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: 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.	IIa, B
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	IIa, B

Recommendations Related to HCV Medication Interactions with HIV Antiretroviral Medications

as part of their antiretroviral therapy.	
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
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.

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