Management of Unique Populations with HCV Infection

The following pages include guidance for management of patients with HCV in unique populations.

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Unique Patient Populations: Patients with HIV/HCV Coinfection

This section provides guidance on the treatment of chronic HCV infection in HIV/HCV-coinfected patients. For individuals with acute HCV infection, please refer to the Acute HCV section. HIV/HCV-coinfected patients suffer from more liver-related morbidity and mortality, nonhepatic organ dysfunction, and overall mortality than HCV-monoinfected patients (Lo Re, 2014); (Chen, 2009). Even in the potent HIV antiretroviral therapy era, HIV infection remains independently associated with advanced liver fibrosis and cirrhosis in patients with HCV coinfection (Thein, 2008a); (de Ledinghen, 2008); (Fierer, 2013); (Kirk, 2013).

Similar to HCV-monoinfected patients, HIV/HCV-coinfected patients cured with PEG-IFN/ribavirin have lower rates of hepatic decompensation, hepatocellular carcinoma (HCC), and liver-related mortality (Berenguer, 2009); (Limketkai, 2012); (Mira, 2013). Uptake of HCV therapy was lower in the HIV/HCV-coinfected population, owing to historically lower response rates, patient comorbidities, patient and practitioner perceptions, and adverse events associated with IFN-based therapy (Mehta, 2006a); (Thomas, 2008). With the availability of HCV direct-acting antivirals (DAAs), these barriers should diminish; however, treatment of HIV/HCV-coinfected patients requires continued awareness and attention to the complex drug interactions that can occur between DAAs and antiretroviral medications. Drug interactions with DAAs and antiretroviral agents are summarized below as well as in the Department of Health and Human Services treatment guidelines, www.aidsinfo.nih.gov. Another resource for screening for drug interactions with DAAs is the University of Liverpool website, www.hep-druginteractions.org.

Recommendations Related to HCV Medication Interactions with HIV Antiretroviral Medications

RECOMMENDED	RATING
Antiretroviral drug switches, when needed, should be done in collaboration with the HIV practitioner. For HIV antiretroviral and HCV direct-acting antiviral combinations not addressed below, expert consultation is recommended.	I, A
Daclatasvir when used in combination with other antivirals: Daclatasvir requires dose adjustment with ritonavir-boosted atazanavir (a decrease to 30 mg daily) and efavirenz or etravirine (an increase to 90 mg daily).	IIa, B
Daily fixed-dose combination of elbasvir/grazoprevir:	IIa, B

Recommendations Related to HCV Medication Interactions with HIV Antiretroviral Medications

Elbasvir/grazoprevir should be used with antiretroviral drugs with which it does not have clinically significant interactions: abacavir, emtricitabine, enfuvirtide, lamivudine, raltegravir, dolutegravir, rilpivirine, and tenofovir.	
Simeprevir when used in combination with other antivirals: Simeprevir should be used with antiretroviral drugs with which it does not have clinically significant interactions: abacavir, emtricitabine, enfuvirtide, lamivudine, maraviroc, raltegravir, (and probably dolutegravir), rilpivirine, and tenofovir.	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg): Sofosbuvir/velpatasvir can be used with most antiretrovirals, but not efavirenz or etravirine. Because velpatasvir increases tenofovir levels, when given as tenofovir disoproxil fumarate (TDF), concomitant use mandates consideration of renal function and should be avoided in those with eGFR below 60 mL/min. In patients with eGFR >60 mL/min concomitant dosing of velpatasvir and TDF with ritonavir-boosted or cobicistat-boosted regimens did not result in renal toxicity in 56 subjects. Renal monitoring is recommended during the dosing period. Tenofovir alafenamide (TAF) may be an alternative to TDF during sofosbuvir/velpatasvir treatment for patients who take cobicistat or ritonavir as part of their antiretroviral therapy.	IIa, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg): Ledipasvir/sofosbuvir can be used with most antiretrovirals. Because ledipasvir increases tenofovir levels, when given as tenofovir disoproxil fumarate (TDF), concomitant use mandates consideration of estimated glomerular filtration rate (eGFR) and should be avoided in those with eGFR below 60 mL/min. Because potentiation of this effect occurs when TDF is used with ritonavir-boosted or cobicistat-boosted regimens, ledipasvir should be avoided with this combination (pending further data) unless antiretroviral regimen cannot be changed and the urgency of treatment is high. Tenofovir alafenamide (TAF) may be an alternative to TDF during ledipasvir/sofosbuvir treatment for patients who take cobicistat or ritonavir as part of their antiretroviral therapy.	IIa, C
For combinations expected to increase tenofovir levels, baseline and ongoing assessment for tenofovir nephrotoxicity is recommended.	IIa, C
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) (paritaprevir/ritonavir/ombitasvir plus dasabuvir or PrOD): • Paritaprevir/ritonavir/ombitasvir plus dasabuvir should be used with antiretroviral drugs with which they do not have substantial interactions: atazanavir, dolutegravir, emtricitabine, enfuvirtide, lamivudine, raltegravir, and tenofovir. • The dose of ritonavir used for boosting of HIV protease inhibitors may need to be adjusted (or held) when administered with paritaprevir/ritonavir/ombitasvir plus dasabuvir and then restored when HCV treatment is completed. The HIV protease inhibitor should be administered at the same time as the fixed-dose HCV combination.	IIa, C

Regimens Not Recommended for Patients with HIV/HCV Coinfection

NOT RECOMMENDED	RATING
Antiretroviral treatment interruption to allow HCV therapy is Not Recommended.	III, A

Regimens Not Recommended for Patients with HIV/HCV Coinfection	
Elbasvir/grazoprevir should NOT be used with cobicistat, efavirenz, etravirine, nevirapine, or any HIV protease inhibitor.	III, B
Sofosbuvir/velpatasvir should NOT be used with efavirenz, etravirine, or nevirapine.	III, B
Sofosbuvir-based regimens should NOT be used with tipranavir.	III, B
Paritaprevir/ritonavir/ombitasvir plus dasabuvir should NOT be used with darunavir, efavirenz, ritonavir-boosted lopinavir, ritonavir-boosted tipranavir, etravirine, nevirapine, cobicistat, or rilpivirine.	III, B
Paritaprevir/ritonavir/ombitasvir with or without dasabuvir should NOT be used in HIV/HCV-coinfected individuals who are not taking antiretroviral therapy.	III, B
Ribavirin should NOT be used with didanosine, stavudine, or zidovudine.	III, B
Simeprevir should NOT be used with cobicistat, efavirenz, etravirine, nevirapine, or any HIV protease inhibitor.	III, B

Pharmacokinetics and Drug Interactions

Extensive recommendations for antiretroviral therapy use, including for persons anticipating HCV treatment, are found at jama.jamanetwork.com and aidsinfo.nih.gov.

Antiretroviral drug switches may be performed to allow compatibility of DAAs, with the goal of maintaining HIV suppression without compromising future options. Considerations include prior treatment history, responses to antiretroviral therapy, resistance profiles, and drug tolerance (Gunthard, 2014); (DHHS, 2014; aidsinfo.nih.gov). Treatment interruption in HIV/HCV-coinfected individuals is not recommended, as it is associated with increased cardiovascular events (SMART, 2006) and increased rates of fibrosis progression and liver-related events (Tedaldi, 2008); (Thorpe, 2011). If HCV treatment is nonurgent and antiretroviral compatibility and safety with DAAs is unclear, expert consultation should be sought or postponing HCV treatment should be considered until additional data are available.

Daclatasvir

Daclatasvir is approved by the US Food and Drug Administration (FDA) for use in combination with sofosbuvir for persons with HCV genotype 3 infection. Daclatasvir is a substrate and a very weak inducer of CYP3A4 and a substrate and inhibitor of P-gp. Daclatasvir also inhibits OATP1B1, BCRP, and organic cation transporter 1. Given that daclatasvir is a CYP3A4 substrate, it is susceptible to drug interactions with potent inducers and inhibitors of this enzyme. An increased dose of daclatasvir (120 mg vs 60 mg) was studied in combination with efavirenz, a potent CYP3A4 inducer, in uninfected volunteers. The results suggested that doubling the daclatasvir dose was excessive, and based on modeling and simulation, a 90 mg dose of daclatasvir is recommended with efavirenz (Bifano, 2013). A reduced dose of daclatasvir (20 mg vs 60 mg) was studied in combination with ritonavir-boosted atazanavir, a potent CYP3A4 inhibitor, in uninfected volunteers. The results suggested that dose reduction of daclatasvir to 20 mg was excessive, and based on modeling and simulation, a 30 mg dose of daclatasvir is recommended with ritonavir-boosted atazanavir. Based on the results of this study, a similar interaction was expected with ritonavir-boosted darunavir or lopinavir, and individuals received a reduced dose of daclatasvir 30 mg in the ALLY-2 trial (described below). Subsequent studies suggested that individuals should receive full doses of daclatasvir 60 mg with ritonavir-boosted darunavir or lopinavir. The pharmacokinetics of darunavir and lopinavir are not substantially affected by daclatasvir (Gandhi, 2015). Daclatasvir does not have clinically significant interactions with tenofovir (Bifano, 2013) or dolutegravir (Song, 2015). Daclatasvir has not been studied with emtricitabine, abacavir, rilpivirine, raltegravir, cobicistat-boosted elvitegravir, or maraviroc, but substantial interactions are not expected based on the pharmacology of these agents. There is potential for a decrease in daclatasvir levels with etravirine, and an

increased dose (90 mg) of daclatasvir is recommended when used with etravirine, as with efavirenz. Antiretroviral agents allowed in the ALLY-2 trial, which determined the safety and efficacy of daclatasvir and sofosbuvir in HIV/HCV-coinfected individuals, were ritonavir-boosted atazanavir, darunavir, or lopinavir, efavirenz, nevirapine, rilpivirine, raltegravir, and dolutegravir (Wyles, 2015).

Elbasvir/grazoprevir

Elbasvir is a substrate for CYP3A4 and P-gp. Elbasvir is an inhibitor of the drug transporters BCRP and P-gp. Grazoprevir is a substrate for CYP3A4, P-gp, and OATP1B1. Moderate and strong CYP3A and P-gp inducers (including efavirenz) are not recommended for coadministration with EBR/GZR. OATP1B1 inhibitors are also not recommended with grazoprevir. In terms of its ability to act as a perpetrator in interactions, grazoprevir is an inhibitor of CYP3A4 (weak), UGT1A1 (weak), and BCRP. Elbasvir 50 mg and grazoprevir 100 mg are only available in a fixed-dose combination (hereafter, elbasvir/grazoprevir).

Elbasvir/grazoprevir is incompatible with all ritonavir-boosted HIV protease inhibitors and efavirenz. While this DAA combination has not been studied with etravirine or cobicistat-boosted elvitegravir, drug interactions are expected and these combinations should be avoided. Elbasvir/grazoprevir is compatible with raltegravir, dolutegravir, rilpivirine, and the HIV nucleos(t)ide analogs.

Sofosbuvir

Sofosbuvir is not metabolized nor does it induce or inhibit any cytochrome P450 (CYP) enzymes. Sofosbuvir is a substrate (but not an inhibitor) of the drug transporters, p-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Drug interaction studies with antiretroviral drugs (ie, efavirenz, tenofovir, emtricitabine, rilpivirine, ritonavir-boosted darunavir, and raltegravir) in uninfected persons identified no clinically significant interactions (Kirby, 2012). Sofosbuvir is not recommended for use with tipranavir because of the potential of this antiretroviral drug to induce P-gp (see sofosbuvir prescribing information).

Ledipasvir/sofosbuvir

Ledipasvir is available only in a fixed-dose combination tablet with sofosbuvir (hereafter ledipasvir/sofosbuvir). Ledipasvir undergoes minimal metabolism and does not inhibit or induce CYP enzymes. Ledipasvir is a substrate of P-gp and an inhibitor of P-gp and BCRP. Drug interaction studies of ledipasvir (with or without sofosbuvir) with antiretroviral drugs in uninfected persons did not identify clinically significant interactions with abacavir, dolutegravir, emtricitabine, lamivudine, raltegravir, or rilpivirine (German, 2014); (Garrison, 2015). Interactions with maraviroc and enfuvirtide are not expected based on their pharmacologic profiles. Ledipasvir area under the curve (AUC) is decreased by 34% when coadministered with efavirenz-containing regimens and increased by 96% when coadministered with ritonavir-boosted atazanavir (German, 2014). No dose adjustments of ledipasvir are recommended to account for these interactions.

Ledipasvir increases tenofovir levels, which may increase the risk of tenofovir-associated renal toxicity. The magnitude of the increase in tenofovir levels is dependent on the tenofovir formulation used (ie, tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF]) and other concomitant antiretroviral drugs. With the addition of ledipasvir/sofosbuvir, tenofovir levels (when given as TDF) are increased with efavirenz, rilpivirine (German, 2014), dolutegravir, ritonavir-boosted atazanavir, and ritonavir-boosted darunavir (German, 2015). The absolute tenofovir levels are highest when TDF is administered with ritonavir-boosted protease inhibitors. When ledipasvir/sofosbuvir is administered to individuals taking TDF and ritonavir-boosted HIV protease inhibitors, the tenofovir levels exceed those deemed renally safe. Thus, to date, individuals receiving ritonavir-boosted HIV protease inhibitors have been excluded from clinical studies of ledipasvir/sofosbuvir. Individuals receiving elvitegravir and cobicistat have also been excluded from clinical studies of ledipasvir/sofosbuvir because cobicistat trough levels are increased 4-fold (see ledipasvir and sofosbuvir prescribing information) by ledipasvir.

In the ERADICATE study, ledipasvir/sofosbuvir was administered to 37 HIV/HCV-coinfected patients taking combination antiretroviral therapy, including 16 taking regimens containing tenofovir disoproxil fumarate, emtricitabine, and efavirenz,

and all with baseline eGFR of 60 mL/min or higher (Osinusi, 2014). Changes in creatinine level or glomerular filtration rate (GFR) in these 37 patients were similar to patients not taking antiretroviral therapy. Further safety data from the phase III ION-4 study are described below regarding interactions between ledipasvir/sofosbuvir and raltegravir, rilpivirine, or efavirenz, each in combination with fixed-dose tenofovir disoproxil fumarate and emtricitabine.

Renal parameters should therefore be checked at baseline and regularly thereafter while on therapy when ledipasvir/sofosbuvir is administered with tenofovir disoproxil fumarate-containing regimens. Baseline parameters should include measuring creatinine level, electrolytes (including phosphorus), and urinary protein and glucose measurements, according to recent guidelines for management of chronic kidney disease in those with HIV that include indications for nephrology consultation (Lucas, 2014). Changing antiretroviral therapy or delaying HCV treatment if nonurgent may be considered for those at high risk for renal toxicity (especially those with an eGFR between 30 mL/min and 60 mL/min or who have preexisting evidence of Fanconi syndrome) and particularly those taking tenofovir disoproxil fumarate and a ritonavir-boosted HIV protease inhibitor, as there are currently few efficacy or safety data for these combinations (see ledipasvir/sofosbuvir prescribing information). If the urgency of HCV treatment and the risk of switching antiretroviral regimens are both high and there is no safer alternative to ledipasvir/sofosbuvir, then frequent monitoring (every 2-4 weeks) of urine parameters is recommended for concomitant use with tenofovir disoproxil fumarate and a ritonavir-boosted HIV protease inhibitor. Tenofovir disoproxil fumarate should also be properly dosed and adjusted for eGFR at baseline and while on therapy (Lucas, 2014).

Though there is an absence of data at this time on the renal safety of tenofovir when given as TAF with ledipasvir/sofosbuvir, a study of tenofovir pharmacokinetics in healthy volunteers receiving the combination of TAF, emtricitabine, and cobicistat-boosted elvitegravir with ledipasvir/sofosbuvir found that tenofovir levels were only 20% of the typical tenofovir exposures seen with TDF (Garrison, 2015). Based on these pharmacokinetic data in healthy volunteers, TAF may be an alternative to TDF during ledipasvir/sofosbuvir treatment for patients who take elvitegravir/cobicistat or ritonavir-boosted HIV protease inhibitors as part of their antiretroviral therapy; however, there are no safety data for this combination in coinfected patients.

Based on data in healthy volunteers, tenofovir pharmacokinetics are lower with tenofovir alafenamide (TAF) relative to TDF, thus TAF may be an alternative to TDF during ledipasvir/sofosbuvir treatment for patients who take elvitegravir/cobicistat or ritonavir-boosted HIV protease inhibitors as part of their antiretroviral therapy, however there are no safety data for this combination in coinfected patients.

Paritaprevir/ritonavir/ombitasvir + dasabuvir

Paritaprevir is an inhibitor of the organic anion-transporting polypeptide 1B1 (OATP1B1). Ritonavir is coformulated with paritaprevir and ombitasvir and used to improve the pharmacokinetics of paritaprevir. As ritonavir has anti-HIV activity, HIV/HCV-coinfected patients should have achieved HIV RNA suppression prior to initiation of this regimen; those not taking antiretroviral therapy should avoid use of this fixed-dose combination due to the potential for low-dose ritonavir to select for HIV protease-inhibitor resistance.

Ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir are metabolized by, and inhibitors of CYP enzymes (3A4 and 2C8), P-gp, BCRP and the hepatic uptake transporter OATP1B1. Studies of uninfected volunteers did not reveal notable pharmacologic interactions with paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) plus dasabuvir (250 mg) (hereafter PrOD) or tenofovir disoproxil fumarate and emtricitabine (when tested separately from other fixed-dose combinations), raltegravir (Khatri, 2015b), abacavir, lamivudine, or dolutegravir (Khatri, 2015). In uninfected volunteers, when PrOD was combined with efavirenz, emtricitabine, and tenofovir disoproxil fumarate, clinically significant gastrointestinal and neurologic adverse events occurred, coincident with elevations of alanine aminotransferase levels. When PrOD was combined with rilpivirine, exposures to rilpivirine were substantially increased. Therefore, rilpivirine and efavirenz should not be used with PrOD.

Because ritonavir is a component of the fixed-dose combination of paritaprevir and ombitasvir, the total daily dose of ritonavir must be carefully considered when using PrOD with ritonavir-boosted HIV protease inhibitors. Coadministration with ritonavir-boosted lopinavir would result in a 300 mg daily dose of ritonavir, a dose associated with substantial gastrointestinal adverse effects; this combination is not recommended. Once- and twice-daily doses of darunavir have

been studied with PrOD in uninfected individuals. Darunavir trough levels are lowered 48% and 43% with once- and twice-daily doses of darunavir, respectively. The average absolute darunavir trough levels in these studies were 30% to 50% of typical values. Paritaprevir AUC is increased 30% with once-daily darunavir and decreased 41% with twice-daily darunavir. The mechanism and clinical significance of the discrepant effect on paritaprevir is unclear. Thus, PrOD should not be used with ritonavir-boosted darunavir pending further data. PrOD can be given with atazanavir, but the separate ritonavir boosting tablet should be held during PrOD therapy and atazanavir should be administered at the same time as the fixed-dose combination of ritonavir-boosted paritaprevir and ombitasvir. Paritaprevir levels are increased 1.5- to 3-fold with atazanavir, but no dose adjustment of paritaprevir is recommended (Khatri, 2016). Inhibition of OATP1B1 by PrOD increases indirect bilirubin concentrations, and this effect may be attenuated in individuals taking atazanavir (Eron, 2014).

Twenty-eight HIV/HCV-coinfected subjects already taking ritonavir-boosted atazanavir (with ritonavir coming from the HCV regimen during the time of coadministration) were treated with a regimen of PrOD and ribavirin as part of the TURQUOISE-1 study (Sulkowski, 2015).

Simeprevir

Simeprevir is metabolized primarily by CYP3A4 and is therefore susceptible to drug interactions with inhibitors and inducers of this enzyme. Simeprevir is also an inhibitor of OATP1B1 and P-gp. Drug interaction studies with antiretroviral drugs in HIV-uninfected volunteers suggested no substantial interactions with tenofovir, rilpivirine, or raltegravir; however, simeprevir concentrations were substantially decreased when dosed with efavirenz and substantially increased when dosed with ritonavir-boosted darunavir. Use with efavirenz, etravirine, cobicistat, or boosted HIV protease inhibitors is not recommended (Kiser, 2013).

Sofosbuvir/velpatasvir

Velpatasvir is available only in a fixed-dose combination tablet with sofosbuvir (hereafter sofosbuvir/velpatasvir). Velpatasvir is metabolized by CYP3A4, CYP2C8, and CYP2B6. It does not appear to inhibit or induce any CYP enzymes. Velpatasvir is a substrate for P-gp and BCRP, and inhibits P-gp, BCRP, and OATP1B1/1B3, but does not induce any transporters. Velpatasvir absorption is pH-dependent. Refer to product labeling for guidance on temporal separation and dosing of gastric acid modifying agents.

Drug interaction studies with sofosbuvir/velpatasvir have been performed in HIV and HCV seronegative volunteers. As with ledipasvir/sofosbuvir, tenofovir exposures are increased, which may be problematic for individuals with eGFR values of less than 60 mL/min or in those receiving ritonavir or cobicistat-containing antiretroviral therapy with tenofovir disoproxil fumarate (TDF). Fifty-six HIV/HCV coinfected individuals receiving the combination of TDF with ritonavir or cobicistat-containing antiretroviral therapy were treated with sofosbuvir/velpatasvir in the ASTRAL-5 study with no difference in median creatinine clearance before and after sofosbuvir/velpatasvir treatment, but poor renal function was an exclusion for this study. Consider the use of tenofovir alafenamide (TAF) in place of TDF in those requiring ritonavir or cobicistat-containing antiretroviral therapy. If the combination of TDF with a ritonavir- or cobicistat-containing antiretroviral therapy is required, renal parameters should be checked at baseline and regularly thereafter while on sofosbuvir/velpatasvir. Velpatasvir exposures are significantly reduced with efavirenz and this combination is not recommended. Etravirine has not been studied with sofosbuvir/velpatasvir but is also not recommended. Indirect bilirubin level increases have been reported when sofosbuvir/velpatasvir was used in patients on atazanavir/ritonavir. These changes are not considered clinically significant.

Based on data in healthy volunteers, tenofovir pharmacokinetics are lower with tenofovir alafenamide (TAF) relative to TDF, thus TAF may be an alternative to TDF during sofosbuvir/velpatasvir treatment for patients who take elvitegravir/cobicistat or ritonavir-boosted HIV protease inhibitors as part of their antiretroviral therapy, however there are no safety data for this combination in coinfected patients.

Table. Drug Interactions Between Direct-Acting Antivirals and Antiretroviral Drugs

	sofosbuvir (SOF)	**ledipasvir LDV**	**velpatasvir (VEL)**	**simeprevir (SMV)**	**daclatasvir (DCV)**	**elbasvir/ grazoprevir (ELB / GRZ)**	**paritaprevir, ritonavir, ombitasvir + dasabuvir (PrOD)**	**paritaprevir, ritonavir, ombitasvir (PrO)**
Ritonavir-boosted atazanavir (ATZ)	ND	▲ LDV ▲ ATZ[a]	▲ VEL ▲ ATZ[a]	ND	▲ DCV[b]	▲ ELB ▲ GRZ ▲ ATZ	▲ PRV ▲ ATZ	▲ PRV ◀▶ ATZ
Ritonavir-boosted darunavir (DRV)	▲ SOF ◀▶ DRV	▲ LDV ◀▶ DRV[a]	◀▶ VEL ◀▶ DRV[a]	▲ SMV ◀▶ DRV	▲ DCV ◀▶ DRV	▲ ELB ▲ GRZ ◀▶ DRV	▼▲ PRV ▼ DRV	▲ PRV ◀▶ DRV
Ritonavir-boosted lopinavir (LPV)	ND	ND[a]	◀▶ VEL ◀▶ LPV[a]	ND	▲ DCV ◀▶ LPV	▲ ELB ▲ GRZ ◀▶ LPV	▲ PRV ◀▶ LPV	▲ PRV ◀▶ LPV
Ritonavir-boosted tipranavir (TPV/r)	ND	ND	ND	ND	ND	ND	ND	ND
Efavirenz (EFV)	◀▶ SOF ◀▶ EFV	▼ LDV ▼ EFV[a]	▼ VEL ▼ EFV	▼ SMV ◀▶ EFV	▼ DCV[b]	▼ ELB ▼ GRZ ▼ EFV	NPD[c]	ND
Rilpivirine (RPV)	◀▶ SOF ◀▶ RPV	◀▶ LDV ◀▶ RPV	◀▶ VEL ◀▶ RPV	◀▶ SMV ◀▶ RPV	ND	◀▶ ELB ◀▶ GRZ ◀▶ RPV	▲ PRV ▲ RPV	ND
Etravirine (ETV)	ND	ND	ND	ND	▼ DCV[b]	ND	ND	ND
Raltegravir (RAL)	◀▶ SOF ◀▶ RAL	◀▶ LDV ◀▶ RAL	◀▶ VEL ◀▶ RAL	◀▶ SMV ◀▶ RAL	ND	◀▶ ELB ◀▶ GRZ ▲ RAL	◀▶ PrOD ▲ RAL	◀▶ PrO ▲ RAL
Cobicistat-boosted elvitegravir (COB)	▲ SOF[a] ▲ COB	▲ LDV ▲ COB[a]	▲ VEL ▲ COB[a]	ND	▲ DCV[b]	▲ ELB ▲ GRZ ▲ COB	ND	ND

	sofosbuvir (SOF)	**ledipasvir LDV**	**velpatasvir (VEL)**	**simeprevir (SMV)**	**daclatasvir (DCV)**	**elbasvir/ grazoprevir (ELB / GRZ)**	**paritaprevir, ritonavir, ombitasvir + dasabuvir (PrOD)**	**paritaprevir, ritonavir, ombitasvir (PrO)**
Dolutegravir (DTG)	NA	◄► LDV ◄► DTG	◄► VEL ◄► DTG	ND	◄► DCL ▲ DTG	◄► ELB ◄► GRZ ▲ DTG	▼ PRV ▲ DTG	ND
Maraviroc (MVC)	ND	ND	ND	ND	ND	ND	ND	ND
Tenofovir (TFV) disoproxil fumarate	◄► SOF ◄► TFV	◄► LDV ▲ TFV	◄► VEL ▲ TFV	◄► SMV ◄► TFV	◄► DCV ◄► TFV	◄► ELB ◄► GRZ ▲ TFV	◄► PrOD ◄► TFV	◄► PrO ◄► TFV
Tenofovir (TFV) alafenamide	▲ SOF ▲ TFV[d]	◄► LDV ▲ TFV[d]	◄► VEL ▲ TFV[d]	ND	ND	ND	ND	ND

ND, No data; NPD, No pharmacokinetic data.
a. Only problematic when administered with tenofovir disoproxil fumarate; tenofovir levels are increased.
b. Decrease daclatasvir dose to 30 mg once daily with atazanavir; increase daclatasvir dose to 90 mg once daily with efavirenz or etravirine.
c. PrOD administered with efavirenz led to premature study discontinuation owing to toxic effects.
d. Studied as part of fixed-dose combinations with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir plus TAF, emtricitabine, elvitegravir, and cobicistat.

Ribavirin

Ribavirin has the potential for dangerous drug interactions with didanosine resulting in mitochondrial toxicity with hepatomegaly and steatosis, pancreatitis, and lactic acidosis; thus, concomitant administration of these 2 drugs is contraindicated (Fleischer, 2004). The combined use of ribavirin and zidovudine has been reported to increase the rates of anemia and the need for ribavirin dose reduction; thus, zidovudine is not recommended for use with ribavirin (Alvarez, 2006).

Recommended Regimens by level of evidence and alphabetically for:

Recommended Regimens for HIV/HCV-coinfected Individuals

RECOMMENDED	RATING
HIV/HCV-coinfected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications (see Initial Treatment of HCV Infection and Retreatment of Persons in Whom Prior Therapy Has Failed).	I, B

Recommended Regimens by level of evidence and alphabetically for: **Recommended Regimens for HIV/HCV-coinfected Individuals**	
Daily daclatasvir (refer above for dose) plus sofosbuvir (400 mg), with or without ribavirin (refer to Initial Treatment of HCV Infection and Retreatment of Persons in Whom Prior Therapy Has Failed sections for duration) is a Recommended regimen when antiretroviral regimen changes cannot be made to accommodate alternative HCV direct-acting antivirals.	I, B

Regimens Not Recommended for Patients with HIV/HCV Coinfection	
NOT RECOMMENDED	RATING
Treatment courses shorter than 12 weeks, such as the use of 8 weeks of ledipasvir/sofosbuvir.	IIb, C

Although fewer HIV/HCV-coinfected patients than HCV-monoinfected patients have been treated in trials of DAAs, efficacy rates thus far have been remarkably similar between the groups (Sulkowski, 2013); (Sulkowski, 2014); (Dieterich, 2014b); (Rodriguez-Torres, 2015); (Osinusi, 2015); (Sulkowski, 2015); (Dieterich, 2015); (Naggie, 2015); (Wyles, 2015). Thus, results from HCV monoinfection studies largely justify the recommendations for HIV/HCV coinfection (discussed in the Initial Treatment and Retreatment sections). Discussion specific to studies of HIV/HCV coinfection is included here.

Daclatasvir + sofosbuvir

ALLY-2 is a phase III clinical trial that evaluated the 12-week regimen of daclatasvir with sofosbuvir in patients with HIV/HCV coinfection and HCV genotypes 1 to 4 (Wyles, 2015). This open-label clinical trial enrolled both treatment-naive (n=151) and -experienced (n=52) HIV/HCV-coinfected patients. Treatment-naive patients were randomly assigned (2:1), with stratification by cirrhosis status and HCV genotype, to receive 12 weeks or 8 weeks of once-daily daclatasvir 60 mg (dose adjusted based on antiretroviral regimen) and sofosbuvir 400 mg; treatment-experienced patients received daclatasvir and sofosbuvir for 12 weeks. Genotype distribution was 83%, 9%, 6%, and 2% of patients, respectively, for genotypes 1, 2, 3, and 4 HCV infection, and 14% of all participants had cirrhosis. Antiretroviral drugs allowed were ritonavir-boosted darunavir, atazanavir, or lopinavir, efavirenz, nevirapine, rilpivirine, raltegravir, and dolutegravir. The combination of daclatasvir and sofosbuvir once daily for 12 weeks achieved an SVR12 in 97% of HIV/HCV-coinfected patients with HCV genotype 1, 2, 3, or 4, and was safe and well tolerated. Ninety-seven percent of treatment-naive patients and 98% of -experienced patients achieved an SVR. However, among patients who received 8 weeks of combination therapy, only 76% of patients achieved an SVR. Factors associated with relapse in this patient group included high baseline HCV RNA level (>2 million IU/mL; 69%), concomitant use of a boosted darunavir-based antiretroviral regimen with 30 mg of daclatasvir (67%), and the presence of cirrhosis (60%). More data are needed in certain subgroups (eg, patients with HCV genotype 3 and cirrhosis who had lower response rates to this regimen and patients without HIV infection) (Nelson, 2015).

Many HIV/HCV-coinfected patients are on antiretroviral regimens with drug interactions that absolutely preclude otherwise recommended DAA regimens. Switching an optimized antiretroviral regimen carries risks, including adverse effects and HIV viral breakthrough (Eron, 2010). HIV viral breakthrough is a particular concern for those with substantial antiretroviral experience or known resistance to antiretroviral drugs. For these situations, given the compatibility of daclatasvir and sofosbuvir with nearly all antiretroviral regimens (see pharmacologic considerations above), daclatasvir and sofosbuvir is recommended in order to avoid unnecessary switching of effective HIV antiretroviral regimens. When the optimal combination of DAAs and antiretroviral drugs is unclear, expert consultation is recommended.

Elbasvir/grazoprevir

The safety, tolerability, and efficacy of a novel second-generation NS3/4A serine protease inhibitor grazoprevir (MK-5172) plus NS5A inhibitor, elbasvir (MK-8742) was assessed in patients with HCV and HIV coinfection in this study. C-EDGE was a phase III, non-randomized, open-label, single-arm study in which treatment-naive patients with chronic HCV genotype 1, 4, or 6 infection and HIV coinfection, with or without cirrhosis, were enrolled in Europe, the USA, and Australia (Rockstroh, 2015). All patients were either naive to treatment with any antiretroviral therapy (ART) with a CD4+ T cell count more than 500 cells/mm^3 (N=211) or stable on current ART for at least 8 weeks with a CD4+ T cell count more than 200 cells/mm^3 (N=7) and undetectable HIV RNA levels. All 218 enrolled patients received elbasvir (50 mg) plus grazoprevir (100 mg) in a single-pill combination (elbasvir/grazoprevir) once daily for 12 weeks. All 218 patients

completed follow-up at week 12. Median baseline CD4+ T cell counts were 568 (424-626) cells/mm^3. Limited ARVs were allowed: specifically a nucleoside/nucleotide backbone of abacavir (21.6%) versus tenofovir (75.2%), in combination with raltegravir (52%), dolutegravir (27%), or rilpivirine (17%). SVR12 was achieved by 210 (96%) of 218 patients (95% CI 92.9–98.4). One patient did not achieve SVR12 because of a non-virological reason, and seven patients without cirrhosis relapsed (two subsequently confirmed as reinfections, highlighting the requirement of continued harm-reduction strategies post SVR). Thirty-five patients with cirrhosis achieved SVR12. The most common adverse events were fatigue (29; 13%), headache (27; 12%), and nausea (20; 9%). No patient discontinued treatment because of an adverse event. Three out of six patients who relapsed before SVR12 had NS3 and/or NS5A RASs, while the others had wild type at the time of relapse. Two patients receiving ART had transient HIV viremia, but subsequently returned to undetectable levels without change in ART. No significant changes were observed with CD4+ T cell counts or new opportunistic infections. Elbasvir/grazoprevir without ribavirin seems to be effective and well tolerated for patients coinfected with HIV with or without cirrhosis. These data are consistent with previous trials of this regimen in the monoinfected population (Zeuzem, 2017).

Ledipasvir/sofosbuvir

The safety and efficacy of 12 weeks of ledipasvir/sofosbuvir was evaluated in the phase II ERADICATE study, which treated 50 HIV/HCV-coinfected, HCV genotype 1-infected, treatment-naive patients without cirrhosis from an urban population in a single-center, open-label clinical trial (Osinusi, 2015). Thirteen patients were not receiving antiretroviral therapy and 37 patients were on protocol-allowed medications (tenofovir, emtricitabine, rilpivirine, raltegravir, and efavirenz). Although the inclusion criteria for patients receiving antiretroviral therapy allowed CD4+ T cell counts of greater than 100/µL, the median CD4+ T cell count was 576/µL. Overall, 98% achieved sustained virologic response at 12 weeks (SVR12; 13/13 in treatment-naive arm and 36/37 in treatment-experienced arm). There were no deaths, discontinuations, or clinically significant serious adverse events. Renal function was monitored frequently during this trial and after administration of study drugs using a battery of tests (serum creatinine, eGFR, urinary beta-2 microglobulin, proteinuria, and glycosuria). No clinically significant changes in these parameters or renal toxicity were observed. A larger study, ION-4, reported similar outcomes with ledipasvir/sofosbuvir (Naggie, 2015). A total of 335 HCV treatment-naive and -experienced HIV/HCV-coinfected patients were enrolled in the study and received ledipasvir/sofosbuvir once daily for 12 weeks. Patients received tenofovir disoproxil fumarate and emtricitabine with raltegravir (44%), efavirenz (48%), or rilpivirine (9%). HCV genotypes included were 1a (75%), 1b (23%), and 4 (2%); 20% of patients had cirrhosis, 34% were black, and 55% had not responded to prior HCV treatment. Overall, the SVR12 rate was 96% (321/335); 2 patients had on-treatment virologic failure judged to be a result of nonadherence, 10 had virologic relapse after discontinuing treatment, 1 died from endocarditis associated with injection drug use, and 1 was lost to follow-up. SVR12 rate was 94% (63/67) among patients with cirrhosis and 97% (179/185) among treatment-experienced patients. No patients discontinued the study drug because of an adverse event. Although all patients had GFRs above 60 mL/min at study entry, drug interaction studies suggested that some patients would have elevated levels of tenofovir disoproxil fumarate. There were 4 patients in whom serum creatinine level rose to 0.4 mg/dL or higher: 2 remained on tenofovir, 1 had the tenofovir dose reduced, and the other stopped taking tenofovir. Neither study reported clinically significant changes in CD4+ T cell counts or HIV RNA levels in the study subjects. Thus, these data suggest that 12 weeks of ledipasvir/sofosbuvir is a safe and effective regimen for HIV/HCV-coinfected patients with HCV genotype 1 taking select antiretroviral therapy (Osinusi, 2015); (Naggie, 2015). There are limited data regarding an 8-week duration of ledipasvir/sofosbuvir in HIV/HCV-coinfected patients (Ingiliz, 2016). Therefore, a shortened treatment course for HIV-infected persons cannot be recommended at this time.

Paritaprevir/ritonavir/ombitasvir + dasabuvir

PrOD was FDA-approved for use in HCV genotypes 1a and 1b because of its efficacy and safety in treatment-naive patients and PEG-IFN/ribavirin treatment-experienced patients with and without cirrhosis. Available information about response rates with this regimen in HIV/HCV-coinfected patients comes from the first part of the phase II TURQUOISE-1 study. In this study, treatment-naive (n=42) and -experienced (n=21) patients were randomly assigned to receive either 12 weeks or 24 weeks of PrOD and weight-based ribavirin (100 mg [<75 kg] to 1200 mg [≥75 kg]). Of the 63 study subjects, 12 had cirrhosis, 56 had HCV genotype 1a, and 7 had HCV genotype 1b. Two study-permitted antiretroviral regimens were chosen based on pharmacokinetic data from uninfected volunteers: 35 patients entered taking tenofovir disoproxil fumarate and emtricitabine with raltegravir and 28 patients entered taking tenofovir disoproxil fumarate and emtricitabine

with ritonavir-boosted atazanavir (with the ritonavir coming from the HCV regimen during the time of coadministration). Of the 31 patients who received 12 weeks of PrOD and ribavirin, 29 (93.5%) achieved an SVR12, 1 relapsed, and 1 withdrew consent from study participation. Similarly, of the 32 subjects in the 24-week arm, 29 (90.6%) achieved an SVR12, 1 experienced viral breakthrough, and 2 had apparent HCV reinfection. No treatment-related serious adverse events occurred and no subjects discontinued treatment because of medication intolerance (Sulkowski, 2015).

Simeprevir + sofosbuvir

The combination of simeprevir plus sofosbuvir with or without ribavirin has been studied in the phase II COSMOS trial in patients with HCV monoinfection (Lawitz, 2014b). This study is the main basis for the recommendation supporting the use of this all-oral combination for HCV genotype 1a or 1b monoinfection. Simeprevir plus sofosbuvir has been used anecdotally in patients with HIV/HCV coinfection, with a recent report of achieving an SVR in 11 (92%) of 12 patients (Del Bello, 2016). Despite the dearth of study data, this regimen may be considered for the treatment of HCV genotype 1 infection in patients with HIV infection who are receiving antiretroviral therapy that may be coadministered with simeprevir and sofosbuvir.

Similarly, few data exist for the combination of sofosbuvir plus simeprevir for the retreatment of HCV infection in HIV/HCV-coinfected patients. However, preliminary results obtained for HCV-monoinfected patients, including those with prior treatment failure and advanced fibrosis, support the expectation that this regimen will be highly effective in HIV/HCV-coinfected patients receiving compatible antiretroviral therapy as described above (see Retreatment of HCV-monoinfected patients); (Lawitz, 2014b).

Sofosbuvir/velpatasvir

The safety and efficacy of 12 weeks of sofosbuvir/velpatasvir was evaluated in a phase 3 study of 106 antiretroviral controlled HIV/HCV coinfected subjects (Wyles, 2016). HCV genotypes 1-4 were included and 18% (n=19) had compensated cirrhosis. HIV was controlled on ART including non-nucleoside reverse-transcriptase inhibitor (NNRTI-rilpivirine), integrase inhibitor (raltegravir or elvitegravir/cobicistat), or ritonavir-boosted protease inhibitor (PI- atazanavir, lopinavir, or darunavir) based regimens with either tenofovir/emtricitabine or abacavir/lamivudine. Fifty-three percent (n=56) of subjects were on tenofovir with a pharmacologic boosting agent (either ritonavir or cobicistat). Neither efavirenz nor etravirine were allowed in this study as concomitant dosing with sofosbuvir/velpatasvir in healthy volunteers resulted in clinically significant decreases in velpatasvir exposures. SVR12 was 95% with 2 relapses, both occurring in genotype 1a-infected patients. Similar results were noted within genotypes, in subjects with cirrhosis and in those with baseline NS5A RASs (n=12 at 15% threshold, SVR12=100%). There was no clinically significant change in serum creatinine or GFR and no subject required a change in their antiretroviral therapy during the study period.

In general, few HIV/HCV-coinfected patients with cirrhosis have been included in clinical trials of DAAs, and no data are available regarding HIV/HCV-coinfected patients with renal insufficiency or who have undergone solid organ transplantation. Despite a lack of data, it is highly likely that response rates are similar to those of HCV-monoinfected patients, as no study thus far in the DAA era has showed a lower efficacy for HIV/HCV-coinfected patients. Therefore, the respective guidance from these sections should be followed if treatment is otherwise warranted, with consideration of drug interactions.

No data currently exist to guide recommendations for the retreatment of HIV/HCV-coinfected patients or for the retreatment of simeprevir- or sofosbuvir-experienced individuals. When treatment is necessary, guidelines for HCV-monoinfected individuals are recommended.

Last update: April 12, 2017

Unique Populations: Patients with Decompensated Cirrhosis

Recommended for All Patients with HCV Infection Who Have Decompensated Cirrhosis	
RECOMMENDED	RATING
Patients with HCV infection who have decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh [CTP] class B or C) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center).	I, C

In the decompensated population, most subjects receiving DAA therapy experienced improvement in clinical and biochemical indicators of liver disease between baseline and post-treatment week 12 including patients with CTP class C cirrhosis (Fontana, 2015a). However, death and the need for liver transplantation were observed in treatment studies in the decompensated population, highlighting that not everyone benefits from therapy. Most deaths were related to the severity of underlying liver disease. The predictors of improvement or decline have not been clearly identified.

Decompensated Cirrhosis: HCV Genotype 1, 4, 5, or 6 Infection

Recommended Regimens by evidence level and alphabetically for:

Patients with Genotype 1, 4, 5, or 6, Who Have Decompensated Cirrhosis (Moderate or Severe Hepatic Impairment; CTP Class B or C), Who May or May Not Be Candidates for Liver Transplantation, Including Those with Hepatocellular Carcinoma

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated); for patients with genotype 1, 4, 5, or 6	12 weeks	I, A•
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin;‖ for patients with genotype 1, 4, 5, or 6	12 weeks	I, A♦
Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated); for patients with genotype 1 or 4	12 weeks	I, B

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.
‖ Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C.
• Only available data for genotype 6 are in patients with compensated cirrhosis.
♦ Only available data for genotype 5 and 6 are in small numbers of patients with compensated cirrhosis.

Recommended Regimens by evidence level and alphabetically for:

Patients with Genotype 1, 4, 5, or 6, Who Have Decompensated Cirrhosis, and Are Ribavirin Ineligible

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg); for patients with genotype 1, 4, 5, or 6	24 weeks	I, A♦
Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg); for patients with genotype 1 or 4	24 weeks	II, C
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg); for patients with genotype 1, 4, 5, or 6	24 weeks	II, C•

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.
• Only available data for genotype 6 are in patients with compensated cirrhosis.
♦ Only available data for genotype 5 and 6 are in small numbers of patients with compensated cirrhosis.

Recommended Regimens by evidence level and alphabetically for:

Patients with Genotype 1, 4, 5, or 6, Who Have Decompensated Cirrhosis, and in Whom Prior Sofosbuvir-based or NS5A-based Treatment Has Failed

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated); for patients with genotype 1, 4, 5, or 6	24 weeks	II, C•
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin;‖ for patients with genotype 1, 4, 5, or 6	24 weeks	II, C♦

‖ Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C.
• Only available data for genotype 6 are in patients with compensated cirrhosis.
♦ Only available data for genotype 5 and 6 are in small numbers of patients with compensated cirrhosis.

Ledipasvir/sofosbuvir

The SOLAR-1 study was a multicenter, randomized controlled trial of 108 patients with HCV genotype 1 and 4 who had decompensated cirrhosis, of whom 59 were classified as CTP class B (score 7 to 9) and 49 classified as CTP class C (score 10 to 12) cirrhosis. Subjects were randomly assigned to receive daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) and ribavirin (initial dose of 600 mg, increased as tolerated) for 12 or 24 weeks (Charlton, 2015b). After excluding the 7 subjects who underwent transplantation during the study, the SVR rate was 87% in CTP class B patients who received 12 weeks of treatment and 89% in subjects who received 24 weeks of treatment. Post-therapy virologic relapse occurred in 8% and 5% of the 12- and 24-week groups, respectively. Similarly, the rates of SVR were 86% and 87%, respectively, with 12 and 24 weeks of antiviral therapy in the CTP class C subjects. In the majority of subjects with CTP class B and C disease, the Model for End-Stage Liver Disease (MELD) and CTP scores decreased between baseline and post-treatment week 4. Of the 7 transplanted patients, 6 achieved a posttransplant virologic response and 1 died of multiorgan failure at posttransplant week 2. During the study, only 1 patient with CTP class C cirrhosis died. As expected, the frequency of serious adverse events increased with treatment duration in the CTP class B group (34% vs 10% in week 24 vs 12) as well as the CTP class C group (42% vs 26% in week 24 vs 12). Most serious adverse events were related to ribavirin. The mean daily dose of ribavirin in the decompensated patients was 600 mg/day and therapy was discontinued in 7% of the CTP class B patients and 8% of the CTP class C patients treated with 24 weeks.

The SOLAR-2 study was a multicenter randomized controlled trial of 108 patients with HCV genotypes 1 and 4 who had decompensated cirrhosis. Study participants who were treatment-naive or -experienced, with CTP class B cirrhosis or CTP class C cirrhosis, were randomly assigned to receive daily fixed-dose combination ledipasvir (90 mg) and sofosbuvir (400 mg) (hereafter ledipasvir/sofosbuvir) and ribavirin (initial dose of 600 mg, increased as tolerated) for 12 weeks or 24 weeks. All participants had a hemoglobin level greater than 10 g/dL and an estimated glomerular filtration rate (eGFR) greater than 40 mL/min (Manns, 2016).

Excluding 6 patients who had received a transplant, sustained virologic response (SVR) was achieved in 87% of those given the 12-week treatment course and 89% of those given the 24-week treatment course. Post-therapy virologic relapse occurred in 8% and 4% of the 12- and 24-week groups, respectively. Total bilirubin and serum albumin levels improved substantially at week 4 post-therapy compared with baseline in both treatment groups. Baseline CTP and MELD scores improved in more than 50% of the treated patients, but some patients did have worsening hepatic function. During the course of the study, 5 (5%) patients died from various causes but none of the deaths were attributed to antiviral therapy. Grade 3 or 4 adverse events were more common in the 24-week arm (34%) than in the 12-week arm (15%). These results indicate that a 12-week course of ledipasvir/sofosbuvir and ribavirin (initial dose of 600 mg, increased as tolerated) is an appropriate regimen for patients with decompensated cirrhosis who are infected with HCV genotype 1 or 4. Such therapy may lead to objective improvements in hepatic function and reduce the likelihood of recurrent HCV infection after subsequent transplantation. Most patients who started ribavirin at 600 mg per day did not receive higher doses.

A pilot study of 14 patients with compensated cirrhosis and HCV genotype 1 infection in whom prior sofosbuvir-based therapy had failed demonstrated that ledipasvir/sofosbuvir for 12 weeks was associated with a 100% SVR rate (Osinusi, 2014). In addition, results of a study of 51 HCV genotype 1-infected patients in whom prior sofosbuvir-based therapy had failed demonstrated that a 12-week course of ledipasvir/sofosbuvir and weight-based ribavirin (1000 to 1200 mg per day) led to a 98% rate of SVR at 12 weeks and the SVR rate in the 14 patients with compensated cirrhosis was 100% (SVR12) (Wyles, 2015b).

A multicenter, double-blind study from France reported on the use of daily ledipasvir/sofosbuvir for 24 weeks compared with daily ledipasvir/sofosbuvir and ribavirin for 12 weeks, with a 12-week placebo phase, in 154 patients with compensated cirrhosis and HCV genotype 1 infection in whom prior PEG-IFN/ribavirin treatment had failed (for most, treatment with PEG-IFN, ribavirin, and a protease inhibitor had also failed) (Bourliere, 2015). The mean MELD score was 7 (range, 6 to 16), 26% of patients had varices, and 13% had low serum albumin levels. The SVR12 rates were 96% with the 12-week regimen and 97% with the 24-week regimen. The most common adverse events were asthenia, headache,

and pruritus, but the frequency of severe adverse events and the need for early drug discontinuation were low in both treatment groups. In light of these results, it is reasonable to consider daily ledipasvir/sofosbuvir and ribavirin for 12 weeks in patients with decompensated cirrhosis in whom prior sofosbuvir-based treatment has failed.

Ledipasvir/sofosbuvir for 24 weeks also appears to be effective for patients with a 71% SVR in 41 HCV genotype 1-infected patients with compensated liver disease who failed a prior course of sofosbuvir-based therapy for 8 or 12 weeks (Lawitz, 2015b). As of February 2017, there are no data of this regimen given for 24 weeks in decompensated cirrhosis. However, a pilot study of 20 patients with CTP class B cirrhosis treated with ledipasvir/sofosbuvir for 12 weeks demonstrated an SVR of 65% (Gane, 2014a).

Data on the use of ledipasvir/sofosbuvir in patients with HCV genotypes 5 and 6 are very limited. Gane et al reported an SVR12 of 96% in 25 patients with HCV genotype 6 treated with ledipasvir/sofosbuvir in phase II clinical trials (Gane, 2015). Wong et al also reported an SVR12 of 95.3% with ledipasvir/sofosbuvir for 8 to 24 weeks without ribavirin in 65 adult Asian Americans with compensated cirrhosis and genotype 6 infection. The overall SVR was 92.3% in patients with cirrhosis and 97.4% in patients without cirrhosis (Wong, 2017). In an open-label study in France, ledipasvir/sofosbuvir was administered for 12 weeks to 41 treatment-naive or previously-treated subjects with genotype 5 HCV infection, with or without cirrhosis. The overall SVR12 was 93% (38/41) (Abergel, 2016).

Sofosbuvir/velpatasvir

The ASTRAL-4 study was a multicenter, randomized, controlled trial of 267 patients with multiple HCV genotypes and decompensated cirrhosis who were treatment-naive (45%) or -experienced (55%) with CTP class A (10%), B, or C cirrhosis. Patients were randomly assigned to receive daily fixed-dose combination sofosbuvir (400 mg) and velpatasvir (100 mg) (hereafter sofosbuvir/velpatasvir) with or without weight-based ribavirin (initial dose of 1000 mg/day if weight <75 kg and 1200 mg/day if weight ≥75 kg) for 12 weeks or sofosbuvir/velpatasvir for 24 weeks in a 1:1:1 ratio. All participants had a hemoglobin level greater than 10 g/dL and an eGFR greater than 40 mL/min and randomization was stratified by HCV genotype (Curry, 2015b). Overall, 60% of patients had HCV genotype 1a, 18% genotype 1b, 4% genotype 2, 15% genotype 3, 3% genotype 4, and <1% genotype 6. 95% of the patients had a baseline MELD <15.

SVR was achieved in 83% in those who received sofosbuvir/velpatasvir for 12 weeks, 94% in those who received sofosbuvir/velpatasvir with ribavirin for 12 weeks, and 86% in those who received sofosbuvir/velpatasvir for 24 weeks. Among patients with genotype 1, the SVR was 88%, 96%, and 92%, respectively. A total of 22 patients had virological failure including 20 patients with a post-therapy relapse and 2 patients with HCV genotype 3 who had an on-treatment virological breakthrough. The presence of baseline NS5A resistant substitutions was not associated with virological relapse. At post-treatment week 12, 47% had an improvement in CTP score while 42% had no change and 11% had worsening CTP scores. During the course of the study, 9 (3%) patients died from various causes, none of which were felt to be related to antiviral therapy. Serious adverse events were reported in 16% to 19% of the treated patients. Anemia defined as a hemoglobin <10 g/dL was reported in 23% of the group receiving ribavirin and 8% and 9% in those who received 12 and 24 weeks of therapy without ribavirin, respectively.

Sofosbuvir/velpatasvir with weight-based ribavirin for 24 weeks was also given to 65 patients with compensated cirrhosis who had failed a prior NS5A-containing regimen (Gane, 2016). The overall SVR was 95% and was 97% in subjects with HCV genotype 1a and 1b, 91% in genotype 2, and 76% in HCV genotype 3. As of May 2016, there are no data for this regimen given for 24 weeks in patients with decompensated cirrhosis.

In ASTRAL-1, sofosbuvir/velpatasvir without ribavirin was given for 12 weeks to 35 patients with compensated cirrhosis and genotype 5, and 41 patients with compensated cirrhosis and genotype 6 (Feld, 2015). The overall SVR12 was 97% in the genotype 5 patients and 100% in the genotype 6 patients. Of note, a 100% SVR was achieved in the small number of genotype 5 patients (n=5) and genotype 6 patients (n=6) with compensated cirrhosis enrolled in ASTRAL-1.

Daclatasvir + sofosbuvir

In the phase III ALLY-1 study (Poordad, 2016) daily daclatasvir (60 mg) was administered in combination with daily sofosbuvir (400 mg) and low initial dose of ribavirin (600 mg) for 12 weeks to treatment-naive and -experienced patients

who predominantly had HCV genotype 1 infection, in 2 specific populations: those with advanced cirrhosis (CTP class B and C; n=60) and those with recurrent HCV infection posttransplant (n=53). The SVR12 rate was 83% among those with advanced cirrhosis and 94% among those with recurrent HCV infection posttransplant. In the population with advanced cirrhosis, SVR12 rate was 76% among patients with HCV genotype 1a and 100% among patients with HCV genotype 1b. Response rates differed based on severity of disease among those with advanced cirrhosis, SVR12 rate was 94% among patients with CTP class B cirrhosis but only 56% among patients with CTP class C cirrhosis. Among subjects with HCV genotype 3, SVR12 rates were 83% and 91%, respectively, in those with advanced cirrhosis and recurrent HCV infection posttransplant.

Real-world studies

Observational cohort studies have evaluated other combinations of DAA agents in patients with decompensated cirrhosis. Foster and colleagues reported on the use of ledipasvir (90 mg)/sofosbuvir (400 mg) or daclatasvir (60 mg) plus sofosbuvir (400 mg) with or without ribavirin for 12 weeks in 235 genotype-1 patients from the United Kingdom (Foster, 2016). The SVR rates were similar in the 235 genotype-1 subjects receiving ledipasvir/sofosbuvir plus ribavirin or ledipasvir/sofosbuvir (86% to 81%, respectively) and those receiving daclatasvir plus sofosbuvir with ribavirin or daclatasvir plus sofosbuvir therapy (82% to 60%). In this real-world study, 91% of the patients received ribavirin and only 6% discontinued ribavirin while 20% required a ribavirin dose reduction. MELD scores improved in 42% of treated patients and worsened in 11%. In addition, there were 14 deaths and 26% of the patients had an SAE but none were treatment related.

A multicenter study from Spain also described the safety and efficacy of sofosbuvir-based therapy in 739 HCV patients with decompensated cirrhosis (Fernandez-Carillo, 2016). In this study, the majority of patients had HCV genotype 1a or 1b infection, 76% had CTP class A, and 24% had CTP class B/C cirrhosis. Patients were treated with a variety of regimens including simeprevir plus sofosbuvir (45%), daclatasvir plus sofosbuvir (22%), and ledipasvir/sofosbuvir (16%). Overall SVR was 94% in CTP class A patients compared to 78% in CTP class B/C patients and rates of virological relapse were 4% and 14%, respectively. Sixteen patients died. Both deaths and SAEs were significantly more common in those with CTP class B/C. These data highlight the lower efficacy and increased safety concerns when treating patients with more advanced liver failure.

Protease-inhibitor containing regimens

To date, the fixed-dose combination of elbasvir (50 mg) and grazoprevir (100 mg) (hereafter, elbasvir/grazoprevir) has not been studied in decompensated cirrhosis. A phase II, non-randomized, open-label study of elbasvir (50 mg) and grazoprevir (50 mg) for 12 weeks was completed in 30 HCV genotype 1 patients with CTP class B cirrhosis (Jacobson, 2015). The SVR12 rate was 90% and 1 patient died of liver failure at post-treatment week 4. MELD scores improved in 15 treated patients, were unchanged in 9, and increased in 6. However, there are no safety or efficacy data regarding the approved FDC elbasvir/grazoprevir doses in patients with decompensated cirrhosis. Therefore, until further data are available, treatment of patients with decompensated cirrhosis with elbasvir/grazoprevir is not recommended.

Recent data reported by the US FDA have demonstrated that some patients with compensated cirrhosis and HCV genotype 1 treated with paritaprevir, ombitasvir, and dasabuvir may develop rapid onset of direct hyperbilirubinemia within 1 to 4 weeks of starting treatment without ALT elevations that can lead to rapidly progressive liver failure and death. A multicenter cohort study from Israel reported 7 patients who received PrOD and also developed decompensation within 1 to 8 weeks of starting therapy, including 1 patient who died (Zuckerman, 2016). Therefore, this antiviral treatment regimen is CONTRAINDICATED in all patients with decompensated cirrhosis due to concerns of hepatotoxicity. In addition, all patients with cirrhosis receiving this regimen should be monitored for clinical signs and symptoms of hepatic decompensation and undergo hepatic laboratory testing at baseline and at least every 4 weeks on therapy.

Decompensated Cirrhosis: Genotype 2 and 3 HCV Infection

Recommended Regimens by evidence level and alphabetically for:

Patients with Genotype 2 or 3, Who Have Decompensated Cirrhosis (Moderate or Severe Hepatic Impairment; CTP Class B or C), and Who May or May Not Be Candidates for Liver Transplantation, Including Those with Hepatocellular Carcinoma

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin	12 weeks	I, A
Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated)	12 weeks	II, B

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Sofosbuvir/velpatasvir

In the ASTRAL-4 study, the SVR in 12 patients CTP class B cirrhosis with genotype 2 was 100% with sofosbuvir/velpatasvir for 12 weeks with and without ribavirin and 75% with sofosbuvir/velpatasvir for 24 weeks. Similarly, among 39 patients with CTP class B cirrhosis with HCV genotype 3, the SVR was 50% and 85% with sofosbuvir/velpatasvir for 12 weeks without and with ribavirin and 50% with sofosbuvir/velpatasvir without ribavirin for 24 weeks. Therefore, genotype 3 patients in particular appear to benefit from the addition of ribavirin to the regimen (Curry, 2015b). For decompensated HCV patients who are ribavirin ineligible, daily fixed-dose combination sofosbuvir (400 mg)/velpatasvir (100 mg) for 24 weeks is currently recommended but further studies in larger numbers of patients are needed to define the optimal duration of therapy. Sofosbuvir/velpatasvir has not been studied in CTP class C patients.

Daclatasvir + sofosbuvir

Daclatasvir with sofosbuvir for 12 weeks was approved by the FDA for the treatment of HCV genotype 3 infection in patients without and with cirrhosis. Although daclatasvir with sofosbuvir was not approved for the treatment of HCV genotype 2 infection, daclatasvir maintains adequate activity against HCV genotype 2 despite a 50% effective concentration (EC_{50}) that increases by several logs in the presence of the prevalent M31 substitution (Wang, 2014). In fact, daclatasvir with sofosbuvir was associated with high rates of SVR in treatment-naive patients with HCV genotype 2 infection with both 12 weeks and 24 weeks of therapy (Wyles, 2015); (Sulkowski, 2014). It is unclear if there is a subgroup of HCV genotype 2-infected patients who would benefit from extending treatment to 24 weeks. For patients who require treatment but cannot tolerate ribavirin, an alternative regimen of daclatasvir with sofosbuvir for 12 weeks is recommended with consideration of extending treatment to 24 weeks for patients with poor baseline characteristics (ie, decompensated cirrhosis). Relevant data supporting daclatasvir, sofosbuvir, and ribavirin from the ALLY-1 trial are described here. In

addition, use of daclatasvir plus sofosbuvir with or without ribavirin from an ongoing observational cohort study in 121 patients with decompensated cirrhosis and genotype 3 infection from the UK demonstrated an SVR of 70% and 71%, respectively (Foster, 2016). In comparison, the SVR in 68 patients with decompensated genotype 3 treated with ledipasvir/sofosbuvir with or without ribavirin were 43% and 59%, respectively.

A multicenter, compassionate use study of daclatasvir (60 mg), sofosbuvir (400 mg) ± ribavirin for 24 weeks in 101 genotype 3 European patients was reported (Welzel, 2015). 81% of the patients had CTP class B cirrhosis, the MELD score was >15 in 16%, and 7% were LT recipients. To date, SVR 12 data has demonstrated an SVR of 85% to 100%. Twenty-two patients had an SAE and therapy was discontinued in 5, while 2 patients died.

Mixed genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for mixed genotypes with direct-acting antivirals are sparse but utilization of a pangenotypic regimen should be considered. When the correct combination or duration is unclear, expert consultation should be sought.

Last update: April 12, 2017

Unique Patient Populations: Patients Who Develop Recurrent HCV Infection Post-Liver Transplantation

Genotype 1 or 4

Recommended Regimens by evidence level and alphabetically for:

Treatment-naive and -Experienced Patients, with HCV Genotype 1 or 4 Infection in the Allograft, Including Those with Compensated Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin	12 weeks	I, A
Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated)	12 weeks	I, B

Recommended Regimens by evidence level and alphabetically for:

Treatment-naive Patients, with HCV Genotype 1 or 4 Infection in the Allograft, and with Compensated Liver Disease, Who Are Ribavirin Ineligible

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	24 weeks	I, B
Daily daclatasvir (60 mg) plus sofosbuvir (400 mg)	24 weeks	II, C

Recommended Regimen for:

Treatment-naive and -Experienced Liver Transplant Recipients, with Decompensated Cirrhosis (Child Turcotte Pugh [CTP] Class B or C), Who Have HCV Genotype 1 or 4 Infection in the Allograft

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated)	12 weeks	I, B

Alternative Regimen for:

Patients with HCV Genotype 1 Infection in the Allograft, Including Those with Compensated Cirrhosis

ALTERNATIVE	DURATION	RATING
Daily simeprevir (150 mg) plus sofosbuvir (400 mg) with or without weight-based ribavirin	12 weeks	I, B

Alternative Regimen for:

Patients with HCV Genotype 1 Infection in the Allograft, Including Those with Early-stage Fibrosis (Metavir Stage F0-F2)

ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) with weight-based ribavirin	24 weeks	I, B

Genotype 2

Recommended Regimens by evidence level and alphabetically for:

Treatment-naive and -Experienced Patients, with HCV Genotype 2 Infection in the Allograft, Including Those with Compensated Cirrhosis

RECOMMENDED	DURATION	RATING
Daily daclatasvir (60 mg) plus sofosbuvir (400 mg), with low initial dose of ribavirin (600 mg, increased as tolerated)	12 weeks	II, A
Daily sofosbuvir (400 mg) and weight-based ribavirin	24 weeks	II, C

Recommended Regimen for:

Treatment-naive and -Experienced Patients, with HCV Genotype 2 Infection in the Allograft, Including Those with Compensated Cirrhosis, Who Are Ribavirin Ineligible

RECOMMENDED	DURATION	RATING
Daily daclatasvir (60 mg) plus sofosbuvir (400 mg)	24 weeks	II, C

Recommended Regimen for:

Treatment-naive and -Experienced Liver-Transplant Recipients, with Decompensated Cirrhosis (Child Turcotte Pugh [CTP] Class B or C), Who Have HCV Genotype 2 Infection in the Allograft

RECOMMENDED	DURATION	RATING
Daily sofosbuvir (400 mg) and ribavirin (initial dose 600 mg/day, increased monthly by 200 mg/day as tolerated to weight-based dose)	24 weeks	II, C

Genotype 3

Recommended Regimen for:

Treatment-naive and -Experienced Patients, with HCV Genotype 3 Infection in the Allograft, Including Those with Compensated Cirrhosis

RECOMMENDED	DURATION	RATING
Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated)	12 weeks	II, A

Recommended Regimen for:

Treatment-naive and -Experienced Patients, with HCV Genotype 3 Infection in the Allograft, Including Those with Compensated Cirrhosis, Who Are Ribavirin Ineligible

RECOMMENDED	DURATION	RATING
Daily daclatasvir (60 mg) plus sofosbuvir (400 mg)	24 weeks	II, C

Daclatasvir + sofosbuvir

In the phase III ALLY-1 study (Poordad, 2016), daclatasvir (60 mg daily) was administered in combination with daily sofosbuvir (400 mg) and ribavirin (initial dose, 600 mg) for 12 weeks to treatment-naive and -experienced patients who predominantly had HCV genotype 1 infection, in two specific populations: those with advanced cirrhosis (Child Turcotte Pugh [CTP] class B or C; n=60) and those with recurrent HCV infection posttransplant (n=53). Rate of sustained virologic response of 12 weeks (SVR12) was 83% among those with advanced cirrhosis and 94% among those with recurrent HCV infection posttransplant. In the population with advanced cirrhosis, SVR12 rate was 76% among patients with HCV genotype 1a and 100% among patients with HCV genotype 1b. In the population with advanced cirrhosis, SVR12 rate was 94% among patients with CTP class B cirrhosis and 56% among patients with CTP class C cirrhosis. Among subjects with HCV genotype 3, SVR12 rates were 83% and 91%, respectively, in those with advanced cirrhosis and recurrent HCV infection posttransplant.

Fontana and colleagues (Fontana, 2016) reported on the use of daclatasvir-containing regimens with either sofosbuvir (n=77) or simeprevir (n=18) or both (n=2) for 24 weeks in 97 liver-transplant recipients with severe recurrent HCV infection. 93% of the patients had HCV genotype 1, 31% had biopsy-proven cirrhosis, 37% had severe cholestatic HCV, and the proportion with CTP A/B/C was 51%/ 31%/12%. The mean MELD score was 13.0 + 6.0 and 35% of the cohort received ribavirin. The SVR12 rate was 87% overall, 91% in the group that received daclatasvir and sofosbuvir with or without ribavirin, and 72% in the group that received daclatasvir and simeprevir with or without ribavirin. Although 8 patients died during or after therapy from graft dysfunction, CTP and MELD scores were stable or improved in 87% and 83% of patients, respectively. There were 3 virologic breakthroughs and 2 relapses in patients treated with daclatasvir and simeprevir. These data along with those from others suggest that daclatasvir should preferentially be combined with sofosbuvir rather than simeprevir in liver-transplant recipients, particularly in those with advanced liver disease (EASL, 2015a). Herzer and colleagues (Herzer, 2015) described 6 liver-transplant recipients with recurrent HCV infection, 4 (67%) of whom achieved SVR with a regimen of daclatasvir plus simeprevir with ribavirin. Overall, daclatasvir-containing regimens appear to be well tolerated, with anemia noted when ribavirin was used. Cyclosporine and tacrolimus increase daclatasvir area under the curve by 40% and 5%, respectively; these changes are not clinically significant. Daclatasvir does not cause clinically meaningful changes in calcineurin inhibitor, mammalian target of rapamycin (mTOR) inhibitor, steroid, or mycophenolate levels.

Ledipasvir/sofosbuvir

The SOLAR-1 study was a large, multicenter, randomized controlled trial that included liver-transplant recipients (n=223) across a broad spectrum of histologic and clinical severity of recurrence (n=111 with Metavir fibrosis stage F0-F3; n=51 with HCV genotype 1 or 4 and compensated CTP class A cirrhosis; n=61 with decompensated CTP class B or C cirrhosis). Study participants were randomly assigned to receive fixed-dose combination ledipasvir (90 mg) and sofosbuvir (400 mg) (hereafter ledipasvir/sofosbuvir) and weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥ 75 kg]) for either 12 weeks or 24 weeks. On an intention-to-treat basis, SVR was achieved in 96% of patients with Metavir fibrosis stages F0 to F3 and in 96% of those with compensated cirrhosis, in both the 12- and 24-week arms; all patients received ribavirin. Ribavirin dose was weight based for patients with Metavir fibrosis stage F0 to F3 and CTP class A cirrhosis. For patients with CTP class B or C cirrhosis, ribavirin was initiated at 600 mg daily followed by dose escalation as tolerated (Charlton, 2015b). Only 2% of patients discontinued treatment owing to adverse events. Efficacy was lower in patients with CTP class B cirrhosis (85% SVR12) or CTP class C cirrhosis (60% SVR12), with no increase in SVR observed in patients who received 24 weeks of treatment. Mortality rate was 10% during the study among patients with CTP class B or C cirrhosis. Very similar results were achieved using an identical study design in the SOLAR-2 study, which was conducted in Europe, Australia, and New Zealand. SOLAR-2 included 168 posttransplant patients without cirrhosis (fibrosis stage F0-F3) or with compensated cirrhosis (Child Turcotte Pugh [CTP] A) treated for 12 weeks (n=86) or 24 weeks (n=82). There were also 160 pre- and posttransplantation patients with decompensated cirrhosis (CTP B/C) treated for 12 weeks (n=78) or 24 weeks (n=82). SVR12 rates in posttransplant non-cirrhotic or compensated cirrhosis were 95% for 12 weeks of therapy and 98% for 24 weeks of therapy. Among patients with more severe disease, SVR12 rates were 85% for 12 weeks of therapy and 88% for 24 weeks of therapy.

As the importance of ribavirin cannot be ascertained from the SOLAR study, in which all patients received ribavirin, the

safest presumption is that ribavirin may contribute to the high SVR12 rates observed. In a previous study of a similar patient population to that of the SOLAR study, 40 patients with recurrent HCV infection following liver transplantation were treated for 24 weeks with sofosbuvir plus ribavirin, with SVR12 achieved in 70% (Charlton, 2015b). Although the basis for attenuated SVR rate observed in patients with more advanced HCV infection post-liver transplant is not known, these results, together with those of the sofosbuvir compassionate-use program, (Forns, 2015) suggest that the optimal period to initiate therapy may be the first 6 months to 12 months posttransplant to minimize the likelihood of having to treat patients with more advanced liver disease.

No data on ledipasvir/sofusbuvir are available for patients with HCV genotype 3 infection in the posttransplant setting. Very limited phase II data are available from a single-center study (ELECTRON-II) that examined ledipasvir/sofosbuvir used with (n=26) or without (n=25) ribavirin for 12 weeks in treatment-naive patients with HCV genotype 3 infection; 15% of patients had cirrhosis. All 26 (100%) patients in the ribavirin-containing arm achieved SVR12 compared with 16 of 25 (64%) of those in the ribavirin-free arm. Although these data raise the possibility that the addition of ledipasvir to sofosbuvir and ribavirin may shorten the course of therapy for persons with HCV genotype 3 infection, the high effective concentration (EC_{50}) of ledipasvir for HCV genotype 3 (Wong, 2013); (Kohler, 2014) and the homogenous patient population studied limit the generalizability of this study. Until further data are available to confirm these findings, a recommendation for use of this regimen cannot be made at this time (Gane, 2013).

Paritaprevir/ritonavir/ombitasvir + dasabuvir

In a multicenter study of 34 liver-transplant recipients with mild recurrence (Metavir fibrosis stage F0-F2) of HCV genotype 1 infection, fixed-dose combination paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) (PrOD) and weight-based ribavirin was given for 24 weeks and achieved an SVR24 rate of 96% (Kwo, 2014). Because of the drug-drug interactions between ritonavir and calcineurin inhibitors, prospective dose adjustments were needed for cyclosporine and tacrolimus. Interactions between ritonavir and other medications commonly taken by liver-transplant recipients are also possible and will require detailed consideration when using this regimen. The efficacy and tolerability of this regimen in patients with more advanced HCV infection post-liver transplant are unknown.

Simeprevir + sofosbuvir

The GALAXY study prospectively assessed the use of simeprevir with sofosbuvir with or without weight-based ribavirin for 12 to 24 weeks in 46 non-cirrhotic patients with HCV genotype 1 (O'Leary, 2016). The SVR12 rate was 100% with simepevir and sofosbuvir for 12 weeks, 81.8% with simeprevir and sofosbuvir with ribavirin, and 91.7% with simeprevir and sofosbuvir with ribavirin for 24 weeks. A retrospective multicenter analysis of sofosbuvir (400 mg daily) plus simeprevir (150 mg daily) with or without ribavirin in 77 recipients reported an SVR4 rate of 92% (Pungpapong, 2015). Another recent multicenter retrospective study of 151 patients with recurrent HCV genotype 1 treated with simeprevir and sofosbuvir alone (n=119) or with ribavirin (n=32) was reported (Brown, 2016). The duration of therapy was 12 weeks for most patients but 15 did receive 24 weeks of therapy. Allograft cirrhosis had developed in 64.2% and 39.7% of patients had decompensated hepatic function. The overall SVR was 88% and 7% experienced virological relapse. Serious adverse events were reported in 11.9% and 3 deaths were not related to therapy. In healthy volunteers, the coadministration of single-dose cyclosporine with simeprevir resulted in a 19% increase in cyclosporine concentrations and simeprevir concentrations similar to historical data (see simeprevir prescribing information). However, in an interim analysis of an ongoing study in HCV-infected individuals (TMC435HPC3016), concomitant use of simeprevir (plus daclatasvir and ribavirin) with cyclosporine at steady state resulted in an approximately 6-fold increase in plasma concentrations of simeprevir compared with historical data of simeprevir in the absence of cyclosporine. This interaction may be caused by inhibition of organic ion-transporting polypeptide 1B1 (OATP1B1), p-glycoprotein (P-gp), and cytochrome P450 3A (CYP3A) by cyclosporine. Given these findings, simeprevir should not be coadministered with cyclosporine.

In healthy volunteers, the coadministration of single-dose tacrolimus with simeprevir did not result in a notable change of tacrolimus concentrations (see simeprevir prescribing information). In an ongoing study, concomitant use of simeprevir with tacrolimus resulted in a 2-fold increase in plasma concentrations of simeprevir compared with historical data (see simeprevir prescribing information). Based on phase I studies, a 2-fold increase in simeprevir concentrations is unlikely to be clinically significant.

Clinicians may consider the use of sofosbuvir plus simeprevir in patients receiving tacrolimus with therapeutic drug monitoring, particularly in those expected to have difficulty tolerating ribavirin (eg, patients with impaired renal function or anemia) or who are unable to forego proton pump inhibitor therapy (proton pump inhibitors attenuate ledipasvir absorption). A further option in patients who are ribavirin intolerant is 24 weeks of ledipasvir/sofosbuvir.

The interaction of direct-acting antiviral (DAA) agents and calcineurin inhibitors is complex and unpredictable without formal studies of drug-drug interactions. A summary of drug interactions between calcineurin inhibitors and direct-acting antiviral agents with recommended dosing is provided in the Table below. Based on the metabolism of grazoprevir and elbasvir, 15-fold increases in grazoprevir AUC and 2- fold increases in elbasvir AUC can be expected with coadministration with cyclosporine. Therefore, this combination should be avoided. Since a 40%-50% increase in tacrolimus levels is predicted during coadministration with grazoprevir, no dosing adjustments are anticipated, but TAC levels should be monitored.

Elbasvir/grazoprevir

Although fixed-dose combination elbasvir and grazoprevir (hereafter, elbasvir/grazoprevir) have been extensively studied in patients with HCV infection with genotypes 1 and 4 who have compensated liver disease, there are no reports of this combination in liver-transplant recipients. The actual impact of elbasvir or grazoprevir on immunosuppression pharmacokinetics is unknown. For this reason, elbasvir and grazoprevir are not recommended for the treatment of HCV infection in liver-transplant recipients. Data regarding the safety and efficacy of elbasvir and grazoprevir in patients with advanced liver disease are available only from a phase II open-label study of grazoprevir (50 mg)/elbasvir (50 mg), given for 12 weeks in 30 HCV genotype 1 patients with CTP class B cirrhosis (Jacobson, 2015). This grazoprevir dose used in this study is lower than the grazoprevir dose in the commercially available fixed-dose formulation (50 mg vs 100 mg). The great majority of patients had CTP scores of 7 or 8 (28/30). The SVR12 rate was 90%. One patient died of liver failure at posttreatment week 4. MELD scores improved in 15 treated patients, were unchanged in 9, and increased in 6. It is possible that patients receiving elbasvir/grazoprevir will undergo liver transplantation prior to completing therapy. Continuation of elbasvir/grazoprevir following liver transplantation is not recommended. Similarly, although elbasvir/grazoprevir is well tolerated and effective in patients with renal insufficiency, which is common in liver-transplant recipients, the likely drug-drug interactions with immunosuppression agents outweigh the benefits of low renal metabolism of grazoprevir and elbasvir.

Sofosbuvir/velpatasvir

There are no reports of the safety of efficacy of sofosbuvir/velpatasvir fixed-dose combination in liver-transplant recipients. In the non-transplant setting, discussed in detail in the initial and retreatment sections of this guidance, of 624 patients with HCV genotypes 1a (34%), 1b (19%), 2 (17%), 4 (19%), 5 (6%), and 6 (7%) who were randomly assigned to receive fixed-dose combination of sofosbuvir/velpatasvir or placebo for 12 weeks were reported in the ASTRAL-1 study (Feld, 2015). All patients with genotype 5 (n=35) received active treatment. One third of patients were treatment experienced. Nineteen percent had CTP Class A cirrhosis. The 95% confidence interval for SVR12 was 98 to >99%. The side-effect/adverse-event profile of sofosbuvir/velpatasvir was similar to placebo. In a separate study (ASTRAL-3) (Foster, 2015a), among patients with HCV genotype 3 (n=552), the rate of sustained virologic response in the sofosbuvir/velpatasvir group was 95% (95% CI, 92 to 98), which was superior to the rate of 80% (95% CI, 75 to 85) for patients receiving sofosbuvir plus ribavirin for 12 weeks. In a third study (ASTRAL-4) (Curry, 2015b), 267 patients with HCV genotypes 1, 2, 3, 4, and 6 in patients with decompensated cirrhosis (90% CTP Class B or C) in which 55% of patients were treatment experienced, SVR12 was achieved in 83% in those who received sofosbuvir/velpatasvir for 12 weeks, 94% in those who received sofosbuvir/velpatasvir with ribavirin for 12 weeks, and 86% in those who received sofosbuvir/velpatasvir for 24 weeks. Among patients with genotype 1, the SVR was 88% and 96% with sofosbuvir/velpatasvir for 12 weeks without and with ribavirin respectively, and 92% with sofosbuvir/velpatasvir for 24 weeks. Posttreatment virologic relapse occurred in 12% and 9% in the groups that did not receive ribavirin vs 2% of the 12-week group of sofosbuvir/velpatasvir with ribavirin. Although the ASTRAL-4 study was not powered to generate statistical significance, the results suggest that sofosbuvir/velpatasvir with ribavirin for 12 weeks is the optimal choice for patients with genotypes 1 or 3 who have decompensated cirrhosis. The participant numbers were too small for genotypes 2, 4, and 6 to differentiate the comparative efficacy of the treatment arms.

Velpatasvir is a substrate for CYP3A4, CYP2C8, and CYP2B6 and a weak (P-gp, OATP) to moderate (breast cancer resistance protein, BCRP) transport inhibitor and is moderately affected by potent inhibitors and to a greater extent, potent inducers of enzyme/drug transporter systems (Mogalian, 2016). Based on this profile, which is similar to ledipasvir, clinically significant drug-drug interactions would not be expected for coadministration of sofosbuvir/velpatasvir with common immunosuppressive agents (eg, tacrolimus, cyclosporine, corticosteroids, mycophenolate mofetil, or everolimus). However, based on the lack of real-world experience of the pharmacokinetics of sofosbuvir/velpatasvir in liver-transplant recipients and because alternatives with similar projected efficacy are available for which interactions with immunosuppression agents have been reported, we do not recommend the use of velpatasvir in transplant recipients at this time.

Table. DAA Interactions with Calcineurin Inhibitors

	Cyclosporine	Tacrolimus
Sofosbuvir	4.5-fold ? in SOF AUC, but GS-331007 metabolite unchanged; no a priori dose adjustment, but monitor CSA levels and titrate CSA dose as needed	No interaction observed; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed
Ledipasvir	No data; no a priori dose adjustment, but monitor CSA levels and titrate CSA dose as needed	No data; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed
Daclatasvir	No interaction observed; no a priori dose adjustment, but monitor CSA levels and titrate CSA dose as needed	No interaction observed; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed
Simeprevir	5.81-fold ? in SIM AUC; combination is not recommended	85% ? in SIM AUC; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed
PrOD	5.8-fold ? in CSA AUC; modeling suggest using 1/5 of CSA dose during PrOD treatment, monitor CSA levels and titrate CSA dose as needed	57-fold ? in TAC AUC; modeling suggests TAC 0.5 mg every 7 days during PrOD treatment, monitor TAC levels and titrate TAC dose as needed
PrO	4.3-fold ? in CSA AUC; modeling suggest using 1/5 of CSA dose during PrO treatment, monitor CSA levels and titrate CSA dose as needed	86-fold ? in TAC AUC; modeling suggests TAC 0.5 mg every 7 days during PrO treatment, monitor TAC levels and titrate TAC dose as needed
Elbasvir / Grazoprevir	15-fold ? in GZR AUC and 2-fold ? in EBR AUC; combination is not recommended	43% ? in TAC; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed
Velpatasvir	No interaction observed; no a priori dose adjustment, but monitor CSA levels and titrate CSA dose as needed	No data; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed

Mixed genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for

mixed genotypes with direct-acting antivirals are sparse but utilization of a pangenotypic regimen should be considered. When the correct combination or duration is unclear, expert consultation should be sought.

Last update: April 12, 2017

Unique Patient Populations: Patients with Renal Impairment

HCV is independently associated with the development of chronic kidney disease (Rogal, 2016); (Fabrizi, 2015). A recent meta-analysis demonstrated that chronic HCV infection was associated with a 51% increase in the risk of proteinuria and a 43% increase in the incidence of chronic kidney disease (Fabrizi, 2015). There is also a higher risk of progression to ESRD in persons with chronic HCV and chronic kidney disease and an increased risk of all-cause mortality in persons on dialysis (Lee, 2014); (Fabrizi, 2012).

Recommended Dosage Adjustments for Patients with Mild to Moderate Renal Impairment

RECOMMENDED	RATING
For patients with mild to moderate renal impairment (eGFR 30 mL/min-80 mL/min), no dosage adjustment is required when using daclatasvir (60 mg*), fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg), fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg), or fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with (or without for HCV genotype 4 infection) twice-daily dosed dasabuvir (250 mg), simeprevir (150 mg), or sofosbuvir (400 mg) to treat or retreat HCV infection in patients with appropriate genotypes.	I, A

Recommended Regimens by evidence level and alphabetically for:

Patients with Severe Renal Impairment, Including Severe Renal Impairment (eGFR <30 mL/min) or End-Stage Renal Disease (ESRD)

RECOMMENDED	DURATION	RATING
For patients with genotype 1a, or 1b, or 4 infection and eGFR below 30 mL/min, for whom treatment has been elected, daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, B
For patients with genotype 1b infection and eGFR below 30 mL/min, for whom treatment has been elected, daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg)	12 weeks	IIb, B
For patients with HCV genotype 2, 3, 5, or 6 infection and eGFR below 30 mL/min, for whom the urgency to treat is high, PEG-IFN and dose-adjusted ribavirin** (200 mg daily)	-	IIb, B

Recommended Regimens by evidence level and alphabetically for:

Patients with Severe Renal Impairment, Including Severe Renal Impairment (eGFR <30 mL/min) or End-Stage Renal Disease (ESRD)

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.
** Caution is recommended in this group, owing to the potential for hemolytic anemia due to impaired renal clearance in this population, and ribavirin should be restricted to those with a baseline hemoglobin concentration above 10 g/dL.

Alternative Regimen for Genotype 1a-infected Patients with eGFR Below 30 mL/min

ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and dose-adjusted ribavirin** (200 mg daily)	12 weeks	IIb, B

** Caution is recommended in this group, owing to the potential for hemolytic anemia due to impaired renal clearance in this population, and ribavirin should be restricted to those with a baseline hemoglobin concentration above 10 g/dL.

A recent study (C-SURFER) evaluated the safety and efficacy of 12 weeks of a second-generation NS3/NS4A protease inhibitor, grazoprevir (100 mg once daily) and an NS5A inhibitor, elbasvir (50 mg once daily) versus placebo for HCV genotype 1 patients with CKD stages 4/5. The original study was designed to randomize eligible patients to either immediate or deferred treatment with elbasvir and grazoprevir. The delayed treatment arm received placebo and was treated with elbasvir and grazoprevir later. The data for the immediate treatment arm have been published (Roth, 2015). The study participants were HCV genotype 1, CKD stages 4/5 (eGFR <30 mL/min), 75% on hemodialysis, 45% were African Americans. Small numbers of patients with compensated cirrhosis were allowed. The study reported an ITT and modified ITT of 94% and 99% for SVR12. There were no changes in hemoglobin or other adverse events or erythropoietin use in the treatment groups compared to placebo, while most patients in the treatment group normalized ALT and AST values compared to placebo. None of the genotype 1a patients with baseline NS5A RASs experienced viral relapse; the only reported relapse occurred in a patient with genotype 1b. The basis for the lack of impact of NS5A RASs on SVR rates in this population is unclear, but may relate to moderately increased AUCs of grazoprevir or elbasvir observed in stage 4/5 CKD (Elbasvir and Grazoprevir PI, 2016). Based on these data, the fixed-dose combination elbasvir (50 mg) and grazoprevir (100 mg) (hereafter, elbasvir/grazoprevir) is recommended for the treatment of HCV genotype 1 infection in patients with severely compromised renal function. No strong recommendation for NS5A RAS testing can be made in this population. While C-SURFER did not evaluate patients with genotype 4 infection, it is likely that the high efficacy of elbasvir/grazoprevir in genotype 1 and 4 infection in persons with normal renal function can be extrapolated to genotype 4-infected persons with CKD stage 4/5. Treatment with elbasvir/grazoprevir in persons with CKD has been shown to be cost effective in the United States (Elbasha, 2016).

Sofosbuvir and ribavirin are renally eliminated. Safe and effective doses of sofosbuvir in those with eGFR less than 30 mL/min have not been established. If urgency for treatment is high, there is accumulating evidence on use of sofosbuvir-based regimens in persons with eGFR <30 mL/min (Desnoyer, 2016).

Though recommendations exist for reducing ribavirin dose and/or dosing frequency in those with renal impairment, this drug is poorly tolerated in this population. Daclatasvir, elbasvir/grazoprevir, ledipasvir, PrOD, and simeprevir are primarily hepatically metabolized and undergo minimal renal elimination. While exposures to many of these agents are higher in severe renal impairment presumably due to effects of uremic toxins, parathyroid hormone, and/or cytokines on hepatic

metabolism, they do not require dose adjustments in renal impairment. Refer to the table on drug dosing in renal impairment.

The HCV-TARGET study is an ongoing prospective observational cohort study that evaluates the use of direct-acting antiviral (DAA) agents across clinical practices in North America and Europe. The study reported the safety and efficacy of sofosbuvir-containing regimens in patients with mild to severe renal dysfunction (eGFRs <30, 31-45, 46-60, and >60 mL/min) (Saxena, 2016). The patients received different regimens that included sofosbuvir (PEG-IFN, ribavirin, and sofosbuvir; simeprevir and sofosbuvir with or without ribavirin; or sofosbuvir and ribavirin). Overall, the regimens were well tolerated with no increased discontinuation among patients with low eGFRs. The rates of sustained virologic response at 12 weeks (SVR12) were similar across the groups regardless of renal function. Notably, there was progressive deterioration of renal function and renal symptoms in the patients with eGFRs below 30 mL/min, suggesting the need for close monitoring of these patients. In summary, patients with low baseline renal function have a higher frequency of anemia, worsening renal dysfunction, and more severe adverse events, but treatment responses remain high and comparable to those without renal impairment.

Data on patients treated with a regimen of simeprevir and low-dose sofosbuvir without ribavirin have been reported. In one study, 18 HCV-infected patients (11 requiring hemodialysis, 3 with a mean eGFR of 16 mL/min) underwent open-label treatment with simeprevir and sofosbuvir. All patients received full-dose simeprevir (150 mg) daily. Sofosbuvir dose was reduced to 200 mg daily in 15 patients and 400 mg every other day in 3 patients. The length of therapy was 12 weeks in 17 patients and 24 weeks in 1 patient with cirrhosis. One patient developed new onset hepatic encephalopathy and another developed uncontrolled diarrhea, both requiring hospitalizations during treatment. Minor adverse events were fatigue (28%), anemia (11%), rash or itching (11%), and nausea (5%), and were managed medically; there were no treatment discontinuations. Of the 16 patients who completed treatment, only 9 patients reached relevant milestones. Per the current per-protocol analysis, SVR4 was seen in 91% and SVR12 in 89%. One patient with cirrhosis (who had a prior HCV protease inhibitor-containing treatment failure) relapsed within 4 weeks after completion of treatment. In summary, the regimen of simeprevir and reduced-dose sofosbuvir is safe and well tolerated. In another study, 12 patients with eGFRs below 30 mL/min received sofosbuvir (400 mg) and simeprevir (150 mg). The regimen was well tolerated and resulted in viral suppression in all patients (Nazario, 2016).

Twenty patients with HCV genotype 1 infection and stage 4 or 5 (eGFR <30 mL/min) chronic kidney disease (CKD) without cirrhosis were treated with daily fixed-dose combination of paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) (PrOD) with or without ribavirin in a multicenter, open-label phase IIb study (Pockros, 2016). Notably, 70% of patients were black and 65% had CKD requiring hemodialysis. Ribavirin (in those with HCV genotype 1a only) was dosed 4 hours before hemodialysis and monitored with weekly hemoglobin assessments. Ribavirin doses were suspended for a 2 g/dL or more drop in hemoglobin level and resumed when the hemoglobin level normalized. All patients (10/10) achieved SVR4 (Pockros, 2016). Interestingly, the use of ribavirin was associated with more of a drop in hemoglobin level, and 8 of 13 patients required interruption of ribavirin dosing. Four of 8 patients also required erythropoietin treatment during the first 7 weeks of therapy. Mean drug concentrations (C_{trough}) of all drugs were measured and levels were within the range that was observed with previous pharmacokinetic studies in healthy volunteers. In summary, most patients with HCV genotype 1 with or without cirrhosis who were treated with PrOD with or without ribavirin achieved viral suppression. However, ribavirin-induced anemia can occur frequently, and close monitoring of all patients and judicious dose reductions of ribavirin are required. As described in other sections, PrOD should be used with caution in patients with Child Turcotte Pugh A cirrhosis and avoided in patients with CTP B or C cirrhosis.

For patients infected with HCV genotypes 2, 3, 5, or 6 with eGFR ≤30 mL/min for whom the urgency to treat is high, and for whom treatment has been elected before kidney transplantation, standard treatment remains PEG-IFN plus dose-adjusted ribavirin (200 mg daily). However, caution is recommended in this group, owing to the potential for hemolytic anemia due to impaired renal clearance in this population, and ribavirin should be restricted to those with a baseline hemoglobin concentration above 10 g/dL. Ribavirin should be discontinued if hemoglobin level declines by more than 2 g/dL despite the use of erythropoietin. Few data exist to guide treatment with current IFN-free regimens. Consideration may be given on an individualized basis to a sofosbuvir-based regimen, with careful attention paid to patient comorbidities and toxicities. However, additional pangenotypic options are anticipated in this population in mid-2017.

Unique Patient Populations Table: Dose Adjustments Needed for Patients with Renal Impairment

Renal Impairment	Mild	Moderate	Severe	ESRD with HD
eGFR (mL/min)	50-80	30-50	<30	
PEG-IFN	PEG-IFN (2a) 180 µg; PEG-IFN (2b) 1.5 µg/kg	PEG-IFN (2a) 180 µg; PEG-IFN (2b) 1 µg/kg (25% reduction)	PEG-IFN (2a) 135 µg; PEG-IFN (2b) 1 µg/kg (50% reduction)	PEG-IFN (2a) 135 µg/wk or PEG-IFN (2b) 1 µg/kg/wk or standard IFN 3 mU 3x/wk
Ribavirin	Standard	Alternating doses 200 mg and 400 mg every other day	200 mg/d	200 mg/d
Sofosbuvir	Standard	Standard	Limited data available	Limited data available
Ledipasvir	Standard	Standard	Data not available	Data not available
Daclatasvir	Standard	Standard	Limited data available	Limited data available
Ombitasvir	Standard	Standard	Limited data available	Limited data available
Dasabuvir	Standard	Standard	Limited data available	Limited data available
Paritaprevir	Standard	Standard	Limited data available	Limited data available
Simeprevir	Standard	Standard	Standard	Limited data available
Velpatasvir	Standard	Standard	Data not available	Data not available
Elbasvir	Standard	Standard	Standard	Standard
Grazoprevir	Standard	Standard	Standard	Standard
Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HD, hemodialysis.				

DAA Therapy in Kidney Transplant Patients

A recent clinical trial described the safety and efficacy of ledipasvir/sofosbuvir in kidney transplant recipients (N=114) who were more than 6 months posttransplant (Colombo, 2016). The patients were mainly infected with genotype 1 or 4, with or without cirrhosis, and with or without prior treatment experience. Patients were randomized to receive ledipasvir/sofosbuvir for 12 or 24 weeks. Prior to treatment, median eGFR was 50 mL/min for those who were treated for 12 weeks and 60 mL/min for those who were treated 24 weeks. 96% achieved SVR12. Adverse events were common (64%) and 11% had a serious adverse event, but fewer than 1% discontinued treatment due to adverse effects (Colombo, 2016). In 3 patients, eGFR increased to greater than 30 mL/min at the last visit recorded; one patient who had interrupted study treatment had a final value of 14.4 mL/min. All but 1 of the 6 patients with cirrhosis whose eGFR decreased to below 40 mL/min continued study treatment without interruption; none permanently discontinued study treatment.

Several additional reports have described successful outcomes with DAA combination therapy in renal-transplant patients (Sawinski, 2016); (Kamar, 2016). Sawinski et al treated 20 HCV-infected kidney transplant recipients (88% genotype 1, half with advanced fibrosis, and 60% treatment-experienced) with sofosbuvir-based regimens and reported resulted 100%

SVR (Sawinski, 2016). Various sofosbuvir-based DAA combinations were used, including simeprevir plus sofosbuvir (n=9), ledipasvir/sofosbuvir (n=7), sofosbuvir plus ribavirin (n=3), and daclatasvir plus sofosbuvir (n=1). Two patients required dose reductions due to anemia (associated with ribavirin use), however no significant changes in serum creatinine, proteinuria, or graft rejection were seen before or after treatment. Forty-five percent of patients required dose reduction of immunosuppressive agents while on therapy (Sawinski, 2016).

A study of 25 kidney transplant recipients with chronic HCV infection that were treated with sofosbuvir-based regimens reported a 100% SVR (Kamar, 2016). Patients included were infected with genotype 1 (76%), had eGFR >30 mL/min (100%), and had advanced fibrosis (44%). Treatment regimens included ledipasvir/sofosbuvir (n=9), daclatasvir plus sofosbuvir (n=4), sofosbuvir plus ribavirin (n=3), ledipasvir/sofosbuvir plus ribavirin (n=1), simeprevir plus sofosbuvir plus ribavirin (n=1), simeprevir plus sofosbuvir (n=6), and sofosbuvir plus pegylated IFN/ribavirin (n=1). Treatment was well tolerated without any discontinuations, dose reductions, graft rejections, or changes in serum creatinine levels, and no drug interactions with calcineurin inhibitors were observed (Kamar, 2016).

Another study that treated three HCV genotype 4 kidney transplant patients with sofosbuvir (400 mg) plus ribavirin (1000 mg) for 24 weeks reported a 100% SVR (Hussein, 2016). Anemia was reported in two patients related to concomitant ribavirin use. No other adverse events were reported (Hussein, 2016).

Drug interactions are an important consideration with antiviral therapy in kidney transplant recipients. Please see the section titled, "Unique Patient Populations: Patients Who Develop Recurrent HCV Infection Post Liver Transplantation" for a table of drug interactions with DAAs and calcineurin inhibitors.

Mixed genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for mixed genotypes with direct-acting antivirals are sparse but utilization of a pangenotypic regimen should be considered. When the correct combination or duration is unclear, expert consultation should be sought.

Last update: April 12, 2017

Management of Acute HCV Infection

This section provides guidance on the diagnosis and medical management of acute HCV infection, which is defined as presenting within 6 months of the exposure. During this time, there is a 20% to 50% chance of spontaneous resolution of infection (Kamal, 2008). In the past, cure rates of acute infection with IFN-based treatment were very high (Grebely, 2014). The present guidance reflects current trends transitioning toward safer, IFN-sparing treatments for chronic infection and the implications for the approach to acute HCV treatment.

Acute HCV infection may result from exposure to the virus through various routes. The highest risk is associated with repeated parenteral exposures from contaminated equipment in an injection drug use (IDU) setting. Lower rates of HCV transmission occur from needlestick injuries in which healthcare workers are exposed to the blood of an HCV-infected patient. Heterosexual exposure risk is very low. In comparison, transmission rates among HIV-infected men who have unprotected sex with men are much higher, particularly among those who engage in high-risk sexual practices that increase trauma to the mucosal membranes and exposure to blood (Boesecke, 2012).

Recommended Testing for Diagnosing Acute HCV Infection	
RECOMMENDED	RATING

Recommended Testing for Diagnosing Acute HCV Infection	
HCV antibody and HCV RNA testing are recommended when acute HCV infection is suspected due to exposure, clinical presentation, or elevated aminotransferase levels (see Figure).	I, C

Recommendations for HCV testing are also found in the HCV Testing and Linkage to Care section.

Diagnosis of acute infection permits estimation of annual incidence rates and transmission patterns, thereby facilitating implementation and assessment of prevention programs. At the individual level, a diagnosis of acute infection expedites linkage to care, counseling regarding high-risk behavior, and timely interventions to reduce transmission of the virus and progression of liver disease (Bruneau, 2014). Indeed, some persons involved in high-risk behaviors practice serosorting, defined as using anti-HCV antibody serostatus to determine whether to engage in high-risk behaviors with certain individuals (Smith, 2013). Thus, undiagnosed acutely infected persons may be at greater risk of transmitting HCV to their presumably seronegative contacts than would be expected by chance.

The best laboratory evidence to support a diagnosis of acute HCV infection is (1) a positive HCV RNA test in the setting of a negative HCV antibody test (identification during the seronegative "window" period) (Cox, 2005), or (2) a positive HCV antibody test after prior negative HCV antibody test (termed seroconversion). There are rare instances in which these approaches may be misleading, such as in immunosuppressed individuals with impaired antibody production (Chamot, 1990).

Discrete Exposure

The above types of clear laboratory documentation of acute infection are easiest to achieve when there has been a discrete exposure (eg, after new onset or a change in drug injection practice, a percutaneous needlestick exposure to an HCV-infected individual, a potentially nonsterile tattoo, or sexual assault). In those instances, baseline HCV antibody and RNA testing should be done within 48 hours of the exposure to document whether there was antecedent HCV infection (see Figure). If baseline testing is negative, repeat testing is recommended. Frequency of testing can be tailored based on management objectives (eg, monthly testing to identify and treat acute infection). If baseline anti-HCV antibody testing is positive but RNA testing is negative, repeat HCV RNA and alanine aminotransferase (ALT) testing is recommended to identify an acute reinfection. When baseline HCV antibody and RNA testing are both positive, the person most likely already has chronic HCV infection from prior exposures. The frequency of repeat testing should reflect management goals. At a minimum, repeat testing should be done 4 months to 6 months later. When earlier identification of infection or reinfection is desired, HCV RNA and ALT testing every 4 weeks to 6 weeks for 6 months is recommended.

No Discrete Exposure

Often, individuals suspected of having acute HCV infection do not have a discrete exposure or have no prior baseline testing, making a diagnosis of acute infection more difficult (see Table below). Acute infection should be suspected if there is a new rise in the ALT level without an alternate cause (Blackard, 2008); (Kim, 2013). Acute infection should also be suspected when there are low (especially $<10^4$ IU/mL) or fluctuating (>1 $\log_{10}$ IU/mL) HCV RNA values, or spontaneous clearance, which do not commonly occur outside of the first 6 months after acute HCV infection (McGovern, 2009). A low signal-to-cutoff ratio of HCV antibody along with detectable HCV RNA may also be suggestive of the early weeks of acute primary infection, although this information may need to be specifically requested from the testing laboratory (Araujo, 2011). Patients suspected of having acute HCV infection should also have a laboratory evaluation to exclude other or coexisting causes of acute hepatitis (eg, hepatitis A virus, hepatitis B virus, HDV if chronically infected with hepatitis B [Kushner, 2015], or autoimmune hepatitis) and should be tested for HIV.

Not Recommended

NOT RECOMMENDED	RATING
Preexposure or postexposure prophylaxis with antiviral therapy is Not Recommended	III, C

Although new antiviral treatment regimens are highly efficacious and more tolerable than IFN-based therapy, there are no data on the efficacy or cost-effectiveness of antiviral therapy for preexposure or postexposure prophylaxis of HCV infection. Some studies have shown that postexposure treatment with IFN-based regimens does not prevent infection (Nakano, 1995); (Arai, 1996).

Table. Interpretation of Blood Testing During Diagnosis of Acute HCV Infection

Test	Interpretation for Diagnosis of Acute HCV Infection
HCV antibody	• May be negative in the first 6 weeks after exposure • May be delayed or absent when the individual is immunosuppressed • Presence alone does not distinguish between acute and chronic infection • Low signal-to-cutoff ratio may be present during acute HCV infection or represent a false-positive result
HCV RNA	• Viral fluctuations greater than 1 $\log_{10}$ IU/mL may indicate acute HCV infection • May be transiently negative during acute HCV infection • Alone does not distinguish between acute and chronic infection
Alanine amino transferase (ALT)	• Fluctuating peaks during acute HCV infection suggest acute infection • May be normal during acute HCV infection • May be elevated due to other liver insults such as alcohol consumption

Recommendations for Medical Management and Monitoring in Acute HCV Infection

RECOMMENDED	RATING
Regular laboratory monitoring is recommended in the setting of acute HCV infection. Monitoring HCV RNA (eg, every 4 weeks to 8 weeks) for 6 months to 12 months is also recommended to determine spontaneous clearance of HCV infection versus persistence of infection.	I, B
Counseling is recommended for patients with acute HCV infection to avoid hepatotoxic insults, including hepatotoxic drugs (eg, acetaminophen) and alcohol consumption, and to reduce the risk of HCV transmission to others.	I, C
Referral to an addiction medicine specialist is recommended for patients with acute HCV infection related to substance use.	I, B

The patient with acute HCV infection should be counseled to reduce behaviors that could result in transmission, such as

Recommendations for Medical Management and Monitoring in Acute HCV Infection

sharing of injection equipment or high-risk sexual practices. Because the risk of transmission of other infections is higher in the acute infection phase, some experts counsel patients with acute infection to consider using barrier precautions even in stable monogamous relationships (see HCV Testing and Linkage to Care). For individuals with acute HCV infection who have a history of recent injection drug use, referral to an addiction medicine specialist is recommended when appropriate (Litwin, 2009); (Strathdee, 2005).

Patients with acute HCV infection are often asymptomatic or have nonspecific symptoms (fatigue, anorexia, mild or moderate abdominal pain, low-grade fever, nausea, vomiting) that frequently are not recognized as being associated with acute HCV infection. A small proportion (<25%) of patients with acute HCV infection will develop jaundice. Patients diagnosed with acute HCV infection should be initially monitored with hepatic panels (ALT, aspartate aminotransferase [AST], bilirubin, and international normalized ratio [INR] in the setting of increasing bilirubin level) at 2- to 4-week intervals (Blackard, 2008). Laboratory monitoring should continue until the ALT levels normalize and HCV RNA becomes repeatedly undetectable, suggesting spontaneous resolution. If this does not occur, frequency of laboratory monitoring for patients with persistently detectable HCV RNA and elevated ALT levels should follow recommendations for monitoring patients with chronic HCV infection (see Monitoring Patients Who Are Starting Hepatitis C Treatment, Are on Treatment, or Have Completed Therapy).

HCV infection will spontaneously clear in 20% to 50% of patients (Kamal, 2008). In at least two-thirds of patients, this will occur within 6 months of the estimated time of infection (median, 16.5 weeks); only 11% of those who remain viremic at 6 months will spontaneously clear infection at some later time (Grebely, 2014). Thus, detectable HCV RNA at 6 months after the time of infection will identify most persons who need HCV therapy (see When and in Whom to Initiate HCV Therapy). Those with spontaneous clearance should not be treated with antiviral therapy, but they should be counseled about the possibility of reinfection and tested routinely for reinfection if risk behaviors are ongoing (see HCV Testing and Linkage to Care). Of note, transient suppression of viremia can occur in those with acute HCV infection, even in those who progress to chronic infection. Thus, a single undetectable HCV RNA value is insufficient to declare spontaneous clearance (Villano, 1999); (Mosley, 2008) (see HCV Testing and Linkage to Care).

Predictors of spontaneous clearance include jaundice, elevated ALT level, hepatitis B virus surface antigen (HBsAg) positivity, female sex, younger age, HCV genotype 1, and host genetic polymorphisms, most notably those near the IL28B gene (Kamal, 2008); (Mosley, 2008).

There is no need to alter concomitant medications that are metabolized by hepatic enzymes unless there is concern for developing acute liver failure (eg, increasing bilirubin level and INR). Acetaminophen and alcohol consumption should be avoided during acute HCV infection (Proeschold-Bell, 2012); (Dieperink, 2010); (Whitlock, 2004). Hospitalization is rarely indicated unless nausea and vomiting are severe. Although acute liver failure is very rare (<1%), it represents a serious and life-threatening complication of acute HCV infection. Patients with an INR above 1.5 or those who exhibit any signs of acute liver failure (eg, hepatic encephalopathy) should be referred to a liver transplant center immediately. The use of HCV antiviral regimens in acute liver failure should be managed by a clinician experienced in HCV treatment, ideally in consultation with a liver transplant specialist.

Recommended Treatment for Patients with Acute HCV Infection

RECOMMENDED	RATING
If the practitioner and patient have decided that a delay in treatment initiation is acceptable, monitoring for spontaneous clearance is recommended for a minimum of 6 months. When the decision is made to initiate treatment after 6 months, treating as described for chronic hepatitis C is recommended (see Initial Treatment of HCV Infection).	IIa, C

Recommended Treatment for Patients with Acute HCV Infection	
If a decision has been made to initiate treatment during the acute infection period, monitoring HCV RNA for at least 12 weeks to 16 weeks before starting treatment is recommended to allow for spontaneous clearance.	IIa, C

Recommended Regimens for Patients with Acute HCV Infection	
RECOMMENDED	RATING
Owing to high efficacy and safety, the same regimens that are recommended for chronic HCV infection are recommended for acute infection.	IIa, C

Not Recommended	
NOT RECOMMENDED	RATING
For patients in whom HCV infection spontaneously clears, treatment is Not Recommended.	III, B

In the interferon era, the efficacy of the treatment of acute HCV infection (particularly for genotype 1), including with abbreviated regimens, was superior to the treatment of chronic infection (See 2009 AASLD guidelines [Ghany, 2009]). There are emerging data on the treatment of acute HCV infection with shortened courses of all-oral DAA regimens both in HCV monoinfection and HIV/HCV coinfection, but there are, as yet, not enough data to support a particular regimen or duration. Until more definitive data are available, monitoring for spontaneous clearance for a minimum of 6 months before initiating treatment is recommended. When the decision is made to initiate treatment after 6 months, treatment as described for chronic hepatitis C is recommended.

There are instances, however, where clinicians may decide that the benefits of early treatment outweigh waiting for HCV clearance. These include situations where importance is placed on the prevention of HCV transmission (eg, surgeon, IVDU, and or HIV+ MSM with sexual transmission), mitigation of clinical consequences (eg, patient with cirrhosis who is acutely superinfected with HCV), or reduction in likelihood of loss-to-follow-up in patients who may not be engaged in care in 3-to-6 months. Where relevant, referral to addiction specialists and harm reduction counseling should be provided. If for these reasons a decision has been made to initiate treatment during the acute infection period, the same regimens recommended for chronic HCV infection (see Initial Treatment of HCV Infection and When and in Whom to Initiate HCV Therapy sections) are recommended for acute infection given their high efficacy and safety in chronic HCV infection.

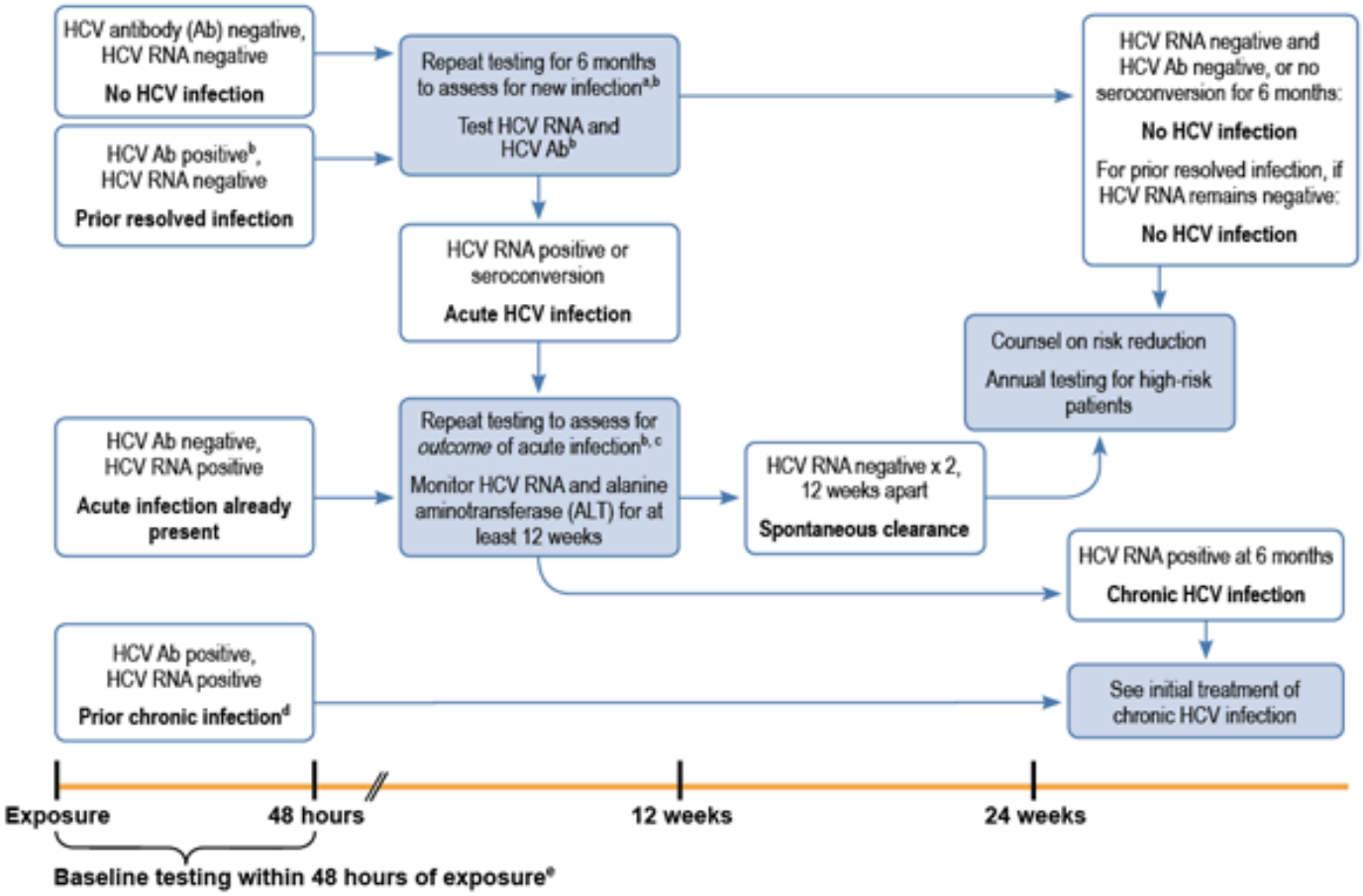
Mixed genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for mixed genotypes with direct-acting antivirals are sparse but utilization of a pangenotypic regimen should be considered. When the correct combination or duration is unclear, expert consultation should be sought.

Last update: July 6, 2016

Acute Figure. Testing Algorithm for Discrete Recognized Hepatitis C Virus (HCV) Exposure

Figure. Testing Algorithm for Discrete Recognized Hepatitis C Virus (HCV) Exposure[a]



[a] Often there is no discrete exposure or the entry to health care occurs with jaundice or elevated liver enzymes. In those instances, baseline testing cannot be done and the diagnosis of acute infection is more challenging (see text).

[b] Repeat HCV Ab is not needed if it is positive at baseline. Frequency of testing can be tailored based on management objectives (eg, monthly testing to identify and treat acute infection).

[c] Some would treat after waiting 8 weeks to 12 weeks for spontaneous clearance (see text). Benefits of HCV antiviral therapy or IFN-based (alternative) within 12 weeks of acute infection are that this may decrease transmission risk to others (eg, among injection drug users or surgeons), prevent severe complications (eg, underlying cirrhosis superinfected with acute HCV infection), and minimize chance of being lost to follow-up.

[d] If there were additional exposures in the preceding 6 months, a patient with a new diagnosis who is HCV RNA and HCV Ab positive may still be in the acute infection phase. Symptoms, high ALT level, or viral fluctuations may help distinguish acute from chronic HCV.

[e] Baseline testing should be done within 48 hours of exposure to determine existing infection status: HCV RNA, HCV Ab, and ALT.

Last update: Reviewed June 2016