Persons With HIV/HCV Coinfection

This section provides guidance on the treatment of chronic HCV infection in people living with HIV. For guidance regarding management of acute HCV infection among individuals with HIV/HCV coinfection, please see the Acute HCV section. People with HIV/HCV coinfection suffer from more liver-related morbidity and mortality, nonhepatic organ dysfunction, and overall mortality than HCV-monoinfected persons (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 persons with HIV/HCV coinfection (Fierer, 2013); (Kirk, 2013); (de Ledinghen, 2008); (Thein, 2008a). As such, HCV treatment in persons with HIV should be a priority for providers, practitioners, 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 people living with HIV. Data from a global sample of persons undergoing DAA 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 Persons Who Are Starting HCV Treatment, Are on Treatment, or Have Completed Therapy). Of the 400 participants, 399 initiated sofosbuvir/velpatasvir treatment. At entry, 42% (n=166) were living with HIV and 94.6% attained SVR, similar to the 95.3% SVR rate in those without HIV (Solomon, 2022). In addition to other exclusion criteria to simplified treatment, individuals receiving a tenofovir disoproxil fumarate-containing regimen with estimated glomerular filtration rate <60 mL/min should not receive simplified HCV treatment given the need for additional monitoring.

Treatment of persons with HIV/HCV coinfection requires continued awareness and attention to the complex drug-drug interactions that can occur between DAAs and ART medications. Drug-drug interactions between DAAs and ART 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. The University of Liverpool drug interactions websites are also resources for screening for drug-drug interactions between DAAs and ART medications. Drug-drug interactions should be carefully reviewed before proceeding with simplified HCV treatment for HIV/HCV coinfection.

Risk for Hepatitis B Virus Reactivation

Due to shared modes of transmission, persons with HIV/HCV coinfection are at risk for hepatitis B virus (HBV) infection. HBV reactivation has been reported in persons starting DAA HCV therapy who are not taking active HBV agents. Consistent with general recommendations for the assessment of both people living with HIV or HCV monoinfection, all persons initiating HCV DAA therapy should be assessed for HBV coinfection with hepatitis B surface antigen (HBsAg), hepatitis B surface antibodies (anti-HBs), and hepatitis B core total antibody (anti-HBc) testing. Persons with HIV who are HBsAg positive should be on antiretroviral agents with activity against HBV, preferably tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (USHHS-OAR, 2023). Persons who are only anti-HBc positive and not on tenofovir-based ART require subsequent monitoring to assess for HBV reactivation 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 individual's 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, lenacapavir, 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, lenacapavir, 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 persons with HIV/HCV coinfection.	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 estimated glomerular filtration rate <60 mL/min. Due to limited experience with this drug combination, renal monitoring is recommended in persons 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 people who take cobicistat or ritonavir as part of their antiretroviral therapy.	IIa, B

Recommendations Related to HCV Medication Interactions With HIV Antiretroviral Medications	
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 estimated glomerular filtration rate <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 people 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, emtricitabine, ibalizumab-uiyk, lamivudine, lenacapavir, maraviroc, raltegravir, rilpivirine, and tenofovir alafenamide. Given increases in voxilaprevir AUC with atazanavir/ritonavir, darunavir/ritonavir lopinavir/ritonavir, tipranavir/ritonavir or elvitegravir/cobicistat coadministration and lack of clinical safety data, monitoring for hepatic toxicity is recommended until additional safety data are available in people with HIV/HCV coinfection. 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 estimated glomerular filtration rate <60 mL/min. In persons concomitantly receiving sofosbuvir/velpatasvir/voxilaprevir and tenofovir disoproxil fumarate, renal monitoring is recommended during the dosing period.	IIa, B
[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 Persons 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, fostemsavir, 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, fostemsavir, ritonavir-boosted atazanavir, ritonavir-boosted darunavir, ritonavir-boosted lopinavir or ritonavir-boosted tipranavir.	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-Drug Interaction Data

Extensive recommendations for ART use (including for persons anticipating HCV treatment) are available on the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents With HIV website.

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 tolerability (DHHS, 2023); (Gunthard, 2014). ART interruption in individuals with HIV/HCV coinfection 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 persons with HIV/HCV coinfection to safely and successfully receive HCV treatment. When possible, clinicians should consider DAA options available to an individual before considering an ART switch to ensure medication compatibility. 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 clinician prior to HCV treatment initiation.

Although fewer people with HIV/HCV coinfection compared with HCV monoinfection have been treated in DAA clinical 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 the treatment of HIV/HCV coinfection is included in this section.

In general, few persons with HIV/HCV coinfection and compensated cirrhosis have been included in DAA clinical trials. Additionally, no data are available regarding persons with HIV/HCV coinfection and renal insufficiency, or coinfected persons who have undergone solid organ transplantation. Despite the lack of data, it is highly likely that response rates are similar to those of persons with HCV monoinfection because no study to date in the DAA era has shown a lower efficacy for persons with HIV/HCV coinfection. 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 persons 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-naive participants with genotype 1, 4, or 6 infection and HIV coinfection (with or without compensated cirrhosis) were enrolled in Europe, the United States, and Australia (Rockstroh, 2015). All participants were either naive to treatment with any ART and a CD4 cell count >500/mm^3 (n=7), or stable on current ART for at least 8 weeks with a CD4 cell count >200/mm^3 (n=211) and undetectable HIV RNA. All 218 participants received the once-daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks. All 218 participants completed follow-up at week 12. The median baseline CD4 cell count was 568/mm^3 (range, 424–626/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 participants. One participant did not achieve SVR12 for a nonvirologic reason and 7 participants without cirrhosis relapsed (2 subsequently confirmed as reinfections, highlighting the requirement of continued harm-reduction strategies after SVR). Thirty-five participants with compensated cirrhosis attained SVR12. The most common adverse events were fatigue (13%), headache (12%), and nausea (9%). No one discontinued treatment because of an adverse event. Three out of 6 participants who relapsed before SVR12 had NS3 and/or NS5A resistance-associated substitutions (RASs); the others had wild type virus at the time of relapse. Two participants 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 (Rockstroh, 2015). Elbasvir/grazoprevir without ribavirin appears effective and well tolerated among people with HIV/HCV coinfection, with or without compensated cirrhosis. These data are consistent with previous trials of elbasvir/grazoprevir in the HCV monoinfected population (Zeuzem, 2017).

Pharmacology and Drug-Drug Interaction Data

Elbasvir is a substrate for cytochrome P450 (CYP) enzyme 3A4 and the efflux transporter P-glycoprotein (P-gp). Grazoprevir is a substrate for CYP3A4, P-gp, and the hepatic uptake transporter organic anion-transporting polypeptide (OATP) 1B1. Moderate and strong CYP3A and P-gp inducers (including efavirenz) are not recommended for coadministration with elbasvir/grazoprevir. OATP 1B1 inhibitors are also not recommended with grazoprevir.

Elbasvir/grazoprevir is not compatible with any ritonavir-boosted or cobicistat-boosted HIV protease inhibitor, elvitegravir/cobicistat, efavirenz, etravirine, or nevirapine (Feng, 2019). Drug-drug interaction studies showed

no clinically significant interactions between elbasvir/grazoprevir and dolutegravir, raltegravir, doravirine, rilpivirine, or TDF (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 adults with HIV/HCV coinfection without cirrhosis, and 12 weeks of glecaprevir/pibrentasvir in 16 adults with HIV/HCV coinfection with compensated cirrhosis. Treatment-naive and treatment-experienced participants with genotype 1, 2, 3, 4, or 6 infection were enrolled. Enrollees were either antiretroviral naive with a CD4 cell count ≥500/mm3, or on a stable ART regimen for at least 8 weeks with a CD4 cell count ≥200/mm3. ART drugs included raltegravir, dolutegravir, rilpivirine, TDF, tenofovir alafenamide, abacavir, emtricitabine, and lamivudine. One participant received elvitegravir/cobicistat. Overall SVR12 rate 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 demonstrated that 8 weeks of glecaprevir/pibrentasvir achieved similar SVR rates to those achieved with 12 weeks of treatment in treatment-naive persons with cirrhosis (Brown, 2020). While people living with HIV were not included in this study, SVR rates are likely to be similar in people with HIV/HCV coinfection.

Pharmacology and Drug-Drug Interaction Data

Glecaprevir is metabolized by CYP3A as a secondary pathway. Glecaprevir and pibrentasvir are substrates for P-gp and the plasma membrane transporter breast cancer resistance protein (BCRP). Glecaprevir is also a substrate for the hepatic uptake transporter 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 OATP 1B1/3. Compounds that inhibit P-gp, BCRP, or OATP 1B1/3 may increase glecaprevir and pibrentasvir concentrations. In contrast, drugs that induce P-gp or 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 participant received this DAA and ART 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 persons with HIV/HCV coinfection. 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 with observed concentrations when given alone in other studies. Therefore, concomitant use of glecaprevir/pibrentasvir and efavirenz 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 persons taking proton pump inhibitors had similar SVR rates compared with those not taking a gastric acid modifier (Flamm, 2019).

Ledipasvir/Sofosbuvir

The safety and efficacy of 12 weeks of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) were evaluated in the phase 2, single-center, open-label ERADICATE trial, which included 50 participants with HIV/HCV coinfection and genotype 1 infection who were treatment naive without cirrhosis (Osinusi, 2015). Thirteen participants were not receiving ART and 37 were on protocol-allowed medications (tenofovir, emtricitabine, rilpivirine, raltegravir, and efavirenz). Although the inclusion criteria for enrollees receiving ART allowed CD4 cell counts >100/mm^3, the median CD4 cell count was 576/mm^3. Overall, 98% achieved SVR12 (13/13 in the treatment-naive 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-naive and treatment-experienced persons with HIV/HCV coinfection were enrolled and received ledipasvir/sofosbuvir once daily for 12 weeks. Participants received TDF and emtricitabine with raltegravir (44%), efavirenz (48%), or rilpivirine (9%). Genotype distribution was 1a (75%), 1b (23%), and 4 (2%). Twenty percent of participants had compensated cirrhosis, 34% were Black, and 55% were HCV treatment experienced. The overall SVR12 rate was 96% (321/335). Two participants 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 persons with compensated cirrhosis and 97% (179/185) among treatment-experienced participants. No enrollees discontinued the study drugs because of an adverse event. Although all participants had an eGFR >60 mL/min/1.73 m^2 at study entry, drug-drug interaction studies suggested that those receiving TDF could have increased tenofovir levels. Four persons experienced an elevation in serum creatinine level to ≥0.4 mg/dL. Two remained on TDF, one had a TDF dose reduction, and the other stopped taking TDF.

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 people with HIV/HCV coinfection and genotype 1 infection taking selected ART (Naggie, 2015); (Osinusi, 2015). There are limited data regarding an 8-week course of ledipasvir/sofosbuvir in persons with HIV/HCV coinfection (Vega, 2019); (Isakov, 2018); (Ingiliz, 2016). Additionally, clinical trial data of daclatasvir (an NS5A inhibitor similar to ledipasvir) plus sofosbuvir in people with HIV/HCV coinfection demonstrated a lower SVR rate (76%) with 8 weeks of treatment compared with 12 weeks (97%) (Wyles, 2015). As such, a shortened treatment course for people with HIV/HCV coinfection is not recommended at this time.

Pharmacology and Drug-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 prescribing information for guidance on temporal separation and dosing of gastric acid modifying agents.

Drug-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 alafanamide (Ankrom, 2019); (Garrison, 2018); (German, 2018);. Ledipasvir AUC is decreased by 34% when coadministered with efavirenz-containing regimens and increased by 96% when coadministered with ritonavir-boosted atazanavir (German, 2018). No dose adjustments of ledipasvir are recommended to account for these interactions.

Ledipasvir/sofosbuvir increases tenofovir levels when given as TDF, which may increase the risk of tenofovir-associated renal toxicity. This combination should be avoided in people with an eGFR <60 mL/min/1.73 m^2. With the addition of ledipasvir/sofosbuvir, tenofovir levels (when given as TDF) are increased with efavirenz, rilpivirine (German, 2018), dolutegravir, ritonavir-boosted atazanavir, and ritonavir-boosted darunavir (German, 2018). The absolute tenofovir levels are highest and may exceed exposures for which there are established renal safety data when TDF is administered with ritonavir-containing or cobicistat-containing regimens; consideration should be given to changing the antiretroviral regimen. Tenofovir alafenamide may be an alternative to TDF during ledipasvir/sofosbuvir treatment for persons who take cobicistat or ritonavir as part of their ART.

Among people with an eGFR <60 mL/min/1.73 m^2 who are taking TDF 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 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/1.73 m^2 and 60 mL/min/1.73 m^2 or who have preexisting evidence of Fanconi syndrome, and particularly those taking TDF and a ritonavir-containing or cobicistat-containing regimen. TDF 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, 2020). 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 TDF (German, 2018). Based on these pharmacokinetic data in healthy volunteers, tenofovir alafenamide may be an alternative to TDF during ledipasvir/sofosbuvir treatment for people on ritonavir-containing or cobicistat-containing regimens.

Sofosbuvir/Velpatasvir

The safety and efficacy of 12 weeks of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) were evaluated in a phase 3 study among 106 ART-controlled adults with HIV/HCV coinfection (Wyles, 2017b). Participants 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-based (rilpivirine), integrase inhibitor-based (raltegravir or elvitegravir/cobicistat), or ritonavir-boosted protease inhibitor-based (atazanavir, lopinavir, or darunavir) regimens with either tenofovir/emtricitabine or abacavir/lamivudine. Fifty-three percent (56/106) of participants were on TDF with a pharmacologic boosting agent (ritonavir or cobicistat). Neither efavirenz nor etravirine were permitted as concomitant dosing with sofosbuvir/velpatasvir in healthy volunteers resulted in clinically significant decreases in velpatasvir exposure. SVR12 rate was 95% with 2 relapses, both occurring in people with genotype 1a infection. Comparable results were noted in participants 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; no participants required a change in their ART during the study period.

Pharmacology and Drug-Drug Interaction Data

Velpatasvir is available only in a fixed-dose combination tablet with sofosbuvir, or a fixed-dose combination of sofosbuvir, velpatasvir, and voxilaprevir. Velpatasvir is metabolized by CYP enzymes 3A4, 2C8, and 2B6. It does not appear to inhibit or induce any CYP enzymes. Velpatasvir is a substrate for P-gp and BCRP. It inhibits P-gp, BCRP, and the hepatic uptake transporter OATP 1B1, 1B3, and 2B1, but does not induce any transporters.

Velpatasvir absorption is pH dependent. Refer to product prescribing information for guidance on temporal separation and dosing of gastric acid modifying agents.

Drug-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/1.73 m^2 or in those receiving ritonavir-containing or cobicistat-containing ART with TDF. Fifty-six individuals with HIV/HCV coinfection receiving the combination of TDF with ritonavir-containing or cobicistat-containing ART were treated with sofosbuvir/velpatasvir in the ASTRAL-5 study with no difference in median creatinine clearance before and after HCV treatment. However, poor renal function was an exclusion for this study (Wyles, 2017b). In individuals with an eGFR <60 mL/min/1.73 m^2 and those requiring ritonavir-containing or cobicistat-containing ART, consider use of tenofovir alafenamide in place of TDF. If the combination of TDF with a ritonavir-containing or cobicistat-containing ART is required or in those with an eGFR <60 mL/min/1.73 m^2, 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 TDF. Thus, tenofovir alafenamide may be an alternative to TDF during sofosbuvir/velpatasvir treatment for people who take cobicistat or ritonavir as part of their ART regimen. However, there are no safety data for this combination in persons with HIV/HCV coinfection.

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 people taking atazanavir/ritonavir. These changes are not considered clinically significant.

Sofosbuvir/Velpatasvir/Voxilaprevir

The data supporting use of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) 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 people with HIV/HCV coinfection. The RESOLVE study included 17 individuals with HIV/HCV coinfection and a previous DAA treatment failure (Wilson, 2019). SVR12 rate was 82% by intention-to-treat analysis and 93% by per protocol analysis. While these data are limited, they suggest response rates are similar in people with HIV/HCV coinfection compared with those with HCV monoinfection. Therefore, the respective guidance from

the aforementioned treatment and retreatment sections should be followed, with consideration of drug-drug interactions.

Pharmacology and Drug-Drug Interaction Data

Voxilaprevir is a substrate for P-gp, the hepatic uptake transporter OATP B1/3, the plasma membrane transporter BCRP, and CYP enzymes 3A, 1A2, and 2C8. Voxilaprevir inhibits OATP 1B1/3, P-gp, and BCRP. Voxilaprevir AUC is increased 331% with ritonavir-boosted atazanavir; this combination is not recommended (Garrison, 2017). Voxilaprevir AUC is increased 171% with tenofovir alafenamide/ emtricitabine/ elvitegravir/ cobicistat, and 143% with tenofovir disoproxil fumarate (TDF) /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 people with HIV/HCV coinfection. Consider liver enzyme testing every 4 weeks.

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

Tenofovir concentrations are increased with sofosbuvir/velpatasvir/voxilaprevir when given as TDF (Garrison, 2017). In individuals with an eGFR <60 mL/min/1.73 m^2, consider use of tenofovir alafenamide in place of TDF in those requiring ritonavir-containing or cobicistat-containing ART. No substantial interactions were observed with bictegravir, emtricitabine, or rilpivirine. Consider an alternative HCV regimen if fostemsavir is a component of the ART regimen.

Drug-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/VOX)
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/VOX)
	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
Capsid Inhibitor	Lenacapavir	ND	ND	ND	ND	ND

		Ledipasvir/ Sofosbuvir (LDV/SOF)	Sofosbuvir/ Velpatasvir (SOF/VEL)	Elbasvir/ Grazoprevir (ELB/GRZ)	Glecaprevir/ Pibrentasvir (GLE/PIB)	Sofosbuvir/ Velpatasvir/ Voxilaprevir (SOF/VEL/VOX)
Color Key: Green indicates coadministration is expected to be safe or not clinically significant based on available data or drug metabolism/clearance. Yellow indicates a dose change or additional monitoring is warranted. Red indicates the combination should be avoided. ND indicates no data. A indicates caution only with tenofovir disoproxil fumarate. B indicates an increase in tenofovir depends on which additional concomitant antiretroviral agents are administered. C indicates tenofovir disoproxil fumarate should be avoided in persons with an eGFR <60 mL/min/1.73 m^2; tenofovir concentrations may exceed those with established renal safety data in individuals taking ritonavir-containing or cobicistat-containing ART regimens. D indicates the DAA/ART pair was studied as part of fixed-dose combinations with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir plus tenofovir alafenamide, emtricitabine, elvitegravir, and cobicistat. For antiretroviral agents not included in this table, please refer to the US Department of Health and Human Services HIV Treatment Guidelines and/or the University of Liverpool drug interactions website.						

Treatment Recommendations for Persons With HIV/HCV Coinfection

RECOMMENDED	RATING
Persons with HIV/HCV coinfection 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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Additional Reading

- Initial Treatment of Adults with HCV Infection
- Retreatment of Persons in Whom Prior Therapy Failed

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