3 37% Gt 4 7%[19]	NR	25/27 (92.6%) ITT	0/27 (0%)	NR
SOF/DCV (400)	Manoj 2018 29676846 India (12)	12 wk	Gt 3 100%	37%[20] (clinical definition)	14/14 (100%) ITT	0/14 (0%)	0/14 (0%)

[14] Includes 5 on HD.

[15] Includes 5 on HD.

[16] 3 studies. REML. I^2 87% (large heterogeneity).

[17] REML. I^2 51% (moderate heterogeneity).

[18] 24 weeks if genotype 3 and cirrhosis (number not reported).

[19] Not tested 33%.

[20] Includes 5 on HD.

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 ±RBV (200)	Eletreby 2020 31858694 Egypt (15)	NR	NR	18.5% (Child B, implied)[21]	506/519 (97.5%) ITT	NR	NR
SOF/DCV Summary					**97.1% (95.7, 98.3)[22] all ITT**	**0% (0, 14) 0/52**	**0% (0, 25) 0/25**
SOF/LDV (400)	Manoj 2018 29676846 India (12)	12 wk	Gt 1 100%	23%[23] (clinical definition)	25/25 (100%) ITT	0/25 (0%)	0/25 (0%)
SOF/LDV (400)	Lawitz 2020 32531259 US, New Zealand (11)	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)[24] 43/43 all ITT**	**0% (0, 16)[25] 0/43**	**0% (0, 16)[26] 0/43**
SOF/SIM (200)	Eletreby 2020 31858694 Egypt (15)	NR	NR	18.5% (Child B, implied)[27]	38/41 (92.7%) ITT	NR	NR
SOF/SIM Summary					**92.7% (79.6, 97.6) all ITT**		
SOF/VEL (400)	Liu 2021 33408122 Taiwan (16)	12 wk	Gt 1a 3%[28] Gt 1b 55% Gt 2 33% Gt 6 4%	14% (TE), 5% (Child B,C)[29]	70/74 (94.6%) ITT	0/74 (0%)	0/74 (0%)

[21] Across all DAAs.

[22] 4 studies. REML. I^2 0% (no heterogeneity).

[23] Includes 1 on HD.

[24] 2 studies. Pooled.

[25] 2 studies. Pooled.

[26] 2 studies. Pooled.

[27] Across all DAAs.

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/VEL Summary					**94.6% (86.5, 98.0) 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, wk: weeks.

[28] Across both dialysis and non-dialysis populations (n=191)
[29] Across both dialysis and non-dialysis populations (n=191)

Summary Table 2.2: 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 2020[30] 31821716 Multiple[31] (17)	8 wk (83%)[32]	Gt 1 55%[33] Gt 2 27% Gt 3 15% Gt 4 4%	14%[34] (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[35])	Said 2019[36] 30791838 Egypt (18)	12 wk	Gt 4 100%	NR	NR	At SVR4: Chg median 3, P=0.48 [22]
PrO±D±RBV	Muñoz-Gómez 2017[37] 27976490 Spain (19)	12 wk (most)[38]	NR	NR	At SVR12: Incident dialysis 0/12	At EOT: Chg median −1, NS [21]

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

[31] Canada, Germany, Greece, Italy, Poland, South Korea, Spain, Sweden, US.

[32] 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-naive/noncirrhotic. Percentages include n=7 with CKD 3b.

[33] Including CKD 3b (n=7).

[34] Including CKD 3b (n=7).

[35] PrO dosages.

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

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

[38] 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 2020 32531259 US, New Zealand (11)	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[39] [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[40] [26.2]
SOF/DCV (200)	Taneja 2018 29484572 India (13)	12 wk (most)[41]	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 2020 32531259 US, New Zealand (11)	12 wk	Gt 1a 78% Gt 1b 22%	11% (not defined)	NR	At SVR12: −1.0 (−3.5, 1.5), P=0.43[42] [24.9]
SOF/VEL (400)	Liu 2021 33408122 Taiwan (16)	12 wk	Gt 1a 3%[43] Gt 1b 55% Gt 2 33% Gt 6 4%	14% (TE), 5% (Child B,C)[44]	NR	CKD G4: 1.6 (−0.1, 3.3), P=0.06 CKD G5ND: −0.3 (−1.6, 1.0), P=0.65

[39] Estimated.

[40] Estimated

[41] 24 weeks if genotype 3 and cirrhosis (number not reported).

[42] Estimated.

[43] Across both dialysis and non-dialysis populations (n=191)

[44] 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[45]	D'Ambrosio 2020 31813755 Italy (20)	12 wk (52%)[46]	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, wk: weeks.

[45] 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%).

[46] Implied that the remainder had <12 weeks treatment

Evidence Profile A: Chapter 2. 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			
								Quality 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
	EBR/GZR	5	857	No limitations	Consistent	Direct	None	High	96.7% (95.4, 97.8)		
	GLE/PIB	2	97	No limitations	Consistent	Direct	None	High	97.9% (92.1, 99.5)		
	PrO±D	3	103	No limitations	Inconsistent	Direct	None	Low	89.4% (75.7, 97.8)		
	SOF	3	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	1	74	No limitations	N/A	Direct	Sparse	Very Low	94.6% (86.5, 98.0)		
Serious AE due to DAA	DCV/ASV	0							ND	Rare, but insufficient evidence. No evidence of differences among regimens.	High
	EBR/GZR	1	14	Serious limitations[3]	N/A	Direct	Sparse	Very Low	0% (0, 39)		
	GLE/PIB	1	32	Some limitations[4]	N/A	Direct	Sparse	Very Low	0% (0, 21)		
	PrO±D	2	53	Some 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	3	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
	EBR/GZR	1	14	Serious limitations[7]	N/A	Direct	Sparse	Very Low	0 (0, 39)		
	GLE/PIB	1	32	Some limitations[8]	N/A	Direct	Sparse	Very Low	6.3% (1.6, 22)		
	PrO±D	2	53	Some limitations[9]	Consistent	Direct	Imprecise	Very Low	0% (0, 13)		
	SOF	3	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			
								Quality of Evidence for Outcome	Description of Findings		Importance of Outcome
Change in CKD category	DCV/ASV	0							ND	Insufficient evidence	High
	EBR/GZR	0							ND		
	GLE/PIB	1	17	No limitations	N/A	Direct	Sparse	Very Low	Variable		
	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	High
	EBR/GZR	0							ND		
	GLE/PIB	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 SVR 12 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.								**Quality 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 (many studies did not report outcome).

[4] Reporting bias (larger study 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 (many studies did not report outcome).

[8] Reporting bias (larger study 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.

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Chapter 2: Treatment of HCV Infection in Patients with CKD

Summary Table 2.3: DAAs in CKD G5D (dialysis[1]) 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] *Transfusion*[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] *Transfusion*[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) 1/274[11]**	**3.8% (2.0, 6.0) 13/341[12]**
EBR/GZR	Atsukawa 2017 28457003 Japan (10)	12 wk	Gt 1b 100%	32% (imaging)	30/31 (96.8%) ITT	1/31 (3.2%)	1/31 (3.2%)
EBR/GZR	Bayu 2020 APASL 360 Indonesia (11)	12 wk	NR	NR	37/38 (97%) ITT	NR	NR
EBR/GZR	Bruchfeld 2017 28576451 US (12)	12 wk	NR	NR	162/164 (98.8%)[13] Per protocol[14]	NR	NR
EBR/GZR	Choi 2020 31862503 US (13)	12 wk	Gt 1a 63%[15] Gt 1b 33%	42% (ICD-9/10 code)[16]	541/563 (96.1%) ITT	NR	NR

[10] 9 studies. I^2 40% (moderate heterogeneity).

[11] 8 studies.

[12] 9 studies. I^2 0% (no heterogeneity).

[13] 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.

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

[15] Including CKD 4-5ND population.

[16] Including CKD 4-5ND population.

Regimen[2]	**Study, PMID Country (Reference)**	**Treatment Duration**	**Genotype**	**Liver Cirrhosis (Definition)**	**SVR12**[3]	**DAA-Related Serious AE**[4] ***Transfusion***[5]	**D/C DAA Due to AE**[6]
EBR/GZR	Liu 2020 32513953 Taiwan (14)	12 wk	Gt 1b 100%	10% (TE)	38/40 (95%) ITT	0/40 (0%)	1/40 (2.5%)
EBR/GZR	Ogawa 2018 30300717 Japan (15)	12 wk	Gt 1 100%	NR	19/21 (90.5%) ITT	NR	NR
EBR/GZR±RBV	Stein 2020[17] 32956186 Germany (16)	12 wk (98%)[18]	Gt 1a 23%[19] Gt 1b 72% Gt 4 5%	14% (TE, imaging, or clinical) [20]	39/42 (92.9%) Unclear[21]	0/45 (0%)	0/45 (0%)
EBR/GZR	Suda 2019 30019127 Japan (17)	12 wk	Gt 1b 100%	31% (TE)	22/23 (95.7%) ITT	0/23 (0%)	0/23 (0%)
EBR/GZR	Suryamin 2020 APASL 1182 Indonesia (18)	12 wk	NR	NR	14/14 (100%) ITT	NR	NR
EBR/GZR Summary					**96.5% (94.8, 97.9)**[22] **902/936** **mostly ITT**	**0.7% (0.1, 5.0)** **1/136**[23]	**2.0% (0.4, 50)** **2/136**[24]
GLE/PIB	Atsukawa 2019 30873651 Japan (19)	8 wk (65%)[25]	Gt 1b 20%[26] Gt 2 46% Gt 3 19% Mixed 1% Unknown 14%	29% (serum markers ± imaging)[27]	99/100 (100%) ITT	0/100 (0%)	1/100 (1%)

[17] Includes patients on peritoneal dialysis (number not reported).

[18] 16 weeks (n=2), reason not reported

[19] Include CKD 4-5ND (n=15).

[20] Include CKD 4-5ND (n=15).

[21] 3/70 omitted from intention-to-treat analysis, but not acknowledged or accounted for.

[22] 9 studies. I^2 17% (small heterogeneity).

[23] 4 studies.

[24] 4 studies. I^2 0% (no heterogeneity).

Regimen[2]	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12[3]	DAA-Related Serious AE[4] *Transfusion*[5]	D/C DAA Due to AE[6]
GLE/PIB	Lawitz 2020 31821716 Multiple[28] (20)	8 wk (~83%)[29]	Gt 1 55%[30] Gt 2 27% Gt 3 15% Gt 4 4%	14% (TE)[31]	NR	0/77 (0%)	NR
GLE/PIB	Morishita 2020 31883211 Japan (21)	8 wk (62%)[32]	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 (22)	8 wk (most)[33]	NR	NR	125/132 (94.7%) ITT	NR	NR
GLE/PIB	Ogawa 2019 30849206 Japan (23)	8 or 12 wk[34]	Gt 1 or 2 100%	NR	23/23 (100%) ITT	NR	0/23 (0%)
GLE/PIB	Persico 2019 Gastro Hep Italy (24)	8 (58%) or 12 wk (42%)[35]	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%)

[25] 12 weeks (n=35) if cirrhosis, genotype 3, or prior DAA treatment failure.

[26] Including n=9 CKD 5ND.

[27] Including n=9 CKD 5ND.

[28] Canada, Germany, Greece, Italy, Poland, South Korea, Spain, Sweden, US.

[29] 12 weeks (~13%) if cirrhotic except genotype 3, 16 weeks (~4%) if genotype 3 except treatment-naive/noncirrhotic. Percentages include n=7 with CKD 3b.

[30] Including CKD 4-5ND.

[31] Including CKD 4-5ND.

[32] 12 weeks if cirrhosis or prior DAA treatment failure (n=9)

[33] 12 weeks if cirrhosis, genotype 3, or prior DAA treatment failure (numbers not reported)

[34] No further details.

[35] Reasons for different durations not reported.

Regimen[2]	**Study, PMID Country (Reference)**	**Treatment Duration**	**Genotype**	**Liver Cirrhosis (Definition)**	**SVR12**[3]	**DAA-Related Serious AE**[4] ***Transfusion***[5]	**D/C DAA Due to AE**[6]
GLE/PIB	Stein 2020[36] 32956186 Germany (16)	8 wk (85%)[37]	Gt 1a 15%[38] Gt 1b 27% Gt 1 undefined 3% Gt 2 9% Gt 3 36% Gt 4 6%	12% (TE, imaging, or clinical)[39]	21/23 (91.3%) Unclear[40]	0/25 (0%)	0/25 (0%)
GLE/PIB	Suda 2019 30778716 Japan (25)	8 (52%) or 12 wk (48%)[41]	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 (26)	8 wk (68%)[42]	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 Summary					**96.7% (94.5, 98.4)**[43] **395/409 mostly ITT**	**0.6% (0.2, 2.4) 2/333**[44]	**1.9% (0.6, 3.8) 4/279**[45]
PrOD±RBV	Abad 2017 28166520 Spain (27)	12 wk (most)[46]	Gt 1a 29% Gt 1b 71%	21% (NR)[47]	31/31 (100%) ITT	0/31 (0%) *Transfusion 0/31 (0%), no RBV*	0/31 (0%)

[36] Includes patients on peritoneal dialysis (number not reported).

[37] 12 weeks (n=2), 16 weeks (n=1), reasons not reported.

[38] Include CKD 4-ND (n=8).

[39] Include CKD 4-ND (n=8).

[40] 3/70 omitted from intention-to-treat analysis, but not acknowledged or accounted for.

[41] 12 week if cirrhosis or failed to respond to previous DAA treatment

[42] 12 weeks (n=14) if cirrhosis.

[43] 8 studies. I^2 14% (small heterogeneity).

[44] 7 studies.

[45] 7 studies. I^2 0% (no heterogeneity).

[46] 24 wk if genotype 1a or cirrhosis (numbers not reported).

Regimen[2]	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12[3]	DAA-Related Serious AE[4] *Transfusion*[5]	D/C DAA Due to AE[6]
PrO±RBV	Elmowafy 2021 33111161 Egypt (28)	12 wk	Gt 1a 8% Gt 4 92%	2% (imaging), 0 (TE)	40/40[48] (100%) ITT	NR	0/40 (0%)
PrOD±RBV[49]	Etik 2019 30719954 Turkey (29)	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 (30)	12 wk	Gt 1b 100%	17% (TE)	48/48 (100%) ITT	0/48 (0%)	0/48 (0%)
PrOD	Liu 2019 30931537 Taiwan (31)	12 wk	Gt 1b 100%	0% (biopsy or TE)	46/46 (100%) ITT	0/46 (0%)	0/46 (0%)
PrO±D±RBV	Londoño 2019[50] 31550267 Spain (32)	12 or 24 wk[51]	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 (33)	12 wk	NR	NR	SVR36 36/36 (100%) Per protocol	NR Transfusion 6/53 (11%), on RBV	NR
PrO/RBV	Mekky 2019 30166253 Egypt (34)	12 wk	Gt 4 100%	11% (TE)	72/75 (96%) ITT	0/75 (0%)	0/75 (0%)
PrO	Morisawa 2017 28621007 Japan (35)	12 wk	Gt 1b 100%	NR	8/10 (80%) ITT	0/10 (0%)	2/10 (20%)

[47] Including n=4 on other treatment (genotype 4).

[48] SVR24 = 38/40 (95%)

[49] N=1 on SOF/LDV.

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

[51] Per "SmPC" indications (not defined). Numbers not reported.

Regimen[2]	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12[3]	DAA-Related Serious AE[4] *Transfusion*[5]	D/C DAA Due to AE[6]
PrOD±RBV	Pockros 2016 26976799 US (36)	12 wk	Gt 1 65%[52] Gt 1b 35%	0% (biopsy, TE, serum markers)	12/14 (85.7%)[53] ITT	0/14 (0%) *Transfusion 0/14 (0%), ~10 on RBV*	0/14 (0%)
PrOD	Ponziani 2017 28258770 Italy (37)	12 wk	Gt 1a 10% Gt 1b 80% Gt 4 10%	70% (TE)[54]	10/10 (100%) ITT	1/10 (10%)	0/10 (0%)
PrO±D±RBV	Sanai 2018 29288514 Saudi Arabia, Canada (38)	12 wk (96%)[55]	Gt 1a 37% Gt 1b 13% Gt 1 unknown 3% Gt 4 48%	21% (TE)	65/67 (97.0%)[56] ITT	0/67 (0%) *Transfusion* 3/54 (5.6%), on RBV[57]	2/67 (2.9%)
PrOD±RBV	Sperl 2018 29669332 Czech Republic (39)	12 wk	Gt 1a 9%[58] Gt 1b 87% Unknown 4%	26% (NR)[59]	19/19 (100%) ITT	0/19 (0%) *Transfusion 0/19 (0%), ~6 on RBV*	0/19 (0%)
PrOD±RBV	Tatar 2019 31994628 Turkey (40)	12 wk	Gt 1a 45% Gt 1b 39% Gt 1 undefined 15%	NR	33/33 (100%) Per protocol[60]	0/33 (0%)	0/33 (0%)
PrOD±RBV	Torun 2019 30762283 Turkey (41)	12 wk	Gt 1a 30% Gt 1b 70%	0% (NR)	10/10 (100%) ITT	0/10 (0%)	0/10 (0%)

[52] Includes 6 with CKD 4.

[53] 1 SVR 12 failure had relatively low adherence, 1 died unrelated to HCV. Unclear if all truly on dialysis.

[54] 30% with F3.

[55] 24 weeks (4%), reasons not reported.

[56] Includes n=2 with CKD 4-5ND

[57] 0/13 without RBV.

[58] Includes n=4 with CKD 4.

[59] Includes n=4 with CKD 4.

[60] 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] *Transfusion*[5]	D/C DAA Due to AE[6]
PrOD±RBV	Yaraş 2019 30666967 Turkey (42)	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)[61] 565/582 mostly ITT**	**0.2% (0.03, 1.7) 1/406[62]**	**1.8% (0.8, 3.3) 4/446[63]**
SOF[64]/RBV	Agarwal 2017 29270489 India (43)	12 wk	Gt 1 65%[65] Gt 2 2% Gt 3 29% Gt 4 3% Gt 6 2%	0% (endoscopy)	39/41 (95.1%) ITT	0/41 (0%) *Transfusion* 3/41 (7.3%) *on RBV*	0/41 (0%)
SOF/RBV	Akhil 2018 28339162 India (44)	12 wk	Gt 1 64% Gt 3 27% Gt 4 9%	NR	16/22 (72.7%)[66] ITT	0/22 (0%) *Transfusion* 0/22 (0%), *on RBV*	0/22 (0%)
SOF/RBV/IFN	Mandhwani 2020 32308935 Pakistan (45)	12 wk	Gt 1 50%[67] Gt 2 1% Gt 3 43% Gt 4 1% Mixed Gt 5%	0% (clinical, imaging)	59/60 (98.3%) ITT	NR *Transfusion* 20/60 (33%) *on RBV*	0/60 (0%)
SOF/RBV Summary					**91.9% (74.5, 99.8)[68] 114/123 all ITT**	**0% (0, 11.5) 0/63[69]**	**0% (0, 6.2) 0/123[70]**

[61] 16 studies. I^2 4% (small heterogeneity).

[62] 13 studies.

[63] 14 studies. I^2 0% (no heterogeneity).

[64] 400 mg every other day n=39/41.

[65] Across interventions.

[66] Includes 2 lost to follow-up pre-SVR12

[67] Across interventions.

[68] 3 studies. I^2 85% (large heterogeneity).

[69] 2 studies.

Regimen[2]	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12[3]	DAA-Related Serious AE[4] *Transfusion*[5]	D/C DAA Due to AE[6]
SOF (QOD[71])/DCV	Agarwal 2017 29270489 India (43)	12 wk	Gt 1 65%[72] 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%) *Transfusion 0/21 (0%), no RBV*
SOF/DCV	Butt 2019 31720170 Pakistan (46)	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 (47)	12 wk (most)[73]	Gt 1b 100%	22% (Various[74])	15/18 (83.3%)[75] ITT	NR	0/18 (0%)
SOF (400 TIW)/DCV					17/18 (94.4%)[76] ITT	NR	1/18 (5.6%)
SOF/DCV/RBV	Mandhwani 2020 32308935 Pakistan (45)	12 wk	Gt 1 50%[77] Gt 2 1% Gt 3 43% Gt 4 1% Mixed Gt 5%	0% (clinical, imaging)	70/73 (95.9%) ITT	NR *Transfusion* 11/73 (15%), on RBV	0/73 (0%)
SOF/DCV	Mehta 2018 29430587 India (48)	12 wk	Gt 1a 54% Gt 1b 46%	NR	12/13 (92.3%) ITT	NR	0/13 (0%)

[70] Pooled. 2 studies.

[71] 400 mg every other day in n=6/21

[72] Across interventions.

[73] 24 weeks if cirrhosis (numbers not reported).

[74] Based on Child-Pugh score and abdominal imaging, TE, and esophagogastroduodenoscopy.

[75] SVR 24 15/18 (83.3%)

[76] SVR 24 14/18 (77.%)

[77] Across interventions.

Regimen[2]	**Study, PMID Country (Reference)**	**Treatment Duration**	**Genotype**	**Liver Cirrhosis (Definition)**	**SVR12**[3]	**DAA-Related Serious AE**[4] ***Transfusion***[5]	**D/C DAA Due to AE**[6]
SOF (400 QOD)/DCV					9/13 (69.2%) ITT	NR	0/13 (0%)
SOF/DCV	Singh 2018 30113115 India (49)	12 wk (most)[78]	Gt 3 100%	26%[79] (TE)[80]	~11/~11 (100%)[81] ITT estimated	0/~11 (0%)[82]	0/~11 (0%)[83]
SOF (200 qD)/DCV	Taneja 2018 29484572 India (50)	12 wk (most)[84]	Gt 1 65% Gt 2 1% Gt 3 34%	32% (TE)[85]	54/54 (100%) ITT	0/54 (0%)	0/54 (0%)
SOF/DCV Summary					**92.9% (87.3, 96.9)**[86] **237/252 all ITT**	**0% (0, 8.6) 0/86**[87]	**0.5% (0.1, 3.1) 1/221**[88]

[78] 24 weeks if cirrhosis (number not reported).

[79] Includes n=8 CKD 4-5ND.

[80] 15% decompensated.

[81] 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.

[82] 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.

[83] 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.

[84] 24 weeks if genotype 3 and cirrhosis (number not reported).

[85] 9% decompensated.

[86] 7 studies (9 cohorts). I^2 50% (moderate heterogeneity).

[87] 3 studies.

[88] Pooled. 8 studies.

Regimen[2]	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12[3]	DAA-Related Serious AE[4] *Transfusion*[5]	D/C DAA Due to AE[6]
SOF (NR)/LDV	Asanbek kyzy 2019 SP641 Kyrgyzstan (51)	12 wk	NR	NR	SVR 24: 11/11 (100%) ITT	0/11 (0%)	0/11 (0%)
SOF/LDV	Chuang 2021[89] 34465694 Multiple[90] (52)	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 (53)	12 wk	Gt 1 92%[91] Gt 5 8%	0% (TE)	13/13 (100%) Per protocol[92]	0/13 (0%) *Transfusion* 0/13 (0%), *No RBV*	0/13 (0%)
SOF/LDV	Gohel 2020 32507712 India (54)	12 wk	Gt 1 93%[93] Gt 3 7%	0% (NR)	40/40 (100%) ITT	0/40 (0%)	0/40 (0%)
SOF/LDV	Mehta 2018 29430587 India (48)	12 wk	Gt 1a 17% Gt 1b 83%	NR	12/12 (100%) ITT	NR	0/12 (0%)
SOF/LDV	Singh 2018 30113115 India (49)	12 wk (most)[94]	Gt 1 94% Gt 4 6%	26%[95] (TE)[96]	~28/~28 (100%)[97] ITT estimated	0/~28 (0%)[98]	0/~28 (0%)[99]

[89] 8/95 on peritoneal dialysis (n=1 8 weeks, n=3 12 weeks, n=4 24 weeks).

[90] Belgium, Germany, Italy, Taiwan, United States

[91] Including n=5 on other regimens.

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

[93] 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] *Transfusion*[5]	D/C DAA Due to AE[6]
SOF (QOD)/LDV	Surendra 2018 28972699 India (55)	12 wk	Gt 1a 63% Gt 1b 37%	0% (TE)	19/21 (90.5%)[100] ITT	0/21 (0%) *Transfusion 0/21 (0%), no RBV*	0/21 (0%)
SOF/LDV Summary					**95.9% (92.8, 98.1)[101] 212/220 mostly ITT**	**0% (0, 3.7) 0/208[102]**	**0% (0, 3.5) 0/220[103]**
SOF (200 qD)/SIM	Bhamidimarri 2015[104] 26095179 US (56)	12 wk[105]	Gt 1a 67% Gt 1b 33%	60% (biopsy)[106]	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)**

[94] 24 weeks if cirrhosis (number not reported).

[95] Includes n=8 CKD 4-5ND.

[96] 15% decompensated.

[97] 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.

[98] 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.

[99] 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.

[100] 2 died pre-SVR12 due to inadequate hemodialysis

[101] 7 studies (1 with 3 arms). I^2 5% (small heterogeneity).

[102] 6 studies (1 with 3 arms).

[103] Pooled. 7 studies (1 with 3 arms).

[104] N=1 on peritoneal dialysis.

[105] 24 wk if cirrhosis (n=1)

[106] Including n=3 CKD 5ND.

Regimen[2]	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12[3]	DAA-Related Serious AE[4] *Transfusion*[5]	D/C DAA Due to AE[6]
SOF/VEL	Borgia 2019[107] 31195062 Multiple[108] (57)	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	Gaur 2020 32405174 India (58)	NR	Gt 1 68% Gt 3 32%	10% (TE)	30/31 (96.8%) ITT	0/31 (0%) *Transfusion* 2/31 (6.5%) *no RBV*	0/31 (0%)
SOF/VEL	Liu 2021[109] 33408122 Taiwan (59)	12 wk	Gt 1a 3%[110] Gt 1b 55% Gt 2 33% Gt 6 4%	14% (TE), 5% (Child B,C)[111]	111/117 (94.9%) ITT	0/117 (0%)	0/117 (0%)
SOF/VEL	Taneja 2020 33025685 India (60)	12 wk	Gt 1 79% Gt 3 15% Gt 4 5%	20% (TE)[112]	49/51 (96.1%) ITT	0/51 (0%)	0/51 (0%)
SOF (NR)/VEL	Yu M-L 2020 AASLD 911 Taiwan (61)	12 wk	NR	NR	132/147 (89.8%) ITT	0/147 (0%)	NR
SOF/VEL Summary					**93.9% (90.8, 96.4)[113] 378/405 all ITT**	**0% (0, 1.9) 0/405[114]**	**0% (0, 3.2) 0/240[115]**

[107] N=5 (8%) on peritoneal dialysis.

[108] Canada, UK, Spain, Israel, New Zealand, Australia.

[109] 3/117 on peritoneal dialysis.

[110] Across both D and ND populations (n=191)

[111] Across both D and ND populations (n=191)

[112] n=1 decompensated.

[113] 5 studies. I^2 27% (small to moderate heterogeneity).

[114] 5 studies.

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, PD: peritoneal dialysis, 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.

[115] Pooled. 4 studies.

Summary Table 2.4: DAAs in CKD G5D (dialysis[116]) population, part 2 (Death)[117]

Regimen[118]	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	Follow-Up	Death[119] % (95% CI)
GLE/PIB	Persico 2019 Gastro Hep Italy (24)	8 (58%) or 12 wk (42%)[120]	Gt 1a 11% Gt 1b 31% Gt 2 36% Gt 3 19% Gt 4 3%	28% (TE)	1 yr	1/36[121] 2.8% (0.4, 17)
PrOD	Liu 2019 30931537 Taiwan (31)	12 wk	Gt 1b 100%	0% (biopsy or TE)	SVR24	0/46 0% (0, 15)
PrOD±RBV	Pockros 2016 26976799 US (36)	12 wk	Gt 1 65%[122] Gt 1b 35%	0% (biopsy, TE, serum markers)	SVR24	1/14[123] 7.1% (1.0, 37)
SOF/DCV	Butt 2019 31720170 Pakistan (46)	12 wk	Gt 1 32% Gt 3 68%	0% (clinical, history, and serum markers)	1 yr	2/31[124] 6.4% (1.6, 22)

[116] 100% hemodialysis populations, unless otherwise noted (for peritoneal dialysis).

[117] 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).

[118] Sofosbuvir doses all were 400 mg daily. All other regimens used standard doses.

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

[120] Reasons for different durations not reported.

[121] Car accident.

[122] Includes 6 with CKD 4.

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

[124] Both due to "natural progression of ESRD."

Regimen[118]	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	Follow-Up	Death[119] % (95% CI)
SOF/VEL	Borgia 2019[125] 31195062 Multiple[126] (57)	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)	≥SVR16	2/59[127] 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, PD: peritoneal dialysis, 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.

[125] N=5 (8%) on peritoneal dialysis.

[126] Canada, UK, Spain, Israel, New Zealand, Australia.

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

Summary Table 2.5: DAAs in CKD G5D (dialysis) population, part 3 (Quality of Life)

Regimen[128]	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	Follow-Up	Quality of Life
GLE/PIB	Lawitz 2020 31821716 Multiple[129] (20)	8 wk (~83%)[130]	Gt 1 55%[131] Gt 2 27% Gt 3 15% Gt 4 4%	14% (TE)[132]	1 yr	"Clinical meaningful improvement": SF-12 PCS: 27/77 (35.1%) SF-12 MCS: 29/77 (37.8%)

Abbreviations. CKD 4-5ND: chronic kidney disease category 4 or 5-nondialysis, DAA: direct acting antivirals, 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.

[128] Regimens used standard doses.

[129] Canada, Germany, Greece, Italy, Poland, South Korea, Spain, Sweden, US.

[130] 12 weeks (~13%) if cirrhotic except genotype 3, 16 weeks (~4%) if genotype 3 except treatment-naive/noncirrhotic. Percentages include n=7 with CKD 3b.

[131] Including CKD 4-5ND.

[132] Including CKD 4-5ND.

Evidence Profile B: Chapter 2. 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			
								Quality of Evidence for Outcome	Description of Findings		Importance of Outcome
Death, ~6-12 mo	DCV/ASV	0								Reported death rates low (0-6%) 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
	EBR/GZR	0									
	GLE/PIB	1	36	Serious limitations	N/A	Direct	Sparse	Very low	2.8% (0.4, 17)		
	PrO±D	2	60	Serious limitations	N/A	Direct	Sparse	Very low	1.7% (0.2, 11)		
	SOF	0									
	SOF/DCV	1	31	Serious limitations	N/A	Direct	Sparse	Very low	6.4% (1.6, 22)		
	SOF/LDV	0									
	SOF/SIM	0									
	SOF/VEL	1	59	Serious limitations	N/A	Direct	Sparse	Very low	3.4% (0.8, 13)		
SVR12	DCV/ASV	9	341	Some limitations[3]	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
	EBR/GZR	9	936	Some limitations[4]	Consistent	Direct	None	Moderate	96.5% (94.8, 97.9)		
	GLE/PIB	8	409	Some limitations[5]	Consistent	Direct	None	Moderate	96.7% (94.5, 98.4)		
	PrO±D	16	582	Some limitations[6]	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	7	252	No limitations	Some inconsistency	Direct	None	Moderate	92.9% (87.3, 96.9)		
	SOF/LDV	7	220	Some limitations[7]	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	5	405	No limitations	Consistent	Direct	None	High	93.9% (90.8, 96.4)		

Outcome	Regimen[8]	# of Studies[9]	Total N of Patients on Treatment	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings			
								Quality of Evidence for Outcome	Description of Findings		Importance of Outcome
Serious AE due to DAA	DCV/ASV	8	274	Some limitations[10]	Consistent	Direct	None	Moderate	0.4% (0.1 2.5)	Rare. No evidence of differences among regimens.	High
	EBR/GZR	4	139	Serious limitations[11]	Consistent	Direct	Incomplete reporting	Low	0.7% (0.1, 5.0)		
	GLE/PIB	7	333	Some limitations[12]	Consistent	Direct	None	Moderate	0.6% (0.2, 2.4)		
	PrO±D	13	406	Some limitations[13]	Consistent	Direct	None	Moderate	0.2% (0.03, 1.7)		
	SOF	2	63	Serious limitations[14]	Consistent	Direct	Imprecise	Very Low	0% (0, 11.5)		
	SOF/DCV	3	86	Serious limitations[15]	Consistent	Direct	Imprecise	Very Low	0% (0, 8.6)		
	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	5	405	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
	EBR/GZR	4	139	Serious limitations[16]	Consistent	Direct	Incomplete reporting	Low	2.0 (0.4, 5.0)		
	GLE/PIB	7	279	Some limitations[17]	Consistent	Direct	None	Moderate	1.9% (0.6, 3.8)		
	PrO±D	14	446	Some limitations[18]	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	221	No limitations	Consistent	Direct	None	High	0.5% (0.1, 3.1)		
	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	4	240	Serious limitations[19]	Consistent	Direct	Some imprecision	Low	0% (0, 3.2)		
Quality of life	GLE/PIB	1	77	Serious limitations	N/A	Direct	Sparse	Very Low	1/3 with clinical improvement in SF-12 PCS and MCS	Insufficient evidence	High
Balance of Potential Benefits and Harms: DAAs yield very high rates of SVR 12 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.								**Quality 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] Some per protocol and analyses with missing data.
[4] Some per protocol and unclear analyses.
[5] Some per protocol and unclear analyses.
[6] Some per protocol analyses.
[7] Some per protocol analyses.
[8] Notation of inclusion of ribavirin omitted from this table.
[9] Single groups, mostly retrospective.
[10] Reporting bias (large study did not report outcome).
[11] Reporting bias (many studies did not report outcome).
[12] Reporting bias (large study did not report outcome).
[13] Reporting bias (large studies did not report outcome).
[14] Reporting bias (large study with half of available patients did not report outcome).
[15] Reporting bias (many studies 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 studies did not report outcome).
[19] Reporting bias (large study with half of available patients did not report outcome).

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Summary Table 2.6: 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] *Transfusion*[4]	D/C DAA Due to AE[5]
EBR/GZR	Eisenberger 2019 30656217 Germany (1)	12 wk (most)[6]	Gt 1a 18% Gt 1b 73% Gt 4 9%	NR	11/11 (100%) ITT	0/11 (0%)	0/11 (0%)
EBR/GZR Summary					**100% (54, 100) all ITT**	**0% (0, 46)**	**0% (0, 46)**
GLE/PIB	Reau 2018 29672891 US (2)	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**		
PrO±D±RBV[7]	Daniş 2019 31418413 Turkey (3)	12 wk (most)[8]	Gt 1a 48% Gt 1b 48%	10% (not defined)	21/21 (100%) ITT	0/21 (0%) *Transfusion 3/21 (14.3%)*[9]	0/21 (0%)
PrOD	Iliescu 2020 31948406 Romania (4)	12 wk	Gt 1b 100%	0% (TE)	12/12 (100%) ITT	0/12 (0%)	0/12 (0%)
PrO±D Summary					**100% (80, 100)[10] 33/33 all ITT**	**0% (0, 20) 0/33** ***Transfusion 14% (5, 36)***	**0% (0, 20) 0/33**

[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] Dasabuvir for genotype 1 (n=20), ribavirin for genotypes 1a and 4 (n=10).
[8] 24 weeks (n=1 patient with cirrhosis).
[9] 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] ***Transfusion***[4]	**D/C DAA Due to AE**[5]
SOF/RBV (400)[11]	Taneja 2018 28703905 India (5)	12 wk	Gt 1 79% Gt 3 14% Gt 4 7%	14% (TE, LSM)	12/14 (85.7%)[12] ITT	2/14 (14.3%) *Transfusion 0/12 (0%)*	2/14 (14.3%)
SOF/RBV (400)	Prasad 2018 29962673 India (6)	12 wk	Gt 1 27%[13] Gt 2 4.5% Gt 3 64% Gt 4 4.5%	45% (TE)[14]	14/14 (100%) ITT	NR	NR
SOF/RBV (400)	Reddy 2018 29942507 India (7)	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%)
SOF/RBV (400)	Sharma 2018 29796311 India (8)	24 wk	Gt 1 33%[15] Gt 3 67%	10% (TE)[16]	29/29 (100%) ITT	0/30 (0%) *Transfusion or EPO 0/30 (0%)*	0/30 (0%)
SOF Summary					**100% (89, 100)**[17] **65/65** **all ITT**	**4.8% (0.4, 14)**[18] **2/54** ***Transfusion 0% (0, 17)***	**4.8% (0.4, 14)**[19] **2/54**
SOF/DCV (400)	Huang 2019 30369001 China (9)	12 wk (89%)[20]	Gt 1 84% Others 16%	16% (FIB4 >3.25)	19/19 (100%) ITT	0/19 (0%)	0/19 (0%)

[10] Pooled. 2 studies.
[11] In n=1, SOF dose 200 mg daily.
[12] 1 patient included in both SOF/RBV and (after rapid virologic response failure) SOF/LDV arms
[13] Including n=8 on other regimens.
[14] Including n=8 on other regimens.
[15] Including n=15 on other regimens.
[16] Including n=15 on other regimens.
[17] 4 studies. Pooled
[18] 3 studies. REML MA, I^2 28% (moderate heterogeneity)
[19] 3 studies. REML MA, I^2 28% (moderate heterogeneity)
[20] 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] *Transfusion*[4]	D/C DAA Due to AE[5]
SOF/DCV (400)	D'Ambrosio 2019 30904073 Italy (10)	12 wk (86%)[21]	Gt 2 71% Gt 3 29%	14% (not defined)	14/14 (100%) ITT	0/14 (0%)	0/14 (0%)
SOF/DCV±RBV (400)	El Maghrabi 2019 31531807 Egypt (11)	24 wk	Gt 1 13%[22] Gt 4 87%	3% (U/S)[23], 0% (TE)	105/105 (100%) ITT	0/105 (0%)	NR
SOF/DCV±RBV (400)	Elmowafy 2020 33111161 Egypt (12)	24 wk	Gt 1 10% Gt 4 90%	2% (U/S), 0% (TE)	125/125 (100%) ITT	NR	0/125 (0%)
SOF/DCV±RBV (400)[24]	Taneja 2018 28703905 India (5)	12 wk (most)[25]	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					**100% (97.2, 100)[26] 275/275 all ITT**	**0% (0, 5.1)[27] 0/150**	**0% (0, 4.5)[28] 0/170**

[21] 24 weeks (n=2), reason not reported.
[22] Including n=9 who received other regimens.
[23] Including n=9 who received other regimens.
[24] In n=3, SOF dose 200 mg daily.
[25] 24 weeks if cirrhosis or detectable RNA at week 4 (n not reported).
[26] Pooled. 5 studies.
[27] Pooled. 4 studies.
[28] Pooled. 4 studies.

Regimen[1]	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12[2]	DAA-Related Serious AE[3] *Transfusion*[4]	D/C DAA Due to AE[5]
SOF/LDV (400)	Colombo 2017 27842383[29] Italy, France, Austria, Germany (13)	12 wk	Gt 1a 12% Gt 1b 74% Gt 1, no subtype 4% Gt 4 11%	14% (multiple)[30]	57/57 (100%) ITT	1/57 (1.8%)	0/57 (0%)
		24 wk	Gt 1a 18% Gt 1b 75% Gt 4 7%	16% (multiple)[31]	57/57 (100%) ITT	2/57 (3.5%)	1/57 (1.8%)
SOF/LDV (400)	Eisenberger 2017 27495770 Germany (14)	12 wk (80%)[32]	Gt 1a 27% Gt 1b 67% Gt 4 7%	NR	15/15 (100%) ITT	NR	NR
SOF/LDV (400)	Weigert 2018 29661427 Portugal (15)	12 wk (most)[33]	Gt 1a 22%)[34] Gt 1b 56% Gt 3 13% Gt 4 9%	13% (TE)[35]	14/14 (100%) ITT	NR	NR
SOF/LDV +RBV (400)	Musialik 2019 30972854 Poland (16)	12 wk (74%)[36]	Gt 1b 90% Gt 4 10%	5% (TE)[37]	31/31 (100%) Per protocol[38]	NR	0/31 (0%)
SOF/LDV +RBV (400)	Akin 2018 29899985 Turkey (17)	12 or 24 wk[39]	Gt 1a 25% Gt 1b 75%	17% (not defined)	12/12 (100%) ITT	0/12 (0%) Transfusion 0/12 (0%)	0/12 (0%)

[29] RCT of 12 vs. 24 wk.
[30] TE, Ishak score >= 5 by biopsy, FibroScan >12.5 kPa, or FibroTest score >0.75 plus APRI >2.
[31] TE, Ishak score >= 5 by biopsy, FibroScan >12.5 kPa, or FibroTest score >0.75 plus APRI >2.
[32] 8 weeks (n=3), unclear reason.
[33] 24 weeks for F4 fibrosis (number not reported).
[34] Including n=9 who received other regimens.
[35] Including n=9 who received other regimens.
[36] 24 weeks for first 8 patients treated.
[37] Including n=9 who received other regimens.
[38] 1 dropout excluded from analysis.
[39] 24 weeks if cirrhosis, previous treatment failure and for specific genotypes (implied) (number not reported).

Regimen[1]	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12[2]	DAA-Related Serious AE[3] *Transfusion*[4]	D/C DAA Due to AE[5]
SOF/LDV +RBV (400)	Bhamidimarri 2017 28332729 US (18)	12 wk (91%)[40]	Gt 1a 74% Gt 1b 26%	0% (TE)	22/23 (95.7%) ITT	NR	0/23 (0%)
SOF/LDV +RBV (400)	Chascsa 2018[41] 29758123 US (19)	12 wk (77%)[42]	Gt 1 82%[43] Gt 1a 54% Gt 1b 29% Gt 2 4% Gt 3 11%	36% (not defined)[44]	22/22 (100%) ITT	0/22 (0%)	0/22 (0%)
SOF/LDV +RBV (400)	Saxena 2017 28504842 US (20)	12 or 24 wk[45]	Gt 1 90%[46] 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[47]	NR	NR
SOF/LDV +RBV (400)	Taneja 2018 28703905 India (5)	12 wk (most)[48]	Gt 1 86% Gt 4 14%	5% (TE, LSM)	22/22 (100%)[49] ITT	0/22 (0%)	0/22 (0%)
SOF/LDV Summary					**97.3% (94.9, 99.0)[50] 294/300 almost all ITT**	**2.6% (0.7, 5.7)[51] 3/170**	**1.7% (0.4, 3.7)[52] 1/224**

[40] 8 weeks (n=1), 24 weeks (n=1); reasons not reported.
[41] Study specific to D+/R+ patients.
[42] 24 weeks (n=5), reasons not reported.
[43] Including n=6 who received other regimens.
[44] Including n=6 who received other regimens.
[45] Numbers and reasons not reported.
[46] Including n=11 on other regimens.
[47] Omitted 1 who discontinued DAA for administrative reasons.
[48] 24 weeks if cirrhosis or detectable RNA at week 4 (n not reported).
[49] 1 patient included in both SOF/RBV and (after rapid virologic response failure) SOF/LDV arms
[50] 10 study arms. REML MA, I^2 18% (small heterogeneity)
[51] 5 study arms. REML MA, I^2 0% (no heterogeneity)

Regimen[1]	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	SVR12[2]	DAA-Related Serious AE[3] *Transfusion*[4]	D/C DAA Due to AE[5]
SOF/VEL	Greco 2019 SP786[53] Italy (21)	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.

[52] 7 study arms. REML MA, I^2 0% (no heterogeneity)

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

Summary Table 2.7: DAAs in kidney transplant recipients, part 2 (graft outcomes and death)

Regimen	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	Timing	Acute Rejection	Graft Loss	Patient Death (≥12 Months)
EBR/GZR	Eisenberger 2019 30656217 Germany (1)	12 wk (91%)[54]	Gt 1a 18% Gt 1b 73% Gt 4 9%	NR	SVR12	NR	1/11 (9.1%)[55]	NR
EBR/GZR Summary							**9.1% (1.3, 44)**	
GLE/PIB	Reau 2018 29672891 US (2)	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)**	
SOF/RBV	Reddy 2018 29942507 India (7)	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±RBV (400)	El Maghrabi 2019 31531807 Egypt (11)	24 wk	Gt 1 13%[56] Gt 4 87%	3% (U/S)[57], 0% (TE)	EOT	4/105 (3.8%)	NR	NR

[54] 16 weeks (n=1 patient with high HCV mRNA at baseline).
[55] Not associated with DAA, but with progressive diabetic nephropathy.
[56] Including n=9 who received other regimens.
[57] Including n=9 who received other regimens.

Regimen	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	Timing	Acute Rejection	Graft Loss	Patient Death (≥12 Months)
SOF/DCV±RBV (400)	Elmowafy 2020 33111161 Egypt (12)	24 wk	Gt 1 10% Gt 4 90%	2% (U/S), 0 (TE)	EOT	4/125 (3.2%)	0/125[58]	NR
SOF/DCV Summary						**3.5% (1.5, 6.2)[59] 8/230**	**0% (0, 6.1)**	
SOF/LDV (400)	Colombo 2017 27842383[60] Italy, France, Austria, Germany (13)	12 wk	Gt 1 4% Gt 1a 12% Gt 1b 74% Gt 4 11%	14% (multiple)[61]	SVR12	NR	NR	NR
SOF/LDV (400)		24 wk	Gt 1a 18% Gt 1b 75% Gt 4 7%	16% (multiple)[62]	SVR12	NR	NR	NR
SOF/LDV (400)	Eisenberger 2017 27495770 Germany (14)	12 wk (80%)[63]	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 (19)	12 wk (77%)[64]	Gt 1 82%[65] Gt 1a 54% Gt 1b 29% Gt 2 4% Gt 3 11%	36% (not defined)[66]	Median 413 d	1/22 (4.5%)[67]	0/22 (0%)	NR

[58] Incident dialysis.
[59] 2 studies. REML MA. I^2 N/A
[60] RCT of 12 vs. 24 weeks.
[61] TE, Ishak score >= 5 by biopsy, FibroScan >12.5 kPa, or FibroTest score >0.75 plus APRI >2.
[62] TE, Ishak score >= 5 by biopsy, FibroScan >12.5 kPa, or FibroTest score >0.75 plus APRI >2.
[63] 8 weeks (n=3), unclear reason.
[64] 24 weeks (n=5), reasons not reported.
[65] Including n=6 who received other regimens.
[66] Including n=6 who received other regimens.
[67] During first week of treatment.

Regimen	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	Timing	Acute Rejection	Graft Loss	Patient Death (≥12 Months)
SOF/LDV±RBV (400)	Saxena 2017 28504842 US (20)	12 or 24 wk[68]	Gt 1 90%[69] 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[70] (400)	Bhamidimarri 2017 28332729 US (18)	12 wk (91%)[71]	Gt 1a 72% Gt 1b 24% Gt 2b 4%	0% (TE)	EOT	4/25 (16%)[72]	NR	NR
SOF/LDV Summary						**6.2% (2.3, 12.0)[73] 7/109**	**1.2% (0.2, 8.0)[74] 1/84**	

[68] Numbers and reasons not reported.
[69] Including n=11 on other regimens.
[70] Also SOF/DCV (n=1), SOF/SIM (n=1).
[71] 8 weeks (n=1), 24 weeks (n=1); reasons not reported.
[72] All resolved.
[73] 4 studies. REML MA. I^2 12% (small heterogeneity).
[74] 3 studies. Pooled.

Regimen	Study, PMID Country (Reference)	Treatment Duration	Genotype	Liver Cirrhosis (Definition)	Timing	Acute Rejection	Graft Loss	Patient Death (≥12 Months)
DAAs, various[75]	Chevallier 2020 32636068 France (22)	12 wk (80%)[76]	Gt 1 68%[77] 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%)[78] 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%)[79]	3/22 (13.6%)[80]
DAAs, various[81]	Gendia 2019 30580473 Italy (23)	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%)

[75] SOF/LDV±RBV (n=23), SOF/DCV (n=14), EBR/GZR (n=4), SOF/SIM (n=1) , SOF/RBV (n=1), PrO (n=1).
[76] 4 weeks (n=2), 8 weeks (n=1), 24 weeks (n=6), reasons not reported.
[77] 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.
[78] 4 of 5 had pre-DAA GFR <30; 5th GFR 50.
[79] Baseline GFR not reported.
[80] 1 hepatocellular carcinoma, 2 septic shock.
[81] 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	Graft Loss	Patient Death (≥12 Months)
DAAs, various[82]	Goetsch 2020 33089036 US (24)	NR	NR	NR	>2 y	NR	2/29 (6.9%) OR 0.17 (0.03, 0.89) Graft loss or death adjHR 0.32 (0.08, 1.21)	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)**	**Unadj OR 0.16 (0.04, 0.61)**
DAAs, various[83]	Weigert 2018 29661427 Portugal (15)	12 (61%) or 24 (39%) wk[84]	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.

[82] 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).
[83] SOF/LDV (n=15), SOF/RBV (n=4), SOF/DCV (n=2), GZR/ELB (n=2).
[84] 24 weeks for F4 fibrosis.

Summary Table 2.8: 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 (1)	12 wk (most)[85]	Gt 1a 18% Gt 1b 73% Gt 4 9%	NR	SVR12	ΔMedians −2, NS [29]	ΔMedians ~−240, NS [~740]
PrOD	Iliescu 2020 31948406 Romania (4)	12 wk	Gt 1b 100%	0% (TE)	Mean 2.6 yr	NR	Decrease (NR), P=0.013 [NR]
SOF/RBV (400)[86]	Taneja 2018 28703905 India (5)	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)	Huang 2019 30369001 China (9)	12 wk (89%)[87]	Gt 1 84% Others 16%	16% (FIB4 >3.25)	SVR12	NR P=0.07 [57.2]	−0.6 (−1.1, 0) P=0.048 [0.95] 8/12 >10% improvement 2/12 >10% worsening
SOF/DCV (400)	Michels 2020 32294735 Brazil[88] (25)	NR	NR	48% (TE)[89]	12 or 24 wk[90]	Mean Δ −1.4 (−6.0, 3.2), P=0.55 [51.4]	NR
SOF/DCV (400)	D'Ambrosio 2019 30904073 Italy (10)	12 wk (86%)[91]	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 (12)	24 wk	Gt 1 10% Gt 4 90%	2% (U/S), 0% (TE)	SVR12	Mean Δ −2.0 (NR), P NR [61.5]	NR

[85] 16 weeks (n=1 patient with high HCV mRNA at baseline).
[86] In n=1, SOF dose 200 mg daily.
[87] 24 weeks for cirrhosis or prior treatment (n=2).
[88] This study did not report DAA or kidney outcomes specifically for the transplant population.
[89] Of whole population (n=241) including hemodialysis and other CKD.
[90] Unclear.
[91] 24 weeks (n=2), reason not reported.

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±RBV (400)[92]	Taneja 2018 28703905 India (5)	12 wk (most)[93]	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[94] Italy, France, Austria, Germany (13)	12 wk	Gt 1a 12% Gt 1b 74% Gt 1, no subtype 4% Gt 4 11%	14% (multiple)[95]	SVR12	ΔMedians 0, P NR [50]	NR
SOF/LDV (400)		24 wk	Gt 1a 18% Gt 1b 75% Gt 4 7%	16% (multiple)[96]	EOT	ΔMedians −5, P NR [60]	NR
SOF/LDV (400)	Eisenberger 2017 27495770 Germany (14)	12 wk (80%)[97]	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 (17)	12 or 24 wk[98]	Gt 1a 25% Gt 1b 75%	17% (not defined)	SVR12	Mean Δ 4.1 (−2.1, 10.3), P=0.20 [68.6]	NR
SOF/LDV+RBV (400)	Taneja 2018 28703905 India (5)	12 wk (most)[99]	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 (16)	12 wk (most)[100]	Gt 1b 90% Gt 4 10%	5% (TE)[101]	EOT	Mean Δ −2 (−4.9, 0.9), P=0.17 [55]	NR

[92] In n=3, SOF dose 200 mg daily.
[93] 24 weeks if cirrhosis or detectable RNA at week 4 (n not reported).
[94] Randomized controlled trial of 12 vs. 24 weeks.
[95] TE, Ishak score >= 5 by biopsy, FibroScan >12.5 kPa, or FibroTest score >0.75 plus APRI >2.
[96] TE, Ishak score >= 5 by biopsy, FibroScan >12.5 kPa, or FibroTest score >0.75 plus APRI >2.
[97] 8 weeks (n=3), unclear reasons.
[98] Numbers not reported. Implied 24 weeks if cirrhosis, previous treatment failure and for specific genotypes.
[99] 24 weeks if cirrhosis or detectable RNA at week 4 (n not reported).
[100] 24 weeks if genotype 2 or 3 and first several treated for genotype 1b or 4 (numbers not reported for this regimen).

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/VEL (400)	Greco 2019 SP786[102] Italy (21)	12 wk	Gt 1 60% Gt 2 40%	0% (not defined)	EOT	Mean Δ 3 (NR), P NR [54][103]	Mean Δ −20 (NR), P NR [430][104]
SOF-based regimens[105] (400)	Prasad 2018 29962673 India (6)	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
DAAs, various[106]	El Maghrabi 2019 31531807 Egypt (11)	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
DAAs, various[107]	Chevallier 2020 32636068 France (22)	12 wk (most)[108]	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, 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, ΔMedian: difference between final and pre-treatment median values (not median change).

[101] Including n=9 who received other regimens.
[102] European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) 2019 conference abstract.
[103] Reported as P<0.01, but this is likely one-sided P for "not worsening."
[104] Reported as P<0.01, but this is likely one-sided P for "not worsening."
[105] SOF/RBV (n=14), SOF/DCV/RBV (n=5), SOF/LDV (n=3).
[106] SOF/DCV+-RBV (n=105), SOF/RBV (n=4), PrO/RBV (n=5).
[107] SOF/LDV±RBV (n=23), SOF/DCV (n=14), EBR/GZR (n=4), SOF/SIM (n=1) , SOF/RBV (n=1), PrO (n=1).
[108] 4 weeks (n=2), 8 weeks (n=1), 24 weeks (n=6), reasons not reported.

Evidence Profile C: Chapter 2. 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: Quality of Evidence for Outcome	Summary of Findings: Description of Findings	Summary 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)	
Graft loss	DCV/ASV	0							ND	Graft 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. Graft loss rate with DAA vs. no DAA unclear. Critical
	EBR/GZR	1	11	No limitations	N/A	Direct	Sparse	Very Low	0.1% (1.3, 44)	
	GLE/PIB	1	20	No limitations	N/A	Direct	Sparse	Very Low	0% (0, 30)	
	PrO±D	0							ND	
	SOF	1	10	Serious limitations[4]	N/A	Direct	Sparse	Very Low	0% (0, 48)	
	SOF/DCV	0							ND	
	SOF/LDV	3	84	Serious limitations[5]	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[6]	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
	EBR/GZR	1	11	No limitations	N/A	Direct	Sparse	Very Low	100% (54, 100)	
	GLE/PIB	1	20	No limitations	N/A	Direct	Sparse	Very Low	100% (70, 100)	
	PrO±D	2	33	No limitations	Consistent	Direct	Imprecise	Very Low	100% (80, 100)	
	SOF	4	65	No limitations	Consistent	Direct	None	High	100% (89, 100)	
	SOF/DCV	5	275	No limitations	Consistent	Direct	None	High	100% (97.2, 100)	
	SOF/LDV	10	300	No limitations	Consistent	Direct	None	High	97.3 (94.9, 99.0)	
	SOF/SIM	0							ND	
	SOF/VEL	1	10	No limitations	Consistent	Direct	Sparse	Very Low	100% (52, 100)	
Serious AE due to DAA	DCV/ASV	0							ND	Rare. No evidence of differences among regimens. High
	EBR/GZR	1	11	No limitations	N/A	Direct	Sparse	Very Low	0% (0, 46)	
	GLE/PIB	0							ND	
	PrO±D	2	33	No limitations	Consistent	Direct	Imprecise	Very Low	0% (0, 20)	
	SOF	3	30	Some limitations[7]	Consistent	Direct	Imprecise	Very Low	4.8% (0.4, 14)	
	SOF/DCV	4	150	Some limitations[8]	Consistent	Direct	Imprecise	Very Low	0% (0, 5.1)	

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		
								Quality of Evidence for Outcome	Description of Findings	Importance of Outcome
	SOF/LDV	5	170	Serious limitations[9]	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[10]	# of Studies[11]	Total N of Patients on Treatment	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings			
								Quality 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
	EBR/GZR	1	11	No limitations	N/A	Direct	Sparse	Very Low	0% (0, 46)		
	GLE/PIB	0							ND		
	PrO±D	2	33	No limitations	Consistent	Direct	Imprecise	Very Low	0% (0, 20)		
	SOF	3	30	Some limitations[12]	Consistent	Direct	Imprecise	Very Low	4.8% (0.4, 4.5)		
	SOF/DCV	4	170	Some limitations[13]	Consistent	Direct	Imprecise	Very Low	0% (0, 5.1)		
	SOF/LDV	7	224	Some limitations[14]	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
	EBR/GZR	0							ND		
	GLE/PIB	1	20	No limitations	N/A	Direct	Sparse	Very Low	0% (0, 30)		
	PrO±D	0							ND		
	SOF	1	10	Serious limitations[15]	N/A	Direct	Sparse	Very Low	0% (0, 48)		
	SOF/DCV	2	230	Some limitations[16]	Consistent	Direct	None	Moderate	3.5% (1.5, 6.2)		
	SOF/LDV	4	109	Some limitations[17]	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 SVR 12 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.								**Quality 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 (many studies did not report outcome).
[6] No adjustment for potential confounders.
[7] Reporting bias (study with half available patients did not report outcome).
[8] Reporting bias (larger study did not report outcome).
[9] Reporting bias (many studies did not report outcome).
[10] Notation of inclusion of ribavirin omitted from this table.
[11] Single groups, mostly retrospective.
[12] Reporting bias (study with half available patients did not report outcome).
[13] Reporting bias (larger study did not report outcome).
[14] Reporting bias (larger study did not report outcome).
[15] Reporting bias (many studies did not report outcome).
[16] Reporting bias (larger study did not report outcome).
[17] Reporting bias (larger study did not report outcome).

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Chapter 4: Management of Patients with HCV before and after Kidney Transplantation

Summary Table 4.1 DAA treatment in HCV-positive donors/HCV-negative recipient kidney transplantation

Study Year PMID[1] (Reference)	Design (Txp Years)	N Kidney: + → − [− → −]	F/up Time	Time to DAA, Days	DAA Regimen (N) [Duration]	SVR12	DAA-Related SAE	Hepatic Events	Graft Survival	Allograft GFR, mL/min/1.73 m^2	Death	DGF	Acute Rejection	QoL
Prospective studies (with protocol)														
Durand 2018 29507971 (1)	Prosp (2015~17)	10 [0]	24 wk	0[2]	EBR/GZR (n=7), EBR/GZR/SOF[3] (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%[4])	4/10 (40%)	0/10 (0%)	NR
Durand 2020 32894697 (2)	Prosp (2018-19)	10 [0]	12 mo	0[5]	GLE/PIB (n=10) [4 wk]	10/10 (100%) ITT	0/10 (0%)	NR	9/10 (90%)[6]	Md 54.5 (IQR 30-79)	0/10 (0%)	NR	1/10 (10%)	NR
Feld 2020 32389183 Canada (3)	Prosp (2019)	10 [0]	36 wk	0[7]	GLE/PIB/ ezetimibe (n=10) [8 d]	10/10 (100%) ITT	1/10 (10%)[8]	0/10 (0%)[9]	0/10 (0%)	Md 74 (IQR 65-92)	0/10 (0%)	NR	0/10 (0%)[10]	NR
Gupta 2020 31652392 (4)	Prosp (2017-18)	50 [0]	Md 8 mo	0[11]	SOF/VEL (n=50) [2-4 d][12]	47/49 (96%[13]) Incomplete	NR	0/50 (0%)	49/50 (98%)[14]	Mn 58 (SD 19)	1/50 (2.0%)[15]	24/50 (48%)	2/50 (4%)	NR

[1] All conducted in the United States, except as indicated.
[2] On call to operating room, per protocol.
[3] Added for genotypes 2 or 3.
[4] Implied.
[5] Before organ perfusion.
[6] One graft loss at day 261 unrelated to HCV or DAA treatment.
[7] 6–12 hours before transplant.
[8] 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.
[9] Acute liver failure or fibrosing cholestatic hepatitis.
[10] Implied.
[11] 6 hours prior to transplant.
[12] All 50 received pre-operative treatment with SOF/VEL followed by a dose on day 1 following transplantation (n=10) or for first 3 days following transplantation (n=40). A 12 week course (varied DAA regimens) was administered to 6 patients who developed viremia.
[13] This assumes that those who did not require full courses of DAA treatment achieved SVR12 after the 1-3 day prophylactic treatment; this is not stated explicitly. Six patients had viremia that required full DAA treatments: 4/5 (80%) achieved subsequent SVR12; the 6th treated patient had not reached 12 week follow-up by study conclusion and is omitted.
[14] No description reported.
[15] Fulminant pneumonia immediately after transplant surgery.

Study Year PMID[1] (Reference)	Design (Txp Years)	N Kidney: + → − [− → −]	F/up Time	Time to DAA, Days	DAA Regimen (N) [Duration]	SVR12	DAA-Related SAE	Hepatic Events	Graft Survival	Allograft GFR, mL/min/1.73 m^2	Death	DGF	Acute Rejection	QoL
Reese 2018 / Mazur 2019 30083748 / 30779252 (5, 6)	Prosp (2016-17)	20 [100[16]]	12 mo	3±1 [17]	EBR/GZR (n=17) [12 wk], EBR/GZR/RBV (n=3, NS5A) [16 wk]	20/20 (100%) ITT	0/20 (0%)	0/40 (0%)[18] [vs. NR]	20/20 (100%) [vs. NR]	Md 72.8 (IQR 58.6-74.4, N=10) [Md 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 [19]
Sise 2020 32843477 (7)	Prosp (2019)	30 [0]	6 mo	2-5 [20]	GLE/PIB (n=30) [8 wk]	30/30 (100%) ITT	NR	NR	30/30 (100%)	Md 57 (IQR 47-57)	1/30 (3.3%)[21]	7/30 (23%)	3/30 (10%)	NR
Terrault 2020 32926749 (8)	Prosp (2018-19)	11 [0]	36 wk	Md 16.5 (IQR 9.8, 24.5)	SOF/VEL (n=10)[22] [12 wk]	11/11 (100%) ITT	0/10 (0%)	0/10 (0%)[23]	10/10 (100%)[24]	NR	0/11 (0%)[25]	2/10 (20%)[26]	0/10 (0%)[27]	NR

[16] Matched by Kidney Donor Profile Index (KDPI) score.
[17] Per protocol.
[18] From Mazur 2019. Unclear description of the additional 20 patients.
[19] SF-36 stabilized higher than baseline by post-op week 16.
[20] Per protocol.
[21] At 9 months post-transplant with sepsis and multiorgan failure, adjudicated as unlikely related to HCV or DAA treatment.
[22] 1 patient did not have viremia, not treated with DAA.
[23] 1 patient who was not treated with DAA was omitted from analysis.
[24] Implied. 1 patient who was not treated with DAA was omitted from analysis.
[25] Implied.
[26] 1 patient who was not treated with DAA was omitted from analysis.
[27] 1 patient who was not treated with DAA was omitted from analysis.

Study Year PMID[1] (Reference)	Design (Txp Years)	N Kidney: + → − [− → −]	F/up Time	Time to DAA, Days	DAA Regimen (N) [Duration]	SVR12	DAA-Related SAE	Hepatic Events	Graft Survival	Allograft GFR, mL/min/1.73 m^2	Death	DGF	Acute Rejection	QoL
Retrospective studies														
Molnar 2021 33333148 (9)	Retro (2018)	65 [59][28]	12 mo[29]	Md 76 (IQR 68-88)	GLE/PIB (n=59), SOF/VEL (n=5)[30] [12 wk[31]]	65/65 (100%) ITT	NR	FCH 1/65 (1.5%)[32] [vs. NR]	65/65 (100%) [vs. 56/59 (95%)][33]	Mn 64 (SD 16) [Adjusted difference: −5.2 (−13.8, 3.5); P=0.2][34]	1/65 (2%) [vs. 3/59 (5%), P=0.3][35]	5/65 (7.7%) [vs. 7/59 (11.9%), P=0.4][36]	3/54 (6%) [vs. 3/42 (7%), P=0.8][37]	NR
Kapila 2019 31659775 (10)	Retro (2018)	64 [0]	≤55 wk	Md 72 (Rn 9-198)	GLE/PIB (n=33), SOF/LDV (n=24), No DAA (n=4)[38] [12 wk[39]]	44/45 (97.8%)[40] Incomplete	NR	2/64 (3.1%) FCH[41]	NR	NR	1/64 (1.5%)[42]	NR	NR	NR
Graham 2020 32072689 (11)	Retro (2018-19)	30 [30[43]]	6 mo	Md 9 (Rn 5-41)	GLE/PIB (n=29)[44] [12 wk]	30/30 (100%) ITT	0/30 (0%)	0/30 (0%) [vs. NR]	30/30 (100%) [vs. 97%]	Mn 55.5 (SD 18) [vs. 48.6 (SD 15), P=0.12][45]	0/30 (0%) [vs. 0%]	8/30 (27%) [vs. 60%, P=0.01]	2/30 (6.6%) [vs. 6.6%]	NR

[28] Outcomes of 65 HCV negative recipients of an HCV positive kidney were compared with 59 HCV negative recipients of an HCV negative kidney during the same time period (2018) .
[29] From Molnar 2021.
[30] Also n=1 SOF/LDV.
[31] 5 patients treated for 16 weeks.
[32] Reported in Molnar 2019 PMID 31306549.
[33] Article reported graft loss including death: 1/65 vs. 6/59, unadjusted P value 0.04.
[34] 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.
[35] Crude comparison (unadjusted).
[36] Crude comparison (unadjusted).
[37] Crude comparison (unadjusted). 28/124 (23%) missing (no biopsy).
[38] 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.
[39] 1 treated for 16 weeks.
[40] Excluding 17 who had not yet reached SVR12. Including 1 who died with viremia who was not treated with DAA.
[41] With complete resolution.
[42] Died day 77 after complicated post-transplantation course. Did not receive DAA despite viremia. Cause of death unknown.
[43] Matched.
[44] Also n=1 SOF/VEL.
[45] Difference somewhat greater at 1 and 3 months, favoring HCV-donor.

Study Year PMID[1] (Reference)	Design (Txp Years)	N Kidney: + → − [− → −]	F/up Time	Time to DAA, Days	DAA Regimen (N) [Duration]	SVR12	DAA-Related SAE	Hepatic Events	Graft Survival	Allograft GFR, mL/min/1.73 m^2	Death	DGF	Acute Rejection	QoL
Jandovitz 2020 33259125 (12)	Retro (2018)	25 [0]	12 mo	Md >20[46]	SOF/LDV (n=14), SOF/VEL (n=8), GLE/PIB (n=3) [12 wk]	24/25 (96%) ITT	NR	NR	24/25 (96%)[47]	NR	NR	16/25 (64%)	NR	NR
Torabi 2020 32810315 (13)	Retro (2018-20)	52 [0]	12 mo	Md 11 (IQR 7-17)	GLE/PIB (n=48), SOF/VEL (n=3)[48] [12 wk]	39/39 (100%)[49] Incomplete	NR	NR	50/52 (96.2%)	Mn 62.3 (SD ~23)	0/52 (0%)	13/52 (25%)	3/52 (5.8%)	NR
Yakubu 2020 ASN PO2440 (14)	Retro (2017-20)	100 [0]	Md 10 mo	0[50]	SOF/VEL (n=80) SOF/VEL/ ezetimibe (n=19)[51] [1, 2, 4, 8 d][52]	52/52 (100%)[53] Incomplete	NR	0/100 (0%)[54]	99/100 (99%)	NR	2/100 (2%)	NR	NR	NR

[46] After viremia detected (mean 7 days post-transplant) and genotype established, median 13 days (range 8-22).
[47] 1 graft loss due to renal artery aneurysm 55 days post-transplant.
[48] Also n=1 SOF/VEL/VOX.
[49] Excluding 13 who did not reach SVR12 follow-up time.
[50] Immediately pre-transplant.
[51] 1 patient omitted from descriptions of DAA regimens.
[52] All had one dose immediately pre-transplant. Per protocols, n=10 1 dose post-transplant day 1, n=42 treated through post-transplant day 3, n=28 treated through post-transplant day 7, and n=19 had triple regimen through post-transplant day 7.
[53] SVR12 reported only for groups 1 and 2 (through 1 or 3 days post-transplant).
[54] Liver dysfunction.

SUMMARY:

N=485 HCV + → − kidney grafts

Summary SVR12:				
	Prospective	138/140 (7 studies)	98.6% (94.5, 99.6)	[simple pooling]
	Retrospective	254/256 (6 studies)	99.2% (96.9, 99.8)	[simple pooling]
	Total	392/396 (13 studies)	99.0% (97.3, 99.6)	[simple pooling]
Summary DAA SAE:				
	Prospective	1/60 (5 studies)	1.7% (0.2, 11)	[simple pooling] (likely an overestimate, SAE not reported for 79 patients)
	Retrospective	0/30 (1 studies)	0% (0, 22)	[simple pooling] (likely an overestimate, SAE not reported for 224 patients)
	Total	0/90 (6 studies)	1.1% (0.2, 7.5)	[simple pooling] (likely an overestimate, SAE not reported for 303 patients)
Summary FCH (assumes studies reporting any hepatic event included FCH):				
	Prospective	0/120 (5 studies)	0% (0, 6.3)	[simple pooling]
	Retrospective	3/259 (4 studies)	1.2% (0.4, 3.5)	[simple pooling] (may be a slight overestimate, not reported for 64 patients)
	Total	3/379 (9 studies)	0.8% (0.3, 2.4)	[simple pooling] (may be a slight overestimate, not reported for 104 patients)
Summary graft survival at 1 year[55]:				
	Prospective	29/30 (2 studies)	96.7% (79.8, 99.5)	[simple pooling] [Only Durand 2020 (2) and Reese 2018 {Reese, 2018 #25]
	Retrospective	238/242 (4 studies)	98.4% (96.4, 99.6)	[meta-analysis. I^2 = 0% (no heterogeneity)] [*Not* Graham 2020 {Graham, 2020 #952}]
	Total	267/272 (6 studies)	98.1% (96.2, 99.4)	[meta-analysis. I^2 = 0% (no heterogeneity)]
Summary death at 1 year[56]:				
	Prospective	0/30 (2 studies)	0% (0, 22)	[simple pooling] [simple pooling] [Only Durand 2020 (2) and Reese 2018 {Reese, 2018 #25]
	Retrospective	4/281 (4 studies)	1.4% (0.5, 3.7)	[simple pooling] [*Not* Graham 2020 {Graham, 2020 #952}
	Total	4/311 (6 studies)	1.3% (0.5, 3.4)	[simple pooling[57]]
Summary DGF:				
	Prospective	42/120 (5 studies)	32.2% (20.6, 45.1), range 20-48%	[meta-analysis. I^2 = 48% (moderate heterogeneity)]
	Retrospective	42/172 (4 studies)	28.3% (8.9,53.5), range 7.7-64%	[meta-analysis. I^2 = 91% (large heterogeneity)]
	Total	84/292 (9 studies)	29.6% (18.5, 42.2), range 7.7-64%	meta-analysis. I^2 = 79% (large heterogeneity)]
Summary acute rejection:				
	Prospective	6/140 (7 studies)	5.2% (2.2, 9.5)	[meta-analysis. I^2 = 0% (no heterogeneity)]
	Retrospective	12/136 (3 studies)	8.5% (4.3,14)	[meta-analysis. I^2 = 6% (small heterogeneity)]
	Total	18/276 (10 studies)	6.8% (4.1, 10.0)	[meta-analysis. I^2 = 0% (no heterogeneity)]]

Abbreviations: +/-: nucleic acid amplification testing (NAT) positive or negative, ASN: American Society of Nephrology (conference), CI: confidence interval, D: donor, DAA: direct acting antiviral, DGF: delayed graft function, EBR: elbasvir, 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.

[55] 10-13 months; thus, omitting Durand 2018, Gupta 2020, Graham 2020, Sise 2020, Terrault 2020, Feld 2020.

[56] 10-13 months; thus, omitting Durand 2018, Gupta 2020, Graham 2020, Sise 2020, Terrault 2020, Feld 2020.

[57] Meta-analysis results in inconsistent estimate.

Evidence Profile D: Chapter 4. DAA treatment for HCV donor-positive to HCV-negative recipients

Outcome	# of Studies[1]	Total N of Patients on Treatment	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings: Quality of Evidence for Outcome	Summary of Findings: Description of Findings		Summary of Findings: Importance of Outcome
Death, ~12 mo	6	311	Some limitations[2]	Consistent	Indirect[3]	None	Low	1.3% (0.5, 3.4)	High likelihood of survival to 1 year.	Critical
	1 vs. D−/R−	65 vs. 59	Some limitations[4]	N/A	Direct	Sparse, imprecise	Very Low	OR 0.29 (0.03, 2.88)		
Graft survival, ~12 mo	6	272	Some limitations[5]	Consistent	Indirect[6]	None	Low	98.1% (96.2, 99.4)	High likelihood of graft survival to 1 year.	Critical
	1 vs. D−/R−	65 vs. 59	Some limitations[7]	N/A	Direct	Sparse, imprecise	Very Low	OR 8.11 (0.41, 160)		
SVR12	13	396	Some limitations[8]	Consistent	Direct	None	Moderate	99.0% (97.3, 99.6)	Very high SVR12	High
Serious adverse events	6	90	Some limitations[9]	Consistent	Direct	None	Moderate	1.1% (0.2, 7.5)	Low reported rate of SAE due to DAAs; likely is an overestimate	High
Fibrosing cholestatic hepatitis	9	379	Some limitations[10]	Consistent	Indirect[11]	None	Low	0.8% (0.3, 2.4)	Low reported rate of hepatic complications	High
Allograft GFR	9	272	No limitations	Consistent	Indirect[12]	None	Moderate	Range mean/median 55-74 mL/min	eGFR mostly in CKD 3b-4 range. Difference between D+/R−/ and D−/R− unclear.	High
	3 vs. D−/R−	115 vs. 189	Some limitations[13]	Inconsistent	Direct	None	Low	Inconsistent		
Delayed graft function	9	292	Some limitations[14]	Inconsistent	Indirect[15]	None	Low	Range 7.7-64%	Estimate unclear. ~1/3 risk compared with D−/R−	Moderate
	3 vs. D−/R−	115 vs. 189	Some limitations[16]	Consistent	Direct	None	Moderate	OR 0.38 (0.20, 0.73)		
Acute rejection	10	276	No limitations	Consistent	Indirect[17]	None	Moderate	6.8% (4.1, 10)	Low reported rate of acute rejection. Difference between D+/R−/ and D−/R− unclear.	Moderate
	2	95 vs. 89	Some limitations[18]	Consistent	Direct	Imprecise	Very Low	OR 0.80 (0.30, 2.15)		
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−.							**Quality of Overall Evidence:** Low			

Abbreviations: CKD: chronic kidney disease (category), D+/R−: donor positive/recipient negative, D−/R−: donor negative/recipient negative, 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.

[1] Single group studies, except as noted.
[2] Incomplete or unclear reporting.
[3] No comparator.
[4] Incomplete or unclear reporting.

[5] Incomplete or unclear reporting.
[6] No comparator.
[7] Unadjusted analysis.
[8] Some incomplete analyses (mostly preliminary analyses before all had reached SVR12, some missing data).
[9] Incomplete or unclear reporting.
[10] Incomplete or unclear reporting.
[11] No comparator.
[12] No comparator.
[13] No or incomplete adjustment.
[14] Incomplete or unclear reporting.
[15] No comparator.
[16] No or incomplete adjustment.
[17] No comparator.
[18] No or incomplete adjustment.

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Chapter 5: Diagnosis and Management of Kidney Diseases Associated with HCV Infection

Summary Table 5.1: 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
Iliescu 2019 31948406 Romania (3)	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%)[7] PR 5/56 (9%) No response 4/56 (7%)
Pérez de José 2021 33623683 Spain (4)	HCV-related MC[8] 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[9] (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] 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.

[8] 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 m^2 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.

[9] Denominator based on reported percentage. One participant apparently missing.

Summary Table 5.2: 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]
Iliescu 2019 31948406 Romania (3)	PrOD	56	NR	"Decreased" (P 0.013)	NR	NR	NR
Pérez de José 2021 33623683 Spain (4)	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, 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)

Evidence Profile E: Chapter 5. Management of HCV-associated glomerulonephritis

Outcome	Treatment	# of Studies[10]	Total N of Patients on Treatment	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings: Quality of Evidence for Outcome	Summary of Findings: Description of Findings	Summary of Findings: Description of Findings	Summary of Findings: Importance of Outcome
Death, ≥12 mo	DAA, various	3	259 (GN in 181)	Some limitations[11]	Consistent	Indirect (no comparator, 30% no GN)	None	Low	3.4% (1.5, 5.9)	Low rate. Indication of possible large effect of DAA.	Critical
	vs. No Tx	1	100 vs 15	No limitation[12]	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[13]	Inconsistent	Indirect (no comparator)	None	Low	Range 0-6%	Possible low rate. Indication of possible large effect of DAA.	High
	vs. No Tx	1	100 vs 15	No limitation[14]	N/A	Direct	Sparse Very large effect	Very Low	OR 0.06 (0.02, 0.12)		
Cryoglobulinemia, complete remission	DAA, various	3	216 (GN in 92)	Some limitations[15]	Some inconsistency[16]	Indirect (no comparator)	None	Low	78% (68, 87) Range 72-84%	High rate of complete remission	High
	DAA comparisons	1	146 (GN in 25)	Serious limitations[17]	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	3	301 (GN in 181)	Some limitations[18]	Consistent	Indirect (40% no GN)	None	Low	97.9% (96.0, 99.2)	Very high SVR12	High
Serious adverse events	0								ND		High
eGFR	DAA vs. No Tx	1	100 vs. 15	Serious limitations[19]	N/A	Direct	Sparse, no analysis	Very Low	NS	NS change with DAA	High
Proteinuria	DAA, various	2	156	Some limitations[20]	Consistent	Indirect (no comparator)	None		Significant decrease	Proteinuria reduced with DAA treatment	Moderate
	vs. No Tx	1	100 vs. 15	Some limitations[21]	N/A	Direct	Sparse, no analysis	Very Low	ND		
Cryocrit, c3, c4	DAA vs. No Tx	1	100 vs. 15	No limitation	N/A	Direct	Sparse, no analysis	Very Low	Significant decreases	Measures reduced with DAA treatment	Moderate

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 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.

Quality of Overall Evidence:
Low

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

[10] Single group studies, except as noted.
[11] Unclear, possibly incomplete reporting.
[12] Unadjusted, but very large effect.
[13] Unclear, possibly incomplete reporting.
[14] Unadjusted, but very large effect.
[15] Unclear, possibly incomplete reporting.
[16] $I^2 = 53\%$
[17] Unclear, possibly incomplete reporting; possibly insufficient adjustment for confounders.
[18] Unclear, possibly incomplete reporting.
[19] No actual data reported, unclear reporting.
[20] Unclear, possibly incomplete reporting.
[21] Unclear, possibly incomplete reporting.

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