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Hepatitis C (K Marks, Section Editor)

Hepatitis C Treatment in HIV Coinfection: Approaches, Challenges, and Future Opportunities

Autumn Bagwell, PharmD, BCPS[1]
Cody A. Chastain, MD[2,*]

Address
[1]Department of Pharmacy, Vanderbilt Specialty Pharmacy, Vanderbilt University Medical Center, Nashville, TN, USA
[*,2]Division of Infectious Diseases, Vanderbilt University Medical Center, A2200 MCN, 1161 21st Avenue South, Nashville, TN, 37232-2605, USA
Email: cody.a.chastain@vanderbilt.edu

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Opinion statement

Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) coinfection is a significant cause of morbidity and mortality in people living with HIV/AIDS. Indeed, HCV is more likely to progress to end-organ dysfunction in HIV-infected people, and fibrosis progresses more quickly in this population than in the general population. While historical treatments combining interferon and ribavirin were less efficacious in HIV/HCV coinfection, modern direct-acting antiviral (DAA) therapies have shown similar clinical efficacy in HIV/HCV coinfection as in HCV monoinfection. In light of these findings, HIV/HCV-coinfected patients may benefit even more from new HCV treatment approaches. The choice of DAA therapy for HCV in HIV-infected patients should be based on the patient's disease stage, prior treatment history, and viral characteristics such as genotype and/or resistance mutations, just as it is in patients with HCV monoinfection. Potential drug-drug interactions between HIV antiretroviral therapy (ART) and HCV DAA therapy must be considered when prescribing HCV treatment and may impact the choice of treatment. Caution is advised when considering DAA regimens that have not been studied in HIV/HCV populations due to lack of data regarding efficacy, the potential for drug-drug interactions, or both. In the era of DAA therapy and with many therapeutic options available to tailor appropriate regimens in order to avoid drug-drug interactions, HCV should be treated aggressively in HIV-infected persons to reduce morbidity and mortality.

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Introduction

Hepatitis C virus (HCV) infection is recognized as a significant cause of morbidity and mortality worldwide, with approximately 184 million people infected as of 2005 [1]. HCV has progressed from the tenth leading cause of death worldwide in 1990 to the seventh leading cause of death worldwide in 2013 [2]. In the USA, HCV has been estimated to infect 2.3–5.2 million people [3–5]. HCV is now thought to contribute to more death than all other CDC-reportable infections in the USA [6•].

Among people living with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), HCV remains a significant cause of morbidity and mortality with up to 5 million people infected worldwide [7]. Due to shared mechanisms of transmission, HCV coinfection occurs in 5–30 % of HIV-infected persons based on prior published studies, although studies of specific geographic populations have detected higher coinfection rates, particularly in regions with prevalent intravenous drug use [8–10]. Liver disease, predominantly caused by HCV, remains one of the leading causes of non-AIDS death in HIV patients along with cardiovascular disease and non-AIDS cancer [11•, 12•, 13•].

The frequency of liver disease as a cause of death in people living with HIV/AIDS is in part due to the natural history of HIV/HCV coinfection. HCV is more likely to result in advanced fibrosis in the setting of HIV, and the rate of liver decompensation and/or hepatocellular carcinoma remains higher in HIV/HCV-coinfected individuals than in HCV-monoinfected individuals [14–17]. Furthermore, rapid progression to advanced or decompensated liver disease has been identified in HIV/HCV-coinfected patients [18]. In light of improving antiretroviral therapies and decreasing mortality attributable to HIV/AIDS, HCV remains a clear target for intervention in HIV-infected persons.

Treatment of HIV/HCV coinfection has historically been limited by poorly tolerated and low-efficacy therapies. Early HCV treatments with pegylated interferon (PEG) and ribavirin (RBV) were not as effective in achieving sustained virologic response (SVR) in coinfected populations as in monoinfected populations; for instance, PEG and RBV achieved SVR rates of 27–40 % in HIV/HCV-coinfected patients, far below that reported in HCV-monoinfected patients [19–21]. The efficacy gap between HCV-monoinfected and HIV/HCV-coinfected patients began to shrink with the introduction of early direct-acting antiviral (DAA) therapy [22, 23]. Today, multiple studies of DAAs in HIV/HCV coinfection have resulted in SVR rates that are comparable to those reported in HCV monoinfection while maintaining similar adverse effect profiles (Fig. 1) [24]. In this article, we review the currently recommended HCV treatments, the data supporting use in HIV/HCV coinfection, and the challenges in utilizing these agents clinically.

Treatment

Direct-acting antiviral overview

HCV is a single-stranded RNA virus enveloped by a lipid bilayer that utilizes structural and non-structural proteins for replication. The ability of DAA agents to target specific steps within HCV replication capitalizes on HCV's rapid replication cycle and error-prone polymerase [25, 26].

The first Food and Drug Administration (FDA)-approved DAA agents were NS3/4 protease inhibitors. The NS3/4A serine protease cleaves two non-structural proteins on the HCV replication complex essential for viral maturation; thus, inhibition of the NS3/4A enzyme prevents viral maturation [26].

The HCV RNA replication cycle is thought to be induced by the non-structural (NS) proteins 4B and 5A. Phosphorylation of NS5A catalyzes the process of RNA replication and viral assembly. NS5A inhibitors have a high potency and broad genotype spectrum of activity but a relatively low barrier to resistance [27].

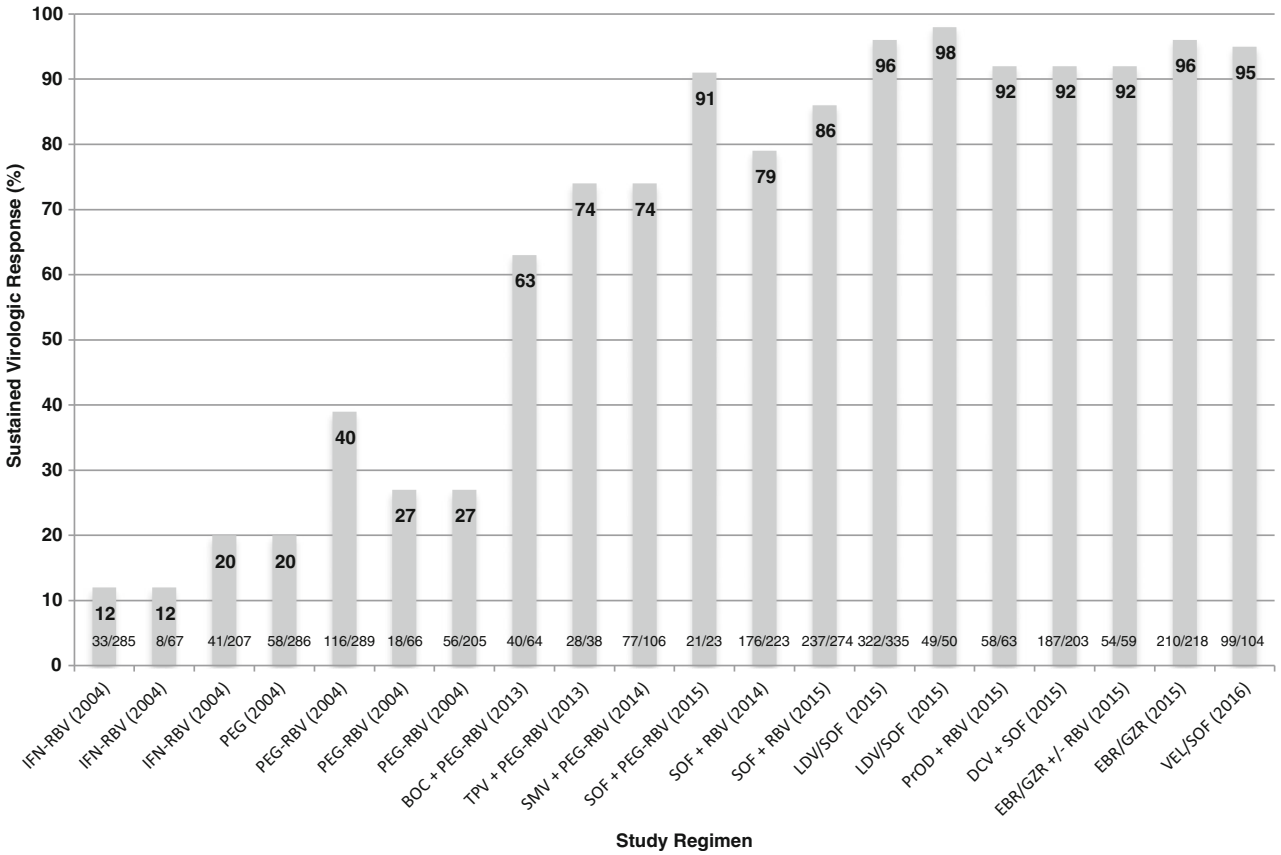

Fig. 1. Sustained virologic response (SVR) rates in HIV/HCV coinfection clinical trials. Each clinical trial included HIV/HCV-coinfected patients or was performed exclusively within this population. Overall SVR for each trial is reported, including all genotypes, treatment durations, treatment experience statuses, and stages of fibrosis. Of note, treatment regimens and durations in these studies do not necessarily reflect subsequent Food and Drug Administration (FDA)-approved and guideline-recommended approaches. The proportion listed on each *bar* reflects the number of HIV/HCV-coinfected subjects who achieved SVR over the subjects analyzed per each study's criteria. Dates listed in *parentheses* after each study regimen refer to the dates of publication (or abstract presentation if trial results have remained unpublished to date). *IFN* standard interferon, *RBV* ribavirin, *PEG* pegylated interferon, *BOC* boceprevir, *TPV* telaprevir, *SMV* simeprevir, *SOF* sofosbuvir, *LDV* ledipasvir, *DCV* daclatasvir, *PrOD* paritaprevir/ritonavir + ombitasvir + dasabuvir, *EBR* elbasvir, *GZR* grazoprevir, *VEL* velpatasvir.

The HCV RNA polymerase NS5B is an ideal target to inhibit HCV viral replication. Nucleoside and nucleotide inhibitors of the NS5B polymerase have excellent adverse effect profiles and minimal drug interactions. NS5B inhibitors cause chain termination of the RNA virus and have an overall high barrier to resistance due to low fitness of resistant mutants [27, 28].

Ledipasvir/sofosbuvir

Ledipasvir (LDV) was the first NS5A inhibitor approved by the FDA, as a coformulation with the NS5B inhibitor sofosbuvir (SOF), also first in its class. SOF is a prodrug that is hydrolyzed to GS-331007, the primary circulating metabolite of SOF. However, it is the final metabolite, GS-461203, acting as a uridine analog, that terminates RNA replication after incorporation in the viral

RNA by NS5B polymerase [28]. Early trials showed efficacy of SOF in combination with PEG and RBV, even in HIV/HCV coinfection [29•]. The fixed-dose combination of LDV/SOF offered patients the first single tablet, interferon-free treatment option for HCV (see Tables 1 and 2 for additional information on LDV/SOF).

Dose recommendations of SOF-containing regimens in patients with an estimated glomerular filtration rate (eGFR) of <30 mL/min have not been established, as safety data of SOF in severe renal impairment and end-stage renal disease (ESRD) is lacking. Both SOF and its active metabolite GS-331007 are renally eliminated, and plasma concentrations have been shown to increase up to 171 and 451 %, respectively, in severe renal impairment [30–32]. Postmarketing data of SOF revealed serious symptomatic bradycardia when used in combination with amiodarone. Therefore, it is recommended to avoid coadministering amiodarone with any SOF-containing HCV regimen [33].

LDV may increase tenofovir disoproxil fumarate (TDF) concentrations, particularly when given in combination with ritonavir- or cobicistat-boosted HIV protease inhibitors or with elvitegravir/cobicistat/emtricitabine. Switching HIV antiretroviral (ARV) medications, including replacing TDF with tenofovir alafenamide (TAF), should be considered to reduce this risk. Coadministration of the strong P-gp inducer tipranavir/ritonavir may decrease LDV/SOF concentrations and is therefore contraindicated. No additional clinically significant ARV interactions are expected with SOF (see Table 1). Further discussion of DAA and ARV interactions may be found in the complementary article within this issue of the journal.

An early study of LDV/SOF in HIV/HCV coinfection was the ERADICATE trial in which 50 HIV/HCV-coinfected patients without cirrhosis received LDV/SOF for 12 weeks, with SVR 12 weeks after treatment completion (SVR12) of 98 % [34••]. The FDA recommendation for use of LDV/SOF in patients with HIV coinfection was based on the larger phase III ION-4 trial in which 335 HIV/HCV-coinfected patients received LDV/SOF for 12 weeks, with an overall SVR12 rate of 96 %. SVR12 rates were similar in all patients regardless of previous treatment status and presence of cirrhosis. Adverse effects reported were similar to those in HCV-monoinfected patients, and no patients experienced HIV virologic failure (see Table 2) [32, 35••].

LDV/SOF is currently the only approved DAA regimen that may be considered for a shortened treatment duration of 8 weeks in select patients (i.e., treatment naïve, without cirrhosis, and with a baseline viral load of less than six million copies/mL) [36, 37•]. Of note, clinical trials including LDV/SOF did not include HIV/HCV-coinfected patients in 8-week treatment arms, and this duration of therapy has not been recommended in this subgroup to date. However, in the real-world GECCO cohort, 27 of 28 HIV/HCV-coinfected patients treated with LDV/SOF for 8 weeks of therapy did achieve SVR; as such, this treatment strategy may be evaluated further in the future in select patients [38•].

Daclatasvir plus sofosbuvir

Daclatasvir (DCV) is a pangenotypic NS5A replication complex inhibitor that works to prevent both HCV RNA synthesis and virion assembly and secretion

Table 1. Direct-acting antiviral agents by class

	Dose	Pharmacokinetics	Selected significant drug interactions (see package insert for additional)	HIV ARV interactions[g]	Comments
NS5B inhibitors					
Sofosbuvir (SOF)	400 mg	Substrate: P-gp and BCRP	Contraindicated or not recommended: -Amiodarone (symptomatic bradycardia) -P-gp inducers[a]	-No clinically significant SOF-specific contraindications	-No dosing recommendation available in eGFR <30 ml/min
Dasabuvir (DSV)	250 mg (PrOD) 200 mg (PrOD XR)	Substrate: CYP2C8, 3A4, P-gp Inhibitor: UGT1A1, BCRP	Contraindicated or not recommended: -P-gp inducers[a] -Gemfibrozil	-No clinically significant DSV-specific interactions	-Activity limited to GT 1 only -Risk of QT prolongation with ↑ DSV -Not recommended in severe hepatic impairment (CTP class B or C)
NS5A inhibitors					
Ledipasvir (LDV)	90 mg	Substrate: P-gp Inhibitor: P-gp, BCRP	Contraindicated or not recommended: -P-gp inducers[a] -Rosuvastatin Other: -Acid-suppressing agents[b]	Other: -HIV ART containing TDF[c]	
Daclatasvir (DCV)	30 mg 60 mg 90 mg	Substrate: CYP3A4, P-gp Inhibitor: CYP3A4, P-gp, BCRP, OATP1B1/1B3	Contraindicated or not recommended: -Strong CYP3A4 inducers[a] -Dabigatran Other: -Strong CYP3A4 inhibitors[e]: ↓ DCV to 30 mg -Moderate CYP3A4 inducers[f]: ↑ DCV to 90 mg	Increase DCV to 90 mg: -Efavirenz, etravirine, nevirapine Decrease DCV to 30 mg: -Atazanavir/ritonavir, indinavir, nelfinavir, saquinavir, cobicistat-containing regimens (excluding darunavir)	-Pangenotypic in vitro activity -Consider pretreatment testing for presence of NS5A RAVs in certain patients (see text)
Elbasvir (EBR)	50 mg	Substrate: CYP3A4, P-gp Inhibitor: P-gp, BCRP	Contraindicated or not recommended: -P-gp and strong CYP3A4 inducers[a] -CYP3A4 inducers: nafcillin, bosentan, modafinil -CYP3A4 inhibitors: ketoconazole Other: -HMG-CoA reductase inhibitors[d]: --Atorvastatin maximum dose 20 mg --Rosuvastatin maximum dose 10 mg	Contraindicated: -Efavirenz -HIV protease inhibitors Not recommended: -Etravirine -Cobicistat-containing regimens	-Pretreatment testing for NS5A RAVs recommended in patients with GT 1a
Ombitasvir (OBV)	12.5 mg (PrOD, PrO) 8.8 mg (PrOD XR)	Substrate: P-gp Inhibitor: CYP2C8, UGT1A1	Contraindicated or not recommended: -P-gp inducers[a]	-No clinically significant OBV-specific interactions	-Pangenotypic in vitro activity -Minimal hepatic metabolism

Table 1. (Continued)

	Dose	Pharmacokinetics	Selected significant drug interactions (see package insert for additional)	HIV ARV interactions[g]	Comments
Velpatasvir (VEL)	100 mg	Substrate: CYP3A4, 2C8, 2B6, P-gp Inhibitor: P-gp, BCRP, OATP1B1/3	Contraindicated or not recommended: -Topotecan -P-gp inducers[a] Other: -Acid-suppressing agents[b] -Rosuvastatin: max dose 10 mg	Not recommended: -Efavirenz -Etravirine -Nevirapine Other: -HIV ART containing TDF[c]	
NS3/4A protease inhibitor					
Simeprevir (SMV)	150 mg	Substrate: CYP3A4, P-gp Inhibitor: CYP1A2, intestinal CYP3A4, P-gp, OATP1B1	Contraindicated or not recommended: -P-gp inducers[a] -CYP3A4 inhibitors and inducers -Erythromycin: increased erythromycin and SMV -Cyclosporine: increased SMV and cyclosporine -Cisapride: increased cisapride Other: -HMG-CoA reductase inhibitors[d]: --Atorvastatin max dose 40 mg --Rosuvastatin initial 5 mg, max dose 10 mg	Not recommended: -Cobicistat-containing products -Efavirenz -Nevirapine, etravirine, delaviridine -Any boosted or unboosted HIV protease inhibitors -Ritonavir	-Screening for NS3 Q80K polymorphism in GT 1a infection is required -Not recommended in severe hepatic impairment (CTP class B or C) -Serious photosensitivity reactions and rash have been observed -Contains a sulfonamide moiety
Paritaprevir/ritonavir (PTV/r)				75 mg/50 mg (PrOD, PrO) 50 mg/33.33 mg (PrOD XR)	Substrate: CYP3A4, CYP3A5, P-gp, OATP1B1, BCRP Inhibitor: CYP2C8, UGT1A1, CYP3A4 (due to ritonavir), P-gp, OATP1B1/3, BCRP
Contraindicated or not recommended: -P-gp inducers:[a] decreased PTV -Strong CYP3A4 inhibitors: alfuzosin, ranolazine, dronedarone, colchicine, lurasidone, pimozide, ergot derivatives,			ethinyl-estradiol-containing products, cisapride, lovastatin, simvastatin, sildenafil, triazolam, midazolam (oral)	Contraindicated: -Efavirenz: severe tolerability issues and ALT elevations -Lopinavir/ritonavir -Rilpivirine -Etravirine -Elvitegravir/cobicistat	-Contraindicated in severe hepatic impairment (CTP B or C) -If ritonavir is used in HIV ARV regimen, hold additional ritonavir upon initiation of PTV/r
Grazoprevir (GZR)	100 mg	Substrate: CYP3A4, P-gp, OATP1B1	Contraindicated or not recommended: -P-gp inducers[a] -Cyclosporine	Contraindicated:	-Contraindicated in severe hepatic impairment (CTP

Table 1. (Continued)

	Dose	Pharmacokinetics	Selected significant drug interactions (see package insert for additional)	HIV ARV interactions[g]	Comments
		Inhibitor: BCRP, UGT1A1	-CYP3A4 inducers: nafcillin, bosentan, modafinil -Ketoconazole -HMG-CoA reductase inhibitors[d]: --Atorvastatin max dose 20 mg --Rosuvastatin max dose 10 mg	-HIV protease inhibitors: Increased risk of ALT elevation -Efavirenz Not recommended: -Etravirine -Cobicistat-containing regimens	B or C) due to increased GZR
General antiviral					
Ribavirin	1000 mg to 1200 mg (weight based)	-Minimal to no CYP, transporter, or enzyme involvement	Contraindicated or not recommended: -Azathioprine	Contraindicated: -Didanosine: risk of mitochondrial toxicity -Stavudine, and zidovudine: decreased antiviral activity, may potentiate anemia	-Pregnancy category X -Dose adjust in patients with CrCl <50 mL/min

ART antiretroviral therapy, *ARV* antiretroviral, *BCRP* breast cancer resistance protein, *CrCl* creatinine clearance, *CTP* Child-Turcotte-Pugh, *eGFR* estimated glomerular filtration rate, *GT* genotype, *HIV* human immunodeficiency virus, *OATP* organic anion-transporting polyprotein, *P-gp* P-glycoprotein, *PI* protease inhibitor, *PPI* proton pump inhibitor, *RAV* resistance-associated variants, *TDF* tenofovir disoproxil fumarate, *UGT* uridine 5′-diphospho-glucuronosyl transferase

[a]P-gp inducers and strong CYP3A4 inducers referenced here include anticonvulsants (carbamazepine, oxcarbamazepine, phenobarbital, phenytoin), rifampin, St. John's wort

[b]Acid-suppressing agents: Antacids should be separated from DAA therapy by 4 hours. H2 antagonists should not to exceed equivalent of famotidine 40 mg twice daily, simultaneously or 12 hours apart. PPI should not to exceed equivalent of omeprazole 20 mg drug-specific administration and should be administered simultaneously with LDV under fasted conditions, while VEL should be taken with food 4 hours before PPI

[c]Increased TDF: Monitor if no other concomitant medications increasing TDF. If TDF is used with LDV and a boosted HIV PI, monitor for tenofovir-associated side effects. Coadministration of LDV/SOF; TDF; and elvitegravir, cobicistat, or emtricitabine is not recommended. If TDF is used with VEL and a boosted HIV PI, elvitegravir, cobicistat, and emtricitabine, monitor for tenofovir-associated side effects

[d]HMG-CoA reductase inhibitors: Use the lowest necessary dose

[e]Strong CYP3A4 inhibitors: clarithromycin, itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, and voriconazole

[f]Moderate CYP3A4 inducers: bosentan, dexamethasone, modafinil, nafcillin, and rifapentine

[g]Tipranavir/ritonavir is contraindicated with all HIV ART due to lack of data and frequent anticipated interactions

Table 2. Currently recommended direct-acting antiviral regimens

	FDA-approved indications	Administration	Adverse effects	HIV/HCV coinfection treatment data
Ledipasvir/sofosbuvir	- GT 1, 4, 5, 6 - HIV/HCV coinfection - Liver transplant patients with or without compensated cirrhosis (GT 1, 4) - Decompensated cirrhosis (GT 1)	1 tablet daily	Common (≥10 %): Headache, fatigue Serious: Symptomatic bradycardia with amiodarone	ERADICATE: phase 2, *n* = 50, treatment naïve, GT 1, HIV RNA <50 copies/mL, CD4 >100 cells/mm^3 LDV/SOF × 12 weeks SVR12 results: -HCV/HIV coinfected on ART, 97 % (36/37) -HCV/HIV coinfected not on ART, 100 % (13/13) Safety: no discontinuations due to adverse effects ION-4: phase 3, *n* = 335, treatment naïve/ exp., GT 1 or 4, +/– compensated cirrhosis, HIV RNA <50 copies/mL, CD4 >100 cells/mm^3 LDV/SOF × 12 weeks SVR12 results: -GT 1a, 96 % (240/250) -GT 1b, 96 % (74/77) -GT 4, 100 % (8/8) Cirrhosis, 94 % (63/67) Safety: no discontinuations due to adverse effects
Paritaprevir/ritonavir/ombitasvir/dasabuvir	- GT 1a (with RBV) and 1b - HIV/HCV coinfection - Liver transplant recipients with ≤F2 fibrosis	PrOD, 3 tablets in the morning with food and 1 tablet in the evening with food PrOD XR, 3 tablets daily with food	Common (≥10 %): Fatigue, nausea, pruritus, insomnia, asthenia, skin reactions Serious: Hepatic decompensation and hepatic failure (not recommended in CTP class B and C), increased risk of ALT elevations	TURQUOISE-1: phase 2/3, *n* = 63, treatment naïve, GT 1, +/– compensated cirrhosis, HIV RNA <40 copies/mL, CD4 >200 cells/mm^3 SVR12 results: -PrOD/RBV × 12 weeks, 93.5 % (29/31) -PrOD/RBV × 24 weeks, 90.6 % (29/32) Safety: no discontinuations due to adverse effects
Daclatasvir plus sofosbuvir	- GT 1 and 3 - Compensated cirrhosis - Decompensated cirrhosis (with RBV) - Transplant recipients (with RBV)	DCV, 1 tablet daily SOF, 1 tablet daily	Common (≥10 %): Headache, fatigue Serious: Symptomatic bradycardia with amiodarone	ALLY-2: phase 3, *n* = 203, treatment naïve/exp., GT 1–4, +/– compensated cirrhosis, HIV RNA <50 copies/mL, CD4 >100 cells/mm^3 DCV/SOF × 12 weeks SVR12 results: -Naïve, GT 1, 96 % (80/83) -Exp., GT 1, 98 % (43/44) -Naïve/Exp., GT 2–4, 100 % (26/26) -Naïve, GT 1, cirrhosis, 89 % (8/9)

Table 2. (Continued)

	FDA-approved indications	Administration	Adverse effects	HIV/HCV coinfection treatment data
				-Exp., GT 1, cirrhosis, 92 % (12/13) Safety: no discontinuations due to adverse effects
Elbasvir/grazoprevir	- GT 1 and 4 - HIV/HCV coinfection - Renal impairment including patients receiving hemodialysis	1 tablet daily	Common (≥10 %): Headache, fatigue, nausea Serious: Increased ALT	C-WORTHY CO-INFECTION: phase 2, *n* = 59, treatment naïve, GT 1, HIV RNA undetectable, CD4 >300 cells/mm^3 SVR12 results: -EBR/GZR × 12 weeks, 87 % (26/30) -EBR/GZR/RBV × 12 weeks, 97 % (28/29) Safety: no discontinuations due to adverse effects C-EDGE Co-Infection: phase 3, *n* = 218, treatment naïve, GT 1, 4, or 6, +/− compensated cirrhosis, HIV RNA <20 copies/mL, CD4 ≥200 cells/mm^3 on HIV ART or HIV RNA <50,000 copies/mL, CD4 ≥500 cells/mm^3 not on HIV ART EBR/GZR × 12 weeks SVR12 results: -Overall, 96 % (210/218) Safety: no discontinuations due to adverse effects
Velpatasvir/sofosbuvir	- GT 1–6 with and without compensated cirrhosis - Decompensated cirrhosis (with RBV)	1 tablet daily	Common (≥10 %): Headache, fatigue Serious: Symptomatic bradycardia with amiodarone	ASTRAL-5: phase 3, *n* = 106, treatment naïve/exp., GT 1, 2, 3, 4, 6, +/− compensated cirrhosis, HIV RNA <50 copies/mL, CD4 ≥100 cells/mm^3 VEL/SOF × 12 weeks SVR12 results: -Overall, 95 % (99/104) -Naïve, 93 % (71/75) -Exp., 97 % (28/29) -No cirrhosis, 94 % (80/85) -Cirrhosis, 100 % (19/19) Safety: discontinuations due to adverse effects, 2 % (2)
Simeprevir plus sofosbuvir	- GT 1 and 4 - HIV/HCV coinfection - Compensated cirrhosis	SMV, 1 tablet daily with food SOF, 1 tablet daily	Common (≥10 %): Headache, fatigue, nausea, diarrhea, photosensitivity, rash, dizziness Serious: Hepatic decompensation and failure (not recommended in CTP	Bello D et al.: Observational, *n* = 89, treatment naïve/exp., GT 1, +/− compensated cirrhosis SVR12 results (intention to treat): -SMV/SOF × 12 weeks, 76 % (31/41) -SMV/SOF/RBV × 12 weeks, 94 % (16/17)

Table 2. (Continued)

	FDA-approved indications	Administration	Adverse effects	HIV/HCV coinfection treatment data
			class B and C), photosensitivity, rash, symptomatic bradycardia with amiodarone	Safety: discontinuations due to adverse effects, 3.4 % (2)
Ribavirin	-See DAA agent	Dosing: >75 kg, 1200 mg daily <75 kg, 1000 mg daily divided into twice-daily dosing with food	Common (≥10 %): Insomnia, nausea, photosensitivity, rash, anemia, mild shortness of breath, nasal congestion, headache, fatigue, pruritus, asthenia Serious: black box warning: severe hemolytic anemia, teratogenicity	-See DAA agent

CTP Child-Turcotte-Pugh; *DCV* daclatasvir; *EBR/GZR* elbasvir/grazoprevir; *Exp* experienced; *FDA* Food and Drug Administration; *GT* genotype; *HCC* hepatocellular carcinoma; *HCV* hepatitis C virus; *HIV* human immunodeficiency virus; *LDV* ledipasvir; *PrO* paritaprevir, ritonavir, ombitasvir; *PrOD* paritaprevir, ritonavir, ombitasvir, dasabuvir; *RBV* ribavirin; *SMV* simeprevir; *SOF* sofosbuvir; *SVR12* sustained virologic response at least 12 weeks after treatment completion; *VEL* velpatasvir

[39, 40]. While it has been studied with a number of DAA agents, it is currently FDA approved in combination with SOF (see Table 2). Resistance testing for NS5A polymorphisms prior to treatment initiation is not required but may be considered in patients with cirrhosis and genotype (GT) 1a infection [41, 42•]. The American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) guidelines also recommend baseline NS5A polymorphism testing in patients with GT 3 infection when considering DCV and SOF treatments [42•].

DCV is the only DAA agent at this time available in multiple doses, with dosing adjusted based on drug interactions (see Table 1). No dose adjustment of DCV is required for patients with renal or hepatic impairment. The combination of DCV and SOF, however, is not recommended in patients with severe renal impairment or in combination with amiodarone for reasons regarding SOF discussed previously. Side effects reported with DCV and SOF are minimal (see Table 2) [41]. Interactions between DCV and HIV ARVs are clinically insignificant other than the need to adjust DCV dosing in certain combinations (see Table 1) [41, 43].

The efficacy of DCV and SOF in patients with HIV/HCV coinfection was assessed in the ALLY-2 trial in which 203 HIV/HCV-coinfected patients with HCV genotypes 1–4 received DCV and SOF for 8 or 12 weeks. Patients received a reduced dose of DCV 30 mg if their HIV antiretroviral therapy (ART) included ritonavir-boosted darunavir, atazanavir, or lopinavir. The results of this trial showed that DCV and SOF for 12 weeks was highly efficacious in patients with HIV coinfection and HCV GT 2, 3, and 4 with a 100 % SVR12 rate in these groups. The SVR12 rate was slightly lower in patients with GT 1 infection, although this was particularly impacted by 8-week DAA treatment durations and in patients treated with a lower prescribed dose of DCV in combination with darunavir/ritonavir (see Table 2). Darunavir/ritonavir was used in 75 % of the patients who experienced virologic relapse. Given this data, a dose of 60 mg of DCV is recommended in patients receiving darunavir/ritonavir. Of note, there were no discontinuations of DCV and SOF due to adverse effects. Two patients did experience HIV virologic failure (one confirmed) but were later undetectable at posttreatment week 12 [44••].

Velpatasvir/sofosbuvir

Velpatasvir (VEL) is a second-generation NS5A inhibitor that is coformulated with SOF for use in all six HCV genotypes in patients with and without cirrhosis who are treatment naïve or treatment experienced (Table 2) [45]. VEL has demonstrated activity against identified NS5A resistance-associated variants (RAVs), positioning this agent as one that may be considered in treating cases of HCV NS5A resistance or NS5A treatment failure [46]. Current AASLD/IDSA guidelines recommend baseline NS5A testing in patients with genotype 3 infection who are treatment naïve with cirrhosis or treatment experienced without cirrhosis [42•].

No dose adjustment of VEL is required for patients with renal or hepatic impairment. The combination of VEL and SOF, however, should not be used in patients with severe renal impairment or in combination with amiodarone for reasons regarding SOF noted previously [45]. In patients without cirrhosis or with compensated cirrhosis, the overall discontinuation rate due to adverse

effects was 0.2 % demonstrated across the ASTRAL-1, ASTRAL-2, and ASTRAL-3 studies (Table 2) [45, 47, 48].

Interactions between HIV ARVs and VEL/SOF were similar to those seen with LDV/SOF. When coadministered with TDF, tenofovir AUC increased by 20–40 % [49]. Therefore, it is recommended to consider the risks and benefits of using VEL/SOF with TDF if part of a concomitant ritonavir- or cobicistat-containing ARV regimen; close monitoring for renal dysfunction, especially in patients with a creatinine clearance <60 mL/min, is recommended if treatment is initiated without ARV changes. Efavirenz significantly decreased VEL levels and is therefore not recommended with VEL/SOF. While etravirine and nevirapine have not been studied with VEL/SOF, they are both weak inducers of CYP3A4 and may impact VEL levels; as such, coadministration is not recommended in the AASLD/IDSA guidelines [50•]. Asymptomatic increases in bilirubin were seen when VEL/SOF was administered with atazanavir, but no dose adjustments are required [50•].

The ASTRAL-5 study evaluated 106 patients with HIV/HCV coinfection and GT 1–4 treated with VEL/SOF for 12 weeks. An impressive 95 % overall SVR12 was demonstrated with a 100 % SVR12 rate in patients with cirrhosis and 97 % SVR12 rate in treatment-experienced patients. Baseline NS5A RAVs did not impact SVR12 rates, and no patients experienced HIV virologic breakthrough [51•].

Paritaprevir/ritonavir/ombitasvir/dasabuvir

Paritaprevir/ritonavir (PTV/r), ombitasvir (OBV), and dasabuvir (DSV) (PrOD) are approved for treatment of HCV GT 1 infection. Paritaprevir (PTV) is a potent NS3 protease inhibitor with in vitro antiviral activity shown against HCV GT 1, 2, 3, 4, and 6 [52]. It is pharmacokinetically enhanced by ritonavir, a CYP3A4 inhibitor, allowing for lower and less frequent dosing [52]. OBV is a strong NS5A inhibitor with in vitro activity against all six HCV genotypes [53]. DSV is a non-nucleoside NS5B polymerase inhibitor and binds in an allosteric position on the enzyme. Its activity is limited to HCV GT 1 [54]. An extended release version of PrOD was recently approved by the FDA, allowing for once-daily dosing of the regimen. While PrOD may be used alone in patients with HCV GT 1b for 12 weeks in patients with and without compensated cirrhosis, it is recommended to add RBV in patients with HCV GT 1a [55]. PrOD is now considered an alternate regimen by the AASLD/IDSA guidelines in patients with HCV genotype 1a and cirrhosis due to the length of recommended treatment (24 weeks) and the need for RBV [37].

PrOD should be avoided in patients with severe hepatic impairment (Child-Turcotte-Pugh [CTP] class B or C) as PTV concentrations may be increased up to 945 % and postmarketing reports have shown increased rates of hepatic decompensation, hepatic failure, and death [55, 56]. An increase in total bilirubin levels, likely secondary to OATP1B1/3 inhibition by PTV, has been observed, although this is thought to be transient and asymptomatic [52]. Common side effects of PrOD can be found in Table 2.

PrOD may be coadministered with atazanavir without ritonavir. The interaction between darunavir and PrOD has recently been debated. An open-label pharmacokinetic study found a moderate decrease in darunavir C_{trough} when used with PrOD and a decrease in PTV kinetic parameters by ~60 %. Based on

this data, it was suggested that no clinically significant interaction was present between the two if darunavir was administered as 800 mg once daily [57]. However, Sollima et al. responded to this study with real-world data of two patients treated with PrOD while on darunavir who did not achieve SVR12. The C_{trough} of PTV in these two patients was found to be greatly reduced despite darunavir taken as directed previously [58]. Part 1b of TURQUOISE-1 evaluated patients taking PrOD with either darunavir 800 mg once daily or 600 mg twice daily. Darunavir C_{trough} levels were decreased 53 and 29 % with daily and twice-daily administration, respectively. All but one patient had HIV RNA suppression at the end of treatment, and SVR12 was achieved by all 22 patients studied [59]. Currently, darunavir is not recommended with PrOD per the US package insert; however, an ongoing study (ACTG 5329) is further addressing the use of PROD with twice-daily dosing of darunavir. Efavirenz is contraindicated with PrOD, as it may reduce the effectiveness of this combination and result in significant alanine transaminase (ALT) elevations. Rilpivirine is a CYP3A4 substrate and may be significantly increased (up to 225 %) by PTV/r, placing patients at high risk of QTc prolongation; thus, this combination is not recommended (see Table 1) [60]. Additional discussion of DAA and ARV interactions may be found in the complementary article within this issue of the journal.

While other treatment options offer smaller pill burdens and fewer drug interactions, PrOD has shown promising results, albeit in a small sample size, for patients with NS3 and NS5 RAVS after failing DAA therapy and remains one of the few regimens with safety and efficacy data in patients with severe renal impairment (eGFR <30 ml/min/1.73m^2) [61, 62].

The TURQUOISE-1 trial assessed PrOD plus RBV for 12 weeks in 63 patients with HCV genotype 1 infection and HIV/HCV coinfection who were treatment naïve or failed prior treatment with peginterferon plus RBV therapy. An overall SVR12 rate of 92 % was found. No patients experienced HIV virologic failure [63••].

The coformulated PTV/r/OBV (PrO) tablet is approved for use with RBV for 12 weeks in patients with HCV GT 4. This regimen was evaluated in 135 HCV-mono-infected patients with HCV GT 4. SVR12 rates were 100 % (42/42) in the treatment-naïve RBV-containing group, 90.9 % (40/44) in the treatment-naïve RBV-free group, and 100 % (49/49) in the treatment-experienced RBV-containing group [64]. This regimen has not been specifically evaluated in patients with HIV/HCV coinfection.

Elbasvir/grazoprevir

The combination of the NS3 inhibitor grazoprevir (GZR) coformulated with the NS5A inhibitor elbasvir (EBR) was recently approved for the treatment of HCV GT 1 and 4 (see Table 2). GZR does not require pharmacokinetic enhancement with ritonavir, and both GZR and EBR exhibit pangenotypic activity, though less effective in genotypes 2 and 3 [65, 66]. Testing for baseline HCV NS5A RAVs is recommended prior to treatment for patients with GT 1a infection, as extension from 12 to 16 weeks and the addition of RBV may improve efficacy in this setting.

GZR is not recommended in moderate to severe hepatic dysfunction as plasma concentrations may be increased up to 388 % in patients with CTP class B hepatic impairment [67]. However, EBR/GZR was the first regimen to gain

FDA approval in patients with ESRD given substantial safety and efficacy data in this population [68]. During clinical trials, approximately 1 % of patients experienced significant increases in ALT, up to greater than five times the upper limit of normal. Therefore, ALT monitoring at week 8 of treatment is recommended [69].

As both EBR and GZR are substrates for CYP3A4, inhibitors such as cobicistat, ritonavir, and other protease inhibitors as well as inducers such as efavirenz and etravirine can dramatically impact drug pharmacokinetics. Co-administration with these agents is not recommended [50•].

The C-WORTHY trial evaluated EBR/GZR for 12 weeks in both HCV-monoinfected and HIV/HCV-coinfected patients with HCV GT 1 infection who were treatment naïve without cirrhosis. The SVR12 rate for 59 patients with HIV/HCV coinfection was 97 % with RBV and 87 % without RBV. These rates were similar in comparison to patients with HCV monoinfection [70••]. Additional promising results were seen in the C-EDGE CO-INFECTION trial, which included 218 HIV/HCV-coinfected patients with HCV GT 1, 4, or 6 who were treatment naïve with or without cirrhosis. EBR/GZR administered for 12 weeks had an overall SVR12 rate of 96 %, with two episodes of HIV virologic failure attributed to patients taking HIV ART incorrectly [71••].

Simeprevir plus sofosbuvir

The first of the later generation NS3/4A inhibitors, simeprevir (SMV), was approved by the FDA in 2013 as a single tablet taken once daily to be used in combination with PEG and RBV, including in HIV/HCV-coinfected patients [72•].

However, it was frequently used off-label in combination with SOF as part of an all-oral, interferon (IFN)-free HCV regimen; FDA recommendations for this treatment strategy were later updated (see Table 2). Its evolving role in treatment is as a salvage regimen for those patients failing DAA therapy with NS5A RAVs without NS3 RAVs in combination with SOF and RBV for 24 weeks [73•].

SMV is not recommended for use in patients with HCV GT 1a with the NS3 Q80K polymorphism as this has been shown to substantially decrease its efficacy. Baseline Q80K testing is recommended in patients with GT 1a infection before treatment with SMV. This agent should be avoided in patients with decompensated cirrhosis (CTP class B or C) given the risk for further hepatic decompensation and failure [74]. Common side effects of SMV with SOF may be found in Table 2.

SMV is hepatically metabolized primarily by CYP3A4 and therefore prone to multiple drug interactions, limiting its use with many HIV ARVs (see Table 1) [74].

Recent real-world data provided the first evaluation of SMV in combination with SOF in patients with HIV/HCV coinfection. Of 89 HIV/HCV-coinfected patients evaluated, 71 % achieved an SVR12 (see Table 2). One patient experienced HIV virologic failure [75•]. Given this data, SMV and SOF could be considered as an alternative regimen in patients with GT 1 infection without cirrhosis, Q80k polymorphisms, or limiting HIV ARV interactions.

Ribavirin

RBV is a guanosine analogue that has been used to treat HCV since the early 1990s [76]. With the advent of the DAA era, its current place in treatment is in

combination with certain DAA regimens to improve the efficacy of the regimen. The interferon-free regimen of SOF and RBV is FDA approved for treatment of HCV GT 2 and 3 infection. Following the approval of DCV and SOF as well as VEL/SOF for these genotypes, this regimen is no longer recommended as a preferred or alternative option by the AASLD/IDSA guidelines [37]. Of note, SOF and RBV were used previously in HIV/HCV coinfection with similar results to HCV monoinfection [77•, 78]. Current guidelines recommend the addition of RBV in select situations for initial treatment, such as PrOD in GT 1a, in GT 3 patients with cirrhosis and HCV harboring the Y93H-resistant variant, with PrO in GT 4, and with additional regimens in treatment-experienced patients [37, 73•].

RBV dose modifications may be required while on therapy due to anemia or other side effects. RBV is contraindicated in women who are pregnant due to severe teratogenicity. Additionally, women who are of childbearing age should use two forms of birth control while on RBV or if they are sexually active with a male on RBV. RBV should not be used in patients with autoimmune hepatitis, hemoglobinopathies, or a previous hypersensitivity reaction to RBV. RBV requires dose adjustment in patients with creatinine clearance ≤50 mL/min with careful clinical and hematologic monitoring while on therapy. RBV should be used with caution and close monitoring in patients with history of cardiovascular disease [79]. While side effects of RBV seem to be less pronounced when combined with DAA treatment rather than PEG, they are still common and may be dose limiting (see Table 2). There are few ARV interactions with RBV (see Table 1) [79].

Emerging therapies

Additional new pangenotypic regimens are currently in development. One coformulated regimen is composed of ABT-493, an NS3/4A protease inhibitor, and ABT-530, an NS5A inhibitor. Phase 3 studies have shown that this once-daily regimen is highly efficacious and tolerable and has a high barrier to resistance. The SURVEYOR-1 and SURVEYOR-2 trials showed 97 to 98 % SVR12 rates with 8 weeks of this regimen in patients with HCV genotypes 1–3 without cirrhosis (33/34 and 81/83 respectively). All patients treated with 12 weeks of the combination achieved SVR12, including those with compensated cirrhosis and genotype 3 (24/24) and genotypes 4–6 without cirrhosis (34/34) [80]. The MAGELLAN-1 study found that this regimen might also be an option for retreating patients who previously failed DAA therapy. In that evaluation, 91 % of patients with HCV GT 1 who failed previous DAA treatment achieved SVR12 with 12 weeks of ABT-493 and ABT-530 without RBV, while 95 % achieved SVR12 with the addition of RBV. Most patients had failed a protease inhibitor-containing regimen, and 50 % had failed NS5A inhibitor treatment. The majority of patients in this study had baseline RAVs. Ongoing studies are evaluating this regimen in patients with and without cirrhosis across all six genotypes with 8- and 12-week treatment durations [81]. The combination of ABT-493 and ABT-530 has been well tolerated in clinical trials with no treatment discontinuations due to adverse effects in SURVEYOR-1 and SURVEYOR-2 or MAGELLAN-1. HIV coinfection has been an exclusion criterion in these studies [82, 83].

Additional trials are focused on triple DAA therapy using combinations of GZR, EBR, MK-3682, an NS5B polymerase inhibitor, and MK-8408, an NS5A inhibitor. These new investigational drugs are all-oral, once-daily medications with pangenotypic activity that have a high barrier to resistance. Ongoing Phase B C-CREST 1 and 2 studies will evaluate GZR, MK-3682, and MK-8408. The most common side effects in part A of the C-CREST studies, which included patients with HIV/HCV coinfection, were headache, fatigue, nausea, diarrhea, flatulence, and insomnia. No patients discontinued treatment due to adverse effects [84].

Cost and cost-effectiveness

Modern DAA therapies have been typically priced using value-based modeling [85]. However, the high cost of these therapies has sparked significant debate, especially in light of the relatively large patient population who may benefit from these treatments [86]. In order to measure the value of DAA therapies, multiple studies assessing their cost-effectiveness have been performed. Many of these studies have found that treating HCV with DAA therapies is cost-effective based on traditional metrics such as quality-adjusted life years as well as patient reported outcomes [87–89]. However, the modeled cost-effectiveness of treatment is dramatically impacted by the predicted cost of each regimen, making estimates of cost-effectiveness fluid with shifts in DAA pricing [87, 90, 91]. Unfortunately, the true cost of these therapies in the US marketplace is obscured by lack of transparency regarding pharmaceutical industry and payer negotiations. Despite the clinical value and cost-effectiveness of modern DAA therapies, the overall financial burden of expensive specialty medications for a disease that impacts millions of people in the USA is tremendous, before even considering the massive cost of global treatment [87, 91]. Cost will likely continue to be a limiting factor in how DAA treatments impact HCV in the near future.

Conclusions

In the era of DAA therapy, there are many effective treatment options for HCV in HIV-coinfected persons. These therapies have demonstrated similar efficacy and side effect profiles in HIV/HCV coinfection as in HCV monoinfection. Special consideration of drug-drug interactions must be made, particularly in regard to HIV ARV therapies. As available therapies are highly effective for the majority of patients with HCV, future HCV therapeutics will likely focus on treating prior treatment failures, overcoming viral resistance, and addressing unique patient populations. Future scientific investigation and public health interventions will continue to address preventing reinfection, caring for end-organ disease, and developing an effective HCV vaccine. In combination with DAA therapy, these interventions may herald a comprehensive plan to eliminate HCV as a significant public health threat while dramatically improving outcomes for HIV/HCV-coinfected patients.

Compliance with Ethical Standards

Conflict of Interest

Dr. Autumn Bagwell declares that she has no conflicts of interest.
Dr. Cody A. Chastain declares that he has no conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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