

Patients With HIV/HCV Coinfection

This section provides guidance on the treatment of chronic HCV infection in HIV/HCV-coinfected patients. For guidance regarding HIV/HCV-coinfected individuals with acute HCV infection, please see 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 (ART) era, HIV infection remains independently associated with advanced liver fibrosis and cirrhosis in patients with HIV/HCV coinfection ([Fierer, 2013](#)); ([Kirk, 2013](#)); ([de Ledinghen, 2008](#)); ([Thein, 2008a](#)). As such, HCV treatment in HIV-infected patients should be a priority for providers, payers, and patients. If HCV treatment is delayed for any reason, however, liver disease progression should be monitored at routine intervals as recommended in the guidance (see [When and in Whom to Initiate Therapy, recommendation for repeat liver disease assessment](#)).

With the availability of HCV direct-acting antivirals (DAAs), efficacy and adverse event rates among persons with HIV/HCV coinfection are similar to those observed with HCV monoinfection ([Rockstroh, 2018](#)); ([Bhattacharya, 2017](#)); ([Wyles, 2017b](#)); ([Naggie, 2015](#)); ([Rockstroh, 2015](#)); ([Sulkowski, 2015](#)); ([Wyles, 2015](#)). [Simplified HCV treatment](#) has also been demonstrated to be effective in persons living with HIV. Recent data from a global sample of patients undergoing antiviral treatment for chronic HCV infection (MINMON study) suggested that a minimal monitoring approach was safe and achieved SVR at a rate comparable to that with standard monitoring (see [Monitoring Patients Who Are Starting HCV Treatment, Are on Treatment, or Have Completed Therapy](#)). Of the 400 participants, 399 initiated sofosbuvir/velpatasvir treatment. At entry, 166 (42%) were living with HIV, and 94.6% achieved SVR, similar to those without HIV (95.3%) (Solomon, 2022). In addition to other exclusion criteria to [simplified treatment](#), individuals receiving a TDF-containing regimen with eGFR < 60 ml/min should not receive simplified HCV treatment given the need for additional monitoring.

Treatment of HIV/HCV-coinfected patients, however, requires continued awareness and attention to the complex drug-drug interactions that can occur between DAAs and antiretroviral medications. Drug interactions with DAAs and antiretroviral agents are summarized in the text and tables of this section as well as in the US Department of Health and Human Services HIV treatment guidelines (<https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/whats-new-guidelines>). The University of Liverpool drug interactions website (www.hep-druginteractions.org) is another resource for screening for drug-drug interactions with DAAs. Drug interactions should be carefully reviewed before proceeding with simplified HCV treatment in HIV/HCV coinfection.

Risk for Hepatitis B Virus Reactivation

Due to shared modes of transmission, HIV/HCV-coinfected patients are at risk for hepatitis B virus (HBV) infection. HBV reactivation has been reported in patients starting DAA HCV therapy who are not on active HBV agents. Consistent with general recommendations for the assessment of both HIV- and HCV-infected patients, all patients initiating HCV DAA therapy should be assessed for HBV coinfection with HBsAg, anti-HBs, and anti-HBc testing. HIV-infected patients with evidence of HBV infection should be on antiretroviral agents with activity against HBV, preferably tenofovir disoproxil fumarate or tenofovir alafenamide. For patients who are only anti-HBc positive and not on tenofovir-based ART, subsequent monitoring for HBV reactivation should be conducted as detailed in the [Monitoring](#) section.

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
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) Elbasvir/grazoprevir should be used with antiretroviral drugs with which it does not have clinically significant interactions: abacavir, bictegravir, cabotegravir, dolutegravir, doravirine, emtricitabine, ibalizumab-uiyk, lamivudine, maraviroc, raltegravir, rilpivirine, and tenofovir.	IIa, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)^a Glecaprevir/pibrentasvir should be used with antiretroviral drugs with which it does not have clinically significant interactions: abacavir, bictegravir, cabotegravir, dolutegravir, doravirine, emtricitabine, fostemsavir, ibalizumab-uiyk, lamivudine, maraviroc, raltegravir, rilpivirine, and tenofovir. Given the increase in glecaprevir exposures and limited data on the safety of elvitegravir/cobicistat with glecaprevir/pibrentasvir, monitoring for hepatic toxicity is recommended until additional safety data are available in HIV/HCV-coinfected patients.	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) Sofosbuvir/velpatasvir can be used with most antiretrovirals but not efavirenz, etravirine, or nevirapine. Because tenofovir levels, when given as tenofovir disoproxil fumarate, may increase with sofosbuvir/velpatasvir, concomitant use mandates consideration of renal function and should be avoided in those with an eGFR <60 mL/min. Due to limited experience with this drug combination, renal monitoring is recommended in patients taking tenofovir disoproxil fumarate and cobicistat or ritonavir with sofosbuvir/velpatasvir. Tenofovir alafenamide may be an alternative to tenofovir disoproxil fumarate 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 this therapy increases tenofovir levels when given as tenofovir disoproxil fumarate, concomitant use mandates consideration of renal function and should be avoided in those with an eGFR <60 mL/min. Absolute tenofovir levels are highest and may exceed exposures for which there are established renal safety data when tenofovir disoproxil fumarate is administered with ritonavir- or cobicistat-containing regimens. Due to lack of sufficient safety data with this drug combination, consideration should be given to changing the antiretroviral regimen. If the combination is used, renal monitoring is recommended during the dosing period. Tenofovir alafenamide may be an alternative to tenofovir disoproxil fumarate during ledipasvir/sofosbuvir treatment for patients taking cobicistat or ritonavir as part of their antiretroviral therapy.	IIa, C
For combinations including tenofovir disoproxil fumarate wherein increased tenofovir levels are expected, baseline and ongoing assessment for tenofovir nephrotoxicity is recommended.	IIa, C
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) Sofosbuvir/velpatasvir/voxilaprevir should be used with antiretroviral drugs with which they do not have substantial interactions: abacavir, bictegravir, cabotegravir, dolutegravir, doravirine,	IIa, B

Recommendations Related to HCV Medication Interactions With HIV Antiretroviral Medications

emtricitabine, ibalizumab-uiyk, lamivudine, maraviroc, raltegravir, rilpivirine, and tenofovir alafenamide.

Given increases in voxilaprevir AUC with darunavir/ritonavir or elvitegravir/cobicistat coadministration and lack of clinical safety data, monitoring for hepatic toxicity is recommended until additional safety data are available in HIV/HCV-coinfected patients.

Because this therapy has the potential to increase tenofovir levels when given as tenofovir disoproxil fumarate, concomitant use mandates consideration of renal function and should be avoided in those with an eGFR <60 mL/min. In patients concomitantly receiving sofosbuvir/velpatasvir/voxilaprevir and tenofovir disoproxil fumarate, renal monitoring is recommended during the dosing period.

^a Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

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
Glecaprevir/pibrentasvir should not be used with atazanavir, efavirenz, etravirine, nevirapine, or ritonavir-containing antiretroviral regimens.	III, B
Sofosbuvir/velpatasvir should not be used with efavirenz, etravirine, or nevirapine.	III, B
Sofosbuvir/velpatasvir/voxilaprevir should not be used with efavirenz, etravirine, nevirapine, ritonavir-boosted atazanavir, or ritonavir-boosted lopinavir.	III, B
Sofosbuvir-based regimens should not be used with tipranavir.	III, B
Ribavirin should not be used with didanosine, stavudine, or zidovudine.	III, B

Clinical Trial, Pharmacokinetic, and Drug Interaction Data

Extensive recommendations for ART use (including for persons anticipating HCV treatment) are available at <https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/whats-new-guidelines>.

Antiretroviral drug switches may be performed to allow compatibility with DAAs with the goal of maintaining HIV suppression without compromising future options. Considerations include prior treatment history, response(s) to ART, resistance profiles, and drug tolerance ([DHHS, 2021](#)); ([Gunthard, 2014](#)). 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 ([Thorpe, 2011](#)); ([Tedaldi, 2008](#)). The availability of multiple effective HCV DAA and HIV antiretroviral regimens makes it possible for all HIV/HCV-coinfected patients to safely and successfully receive HCV treatment. Switching an optimized antiretroviral regimen carries risks, including adverse effects and HIV viral

breakthrough ([Eron, 2010](#)). HIV viral breakthrough is of particular concern for those with substantial antiretroviral experience or known resistance to antiretroviral drugs. If necessary, ART changes should be undertaken in close collaboration with the treating HIV provider prior to HCV treatment initiation.

Although fewer HIV/HCV-coinfected patients than HCV-monoinfected patients have been treated in DAA trials, efficacy rates to date have been remarkably similar between the groups ([Rockstroh, 2018](#)); ([Dieterich, 2015](#)); ([Naggie, 2015](#)); ([Osinusi, 2015](#)); ([Rockstroh, 2015](#)); ([Rodriguez-Torres, 2015](#)); ([Sulkowski, 2015](#)); ([Wyles, 2015](#)); ([Wyles, 2015b](#)); ([Dieterich, 2014b](#)); ([Sulkowski, 2014](#)); ([Sulkowski, 2013](#)). Thus, results from HCV monoinfection studies largely justify the recommendations for HIV/HCV coinfection (discussed in the [Initial Treatment](#), and [Retreatment](#) sections), which are generally similar to HCV monoinfection. Discussion specific to HIV/HCV coinfection research is included here.

In general, few HIV/HCV-coinfected patients with compensated 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 the lack of data, it is highly likely that response rates are similar to those of HCV-monoinfected patients because no study to date in the DAA era has shown 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-drug interactions.

Elbasvir/Grazoprevir

The safety, tolerability, and efficacy of the second-generation NS3/4A serine protease inhibitor grazoprevir plus the NS5A inhibitor elbasvir were assessed in patients with HIV/HCV coinfection in the C-EDGE COINFECTION study. C-EDGE COINFECTION was a phase 3, nonrandomized, open-label, single-arm study in which treatment-naïve patients with genotype 1, 4, or 6 and HIV coinfection (with or without compensated cirrhosis) were enrolled in Europe, the US, and Australia ([Rockstroh, 2015](#)). All patients were either naïve to treatment with any ART and a CD4 cell count $>500/\text{mm}^3$ ($n=7$), or stable on current ART for at least 8 weeks with a CD4 cell count $>200/\text{mm}^3$ ($n=211$) and undetectable HIV RNA. All 218 enrolled patients received the once-daily fixed-dose combination of elbasvir (50 mg) plus grazoprevir (100 mg) for 12 weeks. All 218 patients completed follow-up at week 12. The median baseline CD4 cell count was $568/\text{mm}^3$ (range, $424\text{--}626/\text{mm}^3$). Limited antiretroviral regimens were allowed, specifically a nucleoside/nucleotide backbone of abacavir (21.6%) or tenofovir (75.2%) in combination with raltegravir (52%), dolutegravir (27%), or rilpivirine (17%).

SVR12 was achieved by 96% (210/218) of patients (95% CI, 92.9–98.4). One patient did not achieve SVR12 for a nonvirologic reason and 7 patients without cirrhosis relapsed (2 subsequently confirmed as reinfections, highlighting the requirement of continued harm-reduction strategies after SVR). Thirty-five patients with compensated cirrhosis achieved SVR12. The most common adverse events were fatigue (13%; $n=29$), headache (12%; $n=27$), and nausea (9%; $n=20$). No patient discontinued treatment because of an adverse event. Three out of 6 patients who relapsed before SVR12 had NS3 and/or NS5A resistance-associated substitutions (RASs) while the others had wild type virus at the time of relapse. Two patients receiving ART had transient HIV viremia but subsequently returned to undetectable levels without a change in ART. No significant changes were observed with CD4 cell counts or new opportunistic infections. Elbasvir/grazoprevir without ribavirin appears effective and well tolerated among patients coinfecting with HIV, with or without compensated cirrhosis. These data are consistent with previous trials of this regimen in the HCV monoinfected population ([Zeuzem, 2017](#)).

Pharmacology and Drug Interaction Data

Elbasvir is a substrate for CYP3A4 and the efflux transporter P-glycoprotein (P-gp). Grazoprevir is a substrate for CYP3A4, P-gp, and the liver uptake transporter OATP1B1. Moderate and strong CYP3A and P-gp inducers (including efavirenz) are not recommended for coadministration with elbasvir/grazoprevir. OATP1B1 inhibitors are also not recommended with grazoprevir.

Elbasvir/grazoprevir is not compatible with any ritonavir- or cobicistat-boosted HIV protease inhibitor, elvitegravir/cobicistat, efavirenz, etravirine, or nevirapine ([Feng, 2019](#)). Drug interaction studies showed no clinically significant interactions between elbasvir/grazoprevir and dolutegravir, raltegravir, doravirine, rilpivirine, or tenofovir disoproxil fumarate ([Ankrom, 2019](#)); ([Feng, 2019a](#)); ([Feng, 2019b](#)); ([Yeh, 2015b](#)).

Glecaprevir/Pibrentasvir

The safety and efficacy of glecaprevir (a pangenotypic NS3/4A protease inhibitor) coformulated with pibrentasvir (a pangenotypic NS5A inhibitor) were evaluated in the phase 3, multicenter EXPEDITION-2 study ([Rockstroh, 2018](#)). This study evaluated 8 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) among 137 HIV/HCV-coinfected adults without cirrhosis, and 12 weeks of glecaprevir/pibrentasvir in 16 HIV/HCV-coinfected patients with compensated cirrhosis. Treatment-naïve and -experienced patients with genotype 1, 2, 3, 4, or 6 infection were enrolled. Patients were either antiretroviral naïve with a CD4 cell count $\geq 500/\text{mm}^3$, or on a stable ART regimen for at least 8 weeks with a CD4 cell count $\geq 200/\text{mm}^3$. ART drugs included raltegravir, dolutegravir, rilpivirine, tenofovir disoproxil fumarate, tenofovir alafenamide, abacavir, emtricitabine, and lamivudine. One patient received elvitegravir/cobicistat. Overall SVR12 was 98% (136/136 among those without cirrhosis on the 8-week regimen, and 14/15 in those with compensated cirrhosis on the 12-week regimen). Four serious adverse events were reported, none of which were DAA related. One of these led to treatment discontinuation.

The EXPEDITION-8 trial found that 8 weeks of glecaprevir/pibrentasvir achieved similar SVR rates to those achieved with 12 weeks of treatment in treatment-naïve patients with cirrhosis ([Brown, 2020](#)). While persons with HIV were not included in this study, SVR rates are likely to be similar in PWH.

Pharmacology and Drug Interaction Data

Glecaprevir is metabolized by CYP3A as a secondary pathway, and glecaprevir and pibrentasvir are substrates for P-gp and breast cancer resistance protein (BCRP). Glecaprevir is also a substrate for the hepatic uptake transporter organic anion-transporting polypeptide (OATP) 1B1/3. Glecaprevir and pibrentasvir are weak inhibitors of CYP3A, CYP1A2, and uridine glucuronosyltransferase (UGT) 1A1. Glecaprevir and pibrentasvir inhibit P-gp, BCRP, and OATP1B1/3. Compounds that inhibit P-gp, BCRP, or OATP1B1/3 may increase glecaprevir and pibrentasvir concentrations. In contrast, drugs that induce P-gp/CYP3A may decrease glecaprevir and pibrentasvir concentrations.

Glecaprevir and pibrentasvir area under the curve (AUC) are increased roughly 3-fold and 1.57-fold, respectively, with tenofovir alafenamide/emtricitabine/elvitegravir/cobicistat ([Kosloski, 2020](#)). A single patient received this combination in the EXPEDITION-2 study. Although the increases in AUC of glecaprevir and pibrentasvir when coadministered with elvitegravir/cobicistat are not considered clinically relevant by the manufacturer or the US Food and Drug Administration (FDA), due to lack of sufficient clinical safety data, close monitoring for hepatic toxicity is recommended until additional safety data are available in HIV/HCV-coinfected patients. Consider liver enzyme testing every 4 weeks.

No clinically significant interactions were observed with glecaprevir/pibrentasvir in a drug interaction study with dolutegravir, raltegravir, rilpivirine, abacavir, lamivudine, emtricitabine, or tenofovir ([Kosloski, 2020](#)). Boosted protease inhibitors are not recommended with glecaprevir/pibrentasvir. Glecaprevir and pibrentasvir exposures were both at least 47% lower when coadministered with efavirenz compared to observed concentrations when given alone in other studies and, therefore, concomitant use is not recommended ([Kosloski, 2020](#)). Etravirine and nevirapine should not be used due to the potential for decreased glecaprevir/pibrentasvir exposures.

Glecaprevir absorption is pH dependent and glecaprevir exposures are reduced approximately 50% with 40 mg of omeprazole daily. Despite the reduced glecaprevir exposures, pooled data from the phase 2/3 glecaprevir/pibrentasvir trials found that patients receiving proton pump inhibitors had similar SVR rates compared to patients not receiving a gastric acid modifier ([Flamm, 2019](#)).

Ledipasvir/Sofosbuvir

The safety and efficacy of 12 weeks of ledipasvir/sofosbuvir were evaluated in the phase 2, single-center, open-label ERADICATE trial, which included 50 HIV/HCV-coinfected patients with genotype 1 infection who were treatment naïve without cirrhosis ([Osinusi, 2015](#)). Thirteen patients were not receiving ART and 37 patients were on protocol-allowed medications (tenofovir, emtricitabine, rilpivirine, raltegravir, and efavirenz). Although the inclusion criteria for patients receiving ART allowed CD4 cell counts $>100/\text{mm}^3$, the median CD4 cell count was $576/\text{mm}^3$. Overall, 98% achieved

SVR12 (13/13 in the treatment-naïve arm and 36/37 in the 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, and urine protein and glucose). 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-naïve and -experienced HIV/HCV-coinfecting 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%). Genotypes included were 1a (75%), 1b (23%), and 4 (2%). Twenty percent of patients had compensated cirrhosis, 34% were black, and 55% had not responded to prior HCV treatment. The overall SVR12 was 96% (321/335). Two patients had on-treatment virologic failure judged to be the 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 rates were 94% (63/67) among patients with compensated cirrhosis and 97% (179/185) among treatment-experienced patients. No patients discontinued the study drugs because of an adverse event. Although all patients had an eGFR >60 mL/min at study entry, drug interaction studies suggested that patients receiving tenofovir disoproxil fumarate could have increased tenofovir levels. There were 4 patients in whom serum creatinine level rose to ≥ 0.4 mg/dL. Two remained on tenofovir disoproxil fumarate, one had the tenofovir disoproxil fumarate dose reduced, and the other stopped taking tenofovir disoproxil fumarate.

Neither the ERADICATE nor the ION-4 study investigators reported clinically significant changes in CD4 cell counts or HIV RNA levels. Thus, these data suggest that 12 weeks of ledipasvir/sofosbuvir is a safe and effective regimen for HIV/HCV-coinfecting patients with genotype 1 infection taking selected ART ([Naggie, 2015](#)); ([Osinusi, 2015](#)). There are limited data regarding an 8-week course of ledipasvir/sofosbuvir in HIV/HCV-coinfecting patients ([Vega, 2019](#)); ([Isakov, 2018](#)); ([Ingiliz, 2016](#)). Additionally, clinical trial data of daclatasvir (an NS5A inhibitor similar to ledipasvir) plus sofosbuvir in HIV/HCV-coinfecting patients demonstrated a lower SVR rate (76%) with 8 weeks of treatment compared to 12 weeks (97%) ([Wyles, 2015](#)). Therefore, a shortened treatment course for HIV/HCV-coinfecting persons is not recommended at this time.

Pharmacology and Drug Interaction Data

Ledipasvir and sofosbuvir are P-gp and BCRP substrates; ledipasvir is also an inhibitor of both P-gp and BCRP transporters. Ledipasvir absorption is pH dependent. Refer to product labeling for guidance on temporal separation and dosing of gastric acid modifying agents.

Drug interaction studies of ledipasvir (with or without sofosbuvir) with antiretroviral drugs in uninfected persons did not identify clinically significant interactions with abacavir, bictegravir, dolutegravir, doravirine, emtricitabine, lamivudine, raltegravir, rilpivirine, or tenofovir alafenamide ([Ankrom, 2019](#)); ([Garrison, 2018](#)); ([Garrison, 2015](#)); ([German, 2014](#)). Ledipasvir 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/sofosbuvir increases tenofovir levels when given as tenofovir disoproxil fumarate, which may increase the risk of tenofovir-associated renal toxicity. This combination should be avoided in patients with an eGFR <60 mL/min. With the addition of ledipasvir/sofosbuvir, tenofovir levels (when given as tenofovir disoproxil fumarate) are increased with efavirenz, rilpivirine ([German, 2014](#)), dolutegravir, ritonavir-boosted atazanavir, and ritonavir-boosted darunavir ([German, 2015](#)). The absolute tenofovir levels are highest and may exceed exposures for which there are established renal safety data when tenofovir disoproxil fumarate is administered with ritonavir- or cobicistat-containing regimens; consideration should be given to changing the antiretroviral regimen. Tenofovir alafenamide may be an alternative to tenofovir disoproxil fumarate during ledipasvir/sofosbuvir treatment for patients who take cobicistat or ritonavir as part of their ART.

In patients with an eGFR <60 mL/min who are taking tenofovir disoproxil fumarate with ledipasvir/sofosbuvir, renal parameters should be checked at baseline and monthly while on ledipasvir/sofosbuvir. Baseline parameters should include creatinine level, electrolytes (including phosphorus), and urinary protein and glucose according to recent guidelines for the management of chronic kidney disease in those with HIV, which include indications for nephrology consultation ([Lucas, 2014](#)). A change in ART should 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- or cobicistat-containing regimen. Tenofovir disoproxil fumarate should also be properly dosed and adjusted for eGFR at baseline and while on therapy ([Lucas, 2014](#)).

Data are limited regarding the renal safety of tenofovir when given as tenofovir alafenamide with ledipasvir/sofosbuvir. However, a small pharmacokinetic study among persons with HIV on a boosted protease inhibitor and tenofovir alafenamide containing regimen found that the addition of ledipasvir/sofosbuvir did not worsen renal biomarkers ([Brooks, 2020b](#)). A study of tenofovir pharmacokinetics in healthy volunteers receiving the combination of tenofovir alafenamide, emtricitabine, and cobicistat-boosted elvitegravir with ledipasvir/sofosbuvir found that tenofovir levels were only 20% of the typical tenofovir exposures seen with tenofovir disoproxil fumarate ([Garrison, 2015](#)). Based on these pharmacokinetic data in healthy volunteers, tenofovir alafenamide may be an alternative to tenofovir disoproxil fumarate during ledipasvir/sofosbuvir treatment for patients on ritonavir- or cobicistat-containing regimens.

Sofosbuvir/Velpatasvir

The safety and efficacy of 12 weeks of sofosbuvir/velpatasvir were evaluated in a phase 3 study among 106 ART-controlled, HIV/HCV-coinfected patients ([Wyles, 2017b](#)). Patients with genotype 1, 2, 3, or 4 infection were included; 18% (19/106) had compensated cirrhosis. HIV was controlled on ART including non-nucleoside reverse-transcriptase inhibitor- (rilpivirine), integrase inhibitor- (raltegravir or elvitegravir/cobicistat), or ritonavir-boosted protease inhibitor- (atazanavir, lopinavir, or darunavir) based regimens with either tenofovir/emtricitabine or abacavir/lamivudine. Fifty-three percent (56/106) of participants were on tenofovir disoproxil fumarate with a pharmacologic boosting agent (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 exposure. SVR12 was 95% with 2 relapses, both occurring in genotype 1a-infected patients. Similar results were noted in patients with compensated cirrhosis and in those with baseline NS5A RASs (n=12 at 15% threshold; SVR12=100%). There were no clinically significant changes in serum creatinine or eGFR, and no patients required a change in their ART during the study period.

Pharmacology and Drug Interaction Data

Velpatasvir is available only in a fixed-dose combination tablet with sofosbuvir. 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 OATP1B1/1B3/2B1 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 an eGFR <60 mL/min or in those receiving ritonavir- or cobicistat-containing ART with tenofovir disoproxil fumarate. Fifty-six HIV/HCV-coinfected individuals receiving the combination of tenofovir disoproxil fumarate with ritonavir- or cobicistat-containing ART were treated with sofosbuvir/velpatasvir in the ASTRAL-5 study with no difference in median creatinine clearance before and after sofosbuvir/velpatasvir treatment, however, poor renal function was an exclusion for this study ([Wyles, 2017b](#)). In individuals with an eGFR <60 mL/min and those requiring ritonavir- or cobicistat-containing ART, consider use of tenofovir alafenamide in place of tenofovir disoproxil fumarate. If the combination of tenofovir disoproxil fumarate with a ritonavir- or cobicistat-containing ART is required or in those with an eGFR <60 mL/min, renal parameters should be checked at baseline and monthly while on sofosbuvir/velpatasvir.

Based on data from healthy volunteers, tenofovir pharmacokinetics are lower with tenofovir alafenamide relative to tenofovir disoproxil fumarate. Thus, tenofovir alafenamide may be an alternative to tenofovir disoproxil fumarate during sofosbuvir/velpatasvir treatment for patients who take cobicistat or ritonavir as part of their ART. However, there are no safety data for this combination in HIV/HCV-coinfected patients.

Drug-drug interaction studies in healthy volunteers found no clinically significant interaction between sofosbuvir/velpatasvir and atazanavir/ritonavir, bictegravir, darunavir/ritonavir, dolutegravir, elvitegravir/cobicistat, lopinavir/ritonavir, raltegravir, rilpivirine, emtricitabine, or tenofovir alafenamide ([Garrison, 2018](#)); ([Mogalian, 2018](#)).

Velpatasvir exposures are significantly reduced with efavirenz and this combination is not recommended. Etravirine and nevirapine have not been studied with sofosbuvir/velpatasvir but are 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.

Sofosbuvir/Velpatasvir/Voxilaprevir

The data supporting use of sofosbuvir/velpatasvir/voxilaprevir are described in the [Initial Treatment of HCV Infection](#) and [Retreatment of Persons in Whom Prior Therapy Has Failed](#) sections. There are limited data on sofosbuvir/velpatasvir/voxilaprevir in HIV/HCV-coinfected patients. The RESOLVE study included 17 individuals with HIV coinfection and a previous DAA treatment failure ([Wilson, 2019](#)). SVR12 was 82% by intention-to-treat analysis and 93% by per protocol analysis. While these data are limited, they suggest response rates in HIV/HCV-coinfected patients are similar to those of HCV-monoinfected patients. Therefore, the respective guidance from the aforementioned treatment and retreatment sections should be followed, with consideration of drug-drug interactions.

Pharmacology and Drug Interaction Data

Voxilaprevir is a substrate for P-gp, OATP1B1/3, BCRP, CYP3A, CYP1A2, and CYP2C8. Voxilaprevir inhibits OATP1B1/3, P-gp, and BCRP. Voxilaprevir AUC is increased 331% with ritonavir-boosted atazanavir and this combination is not recommended ([Garrison, 2017](#)). Voxilaprevir AUC is increased 171% with tenofovir alafenamide/emtricitabine/elvitegravir/cobicistat, and 143% with tenofovir disoproxil fumarate/emtricitabine and ritonavir-boosted darunavir. Although these increases in voxilaprevir AUC were not deemed clinically relevant by the manufacturer or the FDA, due to lack of clinical safety data, close monitoring for hepatic toxicity is recommended until additional safety data are available in HIV/HCV-coinfected patients. Consider liver enzyme testing every 4 weeks.

Velpatasvir absorption is pH dependent. Velpatasvir AUC is reduced approximately 50% when given with omeprazole 20 mg daily as part of the fixed-dose sofosbuvir/velpatasvir/voxilaprevir combination. Refer to product labeling for guidance on temporal separation and dosing of gastric acid modifying agents.

Tenofovir concentrations are increased with sofosbuvir/velpatasvir/voxilaprevir when given as tenofovir disoproxil fumarate ([Garrison, 2017](#)). In individuals with an eGFR <60 mL/min, consider use of tenofovir alafenamide in place of tenofovir disoproxil fumarate in those requiring ritonavir- or cobicistat-containing ART. No substantial interactions were observed with bicitgravir, emtricitabine, or rilpivirine.

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

		Ledipasvir/ Sofosbuvir (LDV/SOF)	Sofosbuvir/ Velpatasvir (SOF/VEL)	Elbasvir/ Grazoprevir (ELB/GRZ)	Glecaprevir/ Pibrentasvir (GLE/PIB)	Sofosbuvir/ Velpatasvir/ Voxilaprevir (SOF/VEL/VO X)
Protease Inhibitors	Boosted Atazanavir	A	A			
	Boosted Darunavir	A	A			
	Boosted Lopinavir	ND, A	A			ND
NNRTIs	Doravirine		ND		ND	ND
	Efavirenz				ND	ND
	Rilpivirine					

		Ledipasvir/ Sofosbuvir (LDV/SOF)	Sofosbuvir/ Velpatasvir (SOF/VEL)	Elbasvir/ Grazoprevir (ELB/GRZ)	Glecaprevir/ Pibrentasvir (GLE/PIB)	Sofosbuvir/ Velpatasvir/ Voxilaprevir (SOF/VEL/VO X)
	Etravirine	ND	ND	ND	ND	ND
Integrase Inhibitors	Bictegravir			ND	ND	
	Cabotegravir	ND	ND	ND	ND	ND
	Cobicistat- boosted elvitegravir	C	C			C
	Dolutegravir					ND
	Raltegravir					ND
Entry Inhibitors	Fostemsavir	ND	ND	ND	ND	ND
	Ibalizumab-uiyk	ND	ND	ND	ND	ND
	Maraviroc	ND	ND	ND	ND	ND
NRTIs	Abacavir		ND	ND		ND
	Emtricitabine					
	Lamivudine		ND	ND		ND
	Tenofovir disoproxil fumarate	B, C	B, C			C
	Tenofovir alafenamide	D	D	ND		D

Green indicates coadministration is safe; **yellow** indicates a dose change or additional monitoring is warranted; and **red** indicates the combination should be avoided.

ND: No data

A: Caution only with tenofovir disoproxil fumarate

B: Increase in tenofovir depends on which additional concomitant antiretroviral agents are administered.

C: Avoid tenofovir disoproxil fumarate in patients with an eGFR <60 mL/min; tenofovir concentrations may exceed those with established renal safety data in individuals on ritonavir- or cobicistat-containing regimens.

D: Studied as part of fixed-dose combinations with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir plus TAF, emtricitabine, elvitegravir, and cobicistat.

For antiretroviral agents not included in the table above, please refer to the US Department of Health and Human Services HIV treatment guidelines

(<https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/whats-new-guidelines>) and/or the University of Liverpool drug interactions website (www.hep-druginteractions.org).

Treatment Recommendations for Patients With HIV/HCV Coinfection

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

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