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A changing paradigm: management and treatment of the HCV/HIV-coinfected patient

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Abstract

Hepatitis C virus (HCV) treatment in HIV/HCV co-infected individuals has renewed relevance given the ongoing opioid crisis and rise of new HIV and HCV infections associated with injection drug use. Patients co-infected with HIV and HCV demonstrate increased rates of hepatic fibrosis, progression to liver failure, and liver-related mortality. HIV co-infection does not impact outcomes of current HCV treatments, and patients should be treated the same as HCV mono-infected persons, though attention to drug:drug interactions is required. In this review, we discuss the mechanisms mediating injury to the liver in HIV mono-infection and HIV/HCV co-infection, and present the landmark trials of HCV treatment in HIV-infected individuals.

Keywords

HIV; HCV; Co-infection; Drug–drug interactions; DAA

Introduction

Hepatitis C virus (HCV) infection remains a leading cause of chronic liver disease, liver failure, and liver transplantation around the world [1]. The advent of direct-acting antivirals (DAAs) and oral, interferon-free regimens has dramatically changed the landscape of HCV treatment, with the most recent trials demonstrating approximately 95% chance of cure across all genotypes and special populations [2]. HCV co-infection with HIV impacts an estimated 2.75 million people around the world, predominantly in African and Southeast

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Compliance with ethical standards

Conflict of interest Dr. Sherman has received grants and contracts (paid to institution) from AbbVie, BMS, Gilead, and Merck. He has served on advisory boards for Abbott Laboratories, and Merck on Data Monitoring boards for MedPace and Watermark.

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Asian regions [3]. A background of HIV infection in HCV-infected patients confers faster rates of liver fibrosis, higher viral loads, and faster rates of hepatic decompensation [4, 5]. Despite this, all available data support that HIV/HCV co-infection does not impact HCV treatment outcome. This review seeks to elaborate on HIV's role in liver disease with and without HCV, a summary of the evidence on HCV treatment in HIV-infected persons, and special considerations in treatment initiation and management.

HIV-mediated injury of the liver

The concept of HIV playing an independent role in liver injury stems from numerous studies that observed persistent liver injury in HIV-infected patients after controlling for other known risk factors. Simply being infected with HIV increases your chance of having liver fibrosis, whether or not you have concomitant viral hepatitis [6, 7]. HIV RNA levels are associated with increased FIB-4 scores in females independently of viral hepatitis, ART, or alcohol use [8]. Liver stiffness, a surrogate for fibrosis, is abnormal in HIV mono-infected individuals when compared to healthy controls [9, 10]. Suppression of the virus with combination antiretroviral therapy (cART) slows fibrosis, hepatic decompensation, and death by liver disease [11, 12]. All of these findings suggest an inherent risk of liver disease from HIV infection which is mitigated but not silenced with viral suppression (Fig. 1).

Further study of patient samples and in vitro experiments has suggested that HIV's role in liver injury is mediated by both direct and indirect mechanisms. Interactions between HIV viral proteins, hepatic stellate cells (HSC), and hepatocytes seem to drive a pro-inflammatory cascade that promotes fibrosis in the liver. Additionally, HIV accelerates fibrosis through indirect mechanisms including immunomodulation, ART toxicity, and alteration of the gut barrier [13].

Direct effects of HIV

Of the many cell types in the liver, hepatocytes and hepatic stellate cells (HSC) seem to be the primary players associated with direct effects mediated by HIV and its soluble protein, GP-120. Hepatocytes have been shown to express CCR5 and CXCR4, two important co-receptors for HIV entry in cells [14, 15]. Productive HIV infection has also been shown in HSCs [16]. HIV is thought to have direct apoptotic effects on hepatocytes [17] and accelerate fibrosis in HSCs [16].

Transcripts for CCR5 and CXCR4, both of which bind the HIV viral protein gp120, are detectable in HSCs [18, 19]. HSC exposure to CCR5-tropic recombinant gp120 promotes HSC chemotaxis and increased expression of MCP-1, IL-6, and tissue inhibitor of metalloproteinase-1 (TIMP-1) [20]. HIV-mediated HSC chemotaxis then likely activates macrophages and leads to increased inflammation and subsequent fibrosis in the liver [21, 22]. Regulation of this pathway seems to be related to a CCR5 autocrine loop, as has been shown in in vivo experiments [18, 23]. CCR5 blockade in mice reduced liver fibrosis along with levels of IL-6, MMP-9, and TGF- β 1, suggesting these molecules are potential regulators of liver fibrosis [24–26]. Maraviroc, a CCR5 inhibitor used in cART, significantly

reduces fibrosis in a mouse model of HCC [24] and may reduce liver stiffness in HIV-infected patients [27].

In hepatocytes and HSCs, HIV interaction with cell receptors leads to reactive oxygen species (ROS) formation and NF κ B activation, promoting an accelerated fibrosis in the liver. ROS-mediated activation of p38 MAPK, JNK, and ERK all create a pro-fibrogenic profile with excess accumulation of extracellular matrix (ECM) components, reduction of matrix metalloproteinases (MMP) which remove ECM, and increased production of tissue inhibitors of MMPs [28].

Immunomodulation

Indirectly, HIV can accelerate extracellular matrix production and pro-fibrotic pathways through its alterations in the immune system [29]. Depletion, dysregulation, and activation of immune cells by HIV have all been described, and all seem to play roles in liver inflammation and scarring [30].

CD4 T cell depletion, a hallmark of HIV infection, is an independent predictor of liver-related death [31]. A paucity of CD4 T cells in the hepatic compartment is thought to be directly responsible for liver fibrosis through reduction of IFN-gamma, an anti-fibrotic cytokine. Additionally, HIV infection confers a robust Th2 response with increased production of IL-4, IL-5, IL-10, and IL-13, all pro-fibrotic cytokines [32]. TGF- β 1, a known contributor to liver fibrosis, has been repeatedly shown to have significant increases in HIV and HIV/HCV co-infected patients [33]. TGF- β 1 has also been implicated in HSC activation and ECM production [34].

IP-10 or CXCL10, a CXC chemokine which binds on monocytes, natural killer (NK) cells, and T cells, is increased in some HIV patients and has been linked with poorer antiviral response and increased liver fibrosis [35]. IP-10 may be responsible for T cell recruitment into the hepatic compartment, causing increased inflammation and fibrosis [36]. IL-1 production, often observed in the early stages of HIV infection, is implicated in driving an inflammatory response in the liver and subsequent fibrosis [37]. IL-6, secreted by T cells and macrophages, is a marker of immune activation, and elevated IL-6 levels have been associated with portal hypertension and decompensated liver disease in HIV-infected patients [38].

A major contributor to immune activation in HIV infection is the translocation of gut microbes through the damaged gastrointestinal (GI) tract. Higher levels of lipopolysaccharide (LPS) enter into the systemic circulation, raising the levels of the macrophage activation marker sCD14 [39]. Liver fibrosis is accelerated through TLR-4 activation by LPS in hepatocytes and HSCs, driving TGF β 1 stimulation, prompting the release of pro-fibrogenic cytokines [40].

HCV with HIV

HIV/HCV co-infection has a number of unique features, including faster rates of fibrotic progression [11], increased risk of hepatic decompensation [5], higher HCV viral loads [41],

elevated alanine aminotransferase (ALT) levels [42], increased potential for drug–drug interactions [43], and potential for altered absorption of antivirals [44] (Fig. 2). Many groups have studied HIV/HCV interactions in various tissue compartments to better understand their interplay in these effects.

HIV can promote HCV-driven increases in TGF- β 1 expression in hepatocytes, driving fibrosis [34]. TGF- β 1 induction has been shown to increase HCV viral loads, inhibit the immune response and promote fibrosis and HCC transformation [45, 46]. HIV and HCV proteins can also cooperate to accelerate fibrosis in the liver. In vitro models demonstrate that simultaneous exposure of hepatocytes to HCV-E2 protein and HIV gp120 promotes hepatocyte apoptosis through increased FasL expression [17, 47]. HIV-induced CD4 T cell depletion reduces the anti-fibrotic activity of NK cells, a likely explanation for the accelerated fibrosis phenotype seen in HIV/HCV co-infected individuals. This CD4 T cell loss is seen in both the systemic and hepatic compartments [48]. HIV tat has also been shown to increase HCV replication through an IP-10 mediated mechanism [49].

Treatment of HIV with antiretroviral therapies leads to a biphasic response in HCV. First, HCV replication increases, which appears to be associated with down-regulation of interferon stimulated gene (ISG) pathways. This is followed by improvement in T cell-specific responses directed against HCV which leads to clearance of hepatic hepatocytes and rises in serum ALT. Over a period of 6–12 months, liver injury resolves and HCV replication occurs at a lower setpoint level [50]. These findings suggest that initial management of the co-infected patient should begin with treatment of HIV, prior to treatment of HCV.

Overview of HCV treatment trials in HIV/HCV co-infection

Safe and effective HCV treatment is a priority for all infected persons, especially those co-infected with HIV (Fig. 3). We summarize many of the landmark trials of DAA HCV treatment in HIV/HCV in roughly chronological order below (Table 1). Early trials with telaprevir and boceprevir are not discussed since they are no longer available.

IFN-based regimens

IFN-based regimens are no longer recommended by the American Association for the Study of Liver Diseases (AASLD) for patients with HCV or HIV/HCV co-infection. We will briefly touch on major trials studying IFN-based regimens to provide a historical perspective.

C-212 was an open-label phase 3 study that sought to compare pegylated interferon (PEG-IFN) plus ribavirin (RBV) with and without simeprevir (SMV) in HIV/HCV patients [51]. A total of 106 patients were enrolled, half ($n = 53$) of whom had prior treatment experience with either HCV relapse ($n = 15$), partial response ($n = 10$), or null response ($n = 28$). All patients had genotype (GT) 1 HCV and all were co-infected with HIV. Patients were treated for a minimum of 24 and up to 48 weeks per response guided therapy (treatment discontinuation at week 24 if HCV RNA < 25 IU/mL at week 4 and < 15 IU/mL at week 12). Twelve-week once daily SMV with PEGIFN + RBV led to an SVR rate of 74% across all participants, regardless of prior HCV treatment response. Most patients did not need

treatment past 24 weeks, and SMV was well tolerated with a good safety profile. The study was limited by a lack of a control group.

IFN-free regimens

Several all-oral, IFN-free HCV treatment trials were conducted in HIV/HCV-co-infected patients with regimens including ledipasvir/sofosbuvir (LDV/SOF), SOF + RBV, sofosbuvir/daclatasvir (SOF/DCV), sofosbuvir/velpatasvir (SOF/VEL), grazoprevir/elbasvir (GZR/EBR) with and without RBV, glecaprevir/pibrentasvir (GLE/PIB), and ombitasvir (OBV)/paritaprevir (PTV)/ritonavir (*r*) + dasabuvir (DSV) + RBV. All showed high SVR12 rates and good safety profiles.

In PHOTON-1 [52], 224 HIV/HCV co-infected patients were treated with either 12 or 24 weeks of SOF + RBV. GT-1 treatment naïve and GT-2,3 treatment experienced patients were treated with 24 weeks of therapy, while GT-2,3 treatment naïve patients were treated with 12 weeks. Patients were either on ARV with HIV RNA less than 50 copies per ml, or not on ARV with CD4 > 500/mm³. SVR rates were 76% (GT-1 naïve, *n* = 87), 75% (GT-2,3 naïve, *n* = 51), and 92% (GT,2,3 experienced, *n* = 38) across treatment groups. Two patients had virologic breakthrough, which seemed to be related to treatment non-adherence. Thirty-nine relapsed, 8 of whom did not complete treatment. There was a low rate of discontinuation for adverse events (seven patients stopped therapy), although it was somewhat higher than rates for HCV mono-infected patients. Females and cirrhotics were underrepresented in the study and there was no control group. This was the first all-oral, IFN-free trial in HIV/HCV-co-infected patients, and showed that HCV treatment with DAA in this population was safe and well tolerated.

PHOTON-2 [53] sought to confirm the findings in PHOTON-1 and further bolster the case for IFN-free HCV treatment in HIV/HCV-infected patients. A total of 274 patients were enrolled in the study. GT-1,3,4 treatment naïve (*n* = 200) patients and GT-2,3 treatment experienced (*n* = 55) patients received 24 weeks of treatment, while GT-2 treatment naïve (*n* = 19) patients received 12 weeks. All achieved high SVR rates (83–91%). Multivariate analysis of factors related to SVR12 showed that no cirrhosis and lower HCV viral load (< 6 log) were strongly associated with HCV cure. One patient had virologic breakthrough (GT-3, treatment experienced) and 30 had relapse. Compared to HCV mono-infection studies, HIV did not seem to have any negative effects on SOF-based therapeutic response. Cirrhosis and high HCV viral loads seemed to be possible impediments to achieving SVR12.

The arrival of fixed-dose DAA combinations offered the opportunity to study the first HCV treatments without IFN or RBV. The ERADICATE [54] study did just that, looking at virologic response to 12-weeks LDV/SOF in 50 GT-1, non-cirrhotic HIV/HCV co-infected patients. 49 (98%) achieved SVR12, one had GT-1b relapse. Resistance analysis showed that the patient had IL28B TT genotype and an Y93H resistance associated substitution (RAS). Most of the adverse events were low grade and manageable. This study showed high rates of treatment success in co-infected patients, comparable to mono-infection studies. It was limited by a low sample size (*n* = 50). Additionally, certain populations were not evaluated, including cirrhotics, patients with low CD4 counts (< 100/mm³), and patients on PI or NNRTI-containing ARV regimens.

The larger ION-4 study [55] looked at 12-weeks LDV/SOF therapy in 335 HIV/HCV-co-infected patients. Most of the participants were male, most had GT-1 HCV, and a little over half had HCV treatment experience. Overall SVR12 was 96% ($n = 322$). Treatment experience and cirrhosis did not affect outcome, with SVR12 rates across those subgroups ranging from 94 to 97%. There was a significantly lower response in blacks (SVR12 89%), and all 10 relapses were in black patients. Multivariate analysis of factors associated with relapse showed that black race, IL28B TT genotype, and efavirenz therapy all played a role. The response rate among blacks in this study was lower when compared to larger studies in mono-infected patients. There were no treatment discontinuations, and the single-tablet, once daily regimen was safe and well tolerated by patients.

C-WORTHY looked at another FDC, GZR/EBR, with and without RBV, in HIV/HCV co-infected patients [56]. Fifty-nine HIV/HCV patients were enrolled, half receiving 12-weeks GZR/EBR with RBV, and the other half without. 29/30 patients in the GRZ/EBR with RBV arm had SVR12 (97%) and 26/29 had SVR12 in the no GZR/EBR arm (87%). In the GZR/EBR arm, two patients had early discontinuation of therapy for virologic failure, and two patients had virologic breakthrough. Adding RBV to the treatment regimen was not significantly associated with better outcome.

C-EDGE evaluated GZR/EBR without RBV in HIV/HCV co-infection [57]. Two hundred eighteen GT-1 or 4 treatment naïve patients were enrolled and treated with 12 weeks GZR/EBR. SVR12 was 96% ($n = 210$), with minimal difference across subgroups including age, sex, race, IL28B genotype, cirrhosis, baseline HCV viral load, and ARV regimen. Five patients relapsed, all of whom were non-cirrhotic. Two patients were re-infected with HCV during treatment, with week 12 testing showing GT-3 HCV, different from their GT-1 HCV at enrollment. The response rates in C-EDGE were comparable to mono-infection studies and there was a low rate of adverse events. Two patients had HIV breakthrough and were re-suppressed with no change in their ARVs or CD4 counts.

ALLY-2 looked at a different DAA combination, SOF/DCV [58] and enrolled a total of 203 patients. Treatment experienced patients ($n = 52$) received 12 weeks SOF/DCV. The remaining patients were treatment naïve and randomized 2:1 to 8-weeks SOF/DCV ($n = 50$) or 12-weeks SOF/DCV ($n = 101$). After 12 weeks of treatment, SVR12 rate was 97% ($n = 149$), with no significant changes in outcome across race, baseline viral load, cirrhosis, or ARV regimen. For patients receiving 8-weeks SOF/DCV, SVR12 rates were 76% ($n = 38$), and shorter therapy was associated with higher chances of HCV relapse. Increased relapse was also seen in patients with higher baseline HCV viral load, and DRV/r-based cART. HIV suppression did not change with SOF/DCV treatment. SOF/DCV is compatible with all commonly prescribed ART regimens, though DCV dose may need to be adjusted in certain circumstances.

The TURQUOISE-1 study treated HIV/HCV-co-infected patients with OBV/PTV/r + DSV + RBV for either 12 or 24 weeks [59, 60]. In part 1a of the study, patients were randomized 1:1 to either 12 weeks ($n = 31$) or 24 weeks ($n = 32$) of therapy. SVR12 rates were high regardless of treatment duration, with 94% ($n = 30$) in the 12-week group and 91 % ($n = 29$) in the 24-week group. There were no HIV RNA failures and no HCV treatment

discontinuations for adverse events. The two treatment failures, one virologic breakthrough and one relapse, occurred in GT-1a cirrhotic patients. In part 1a, ARV regimens were limited to ATV/r or raltegravir (RAL) containing regimens. In part 1b, patients on darunavir (DRV) containing regimens were included and treated with 12-weeks OBV/PTV/r + DSV + RBV. Ten patients were on daily DRV dosing (ritonavir stopped), and 12 patients were on twice daily DRV. All patients ($n = 22$, 100%) obtained SVR12 and maintained HIV viral suppression, with infrequent episodes of HIV viremia.

ASTRAL-5 was the first study to evaluate a pan-genotypic HCV therapy in HIV/HCV co-infected patients [61]. One hundred six patients with GT 1–4 were treated with 12-weeks SOF/VEL, with an overall SVR rate of 95% ($n = 101$). All patients with cirrhosis ($n = 19$) achieved SVR, and 96% of patients with treatment experience ($n = 31$) achieved SVR. RAS at baseline did not impact SVR rates, and treatment was safe and well tolerated. Three patients receiving TDF-containing regimens had a change in their baseline creatinine levels while on treatment. No patient had HIV breakthrough and CD4 counts remained stable throughout.

GLE/PIB, another pan-genotypic therapy recently approved by the United States Food and Drug Administration (US FDA), was studied in HIV/HCV-co-infected patients in the EXPEDITION-2 and ENDURANCE-1 studies [62, 63]. In ENDURANCE-1, depending on the arm, patients either received 8 or 12 weeks GLE/PIB. HIV co-infected patients represented 5% (33 patients) of all enrollees. All achieved SVR12. In EXPEDITION-2, HIV co-infected non-cirrhotic patients ($n = 137$) were treated with 8 weeks GLE/PIB, and cirrhotics ($n = 16$) were treated with 12 weeks. SVR12 was 99.3% in patients without cirrhosis (136/137) with one patient having missing data. In cirrhotic patients, 14/16 (87.5%) had SVR. One patient discontinued therapy for an adverse event and one had virologic breakthrough of their HCV. CD4 counts remained stable and there was no HIV breakthrough.

DAA–ARV interactions in HIV/HCV coinfection

Several DAA–ARV interactions can occur during HCV treatment in HIV-infected patients (Table 2), requiring some patients to change their ARV regimen [64]. In a study reviewing ARV interactions with SOF [65], no significant drug–drug interactions (DDI) were found across the studied ARVs (raltegravir, atazanavir, darunavir, ritonavir, efavirenz, zidovudine, lamivudine, tenofovir, and emtricitabine). Interruption of HIV therapy during HCV treatment is unsafe and should be avoided [66]. The University of Liverpool HEP interactions website [67] is a useful resource in evaluating DDI between ARVs and DAA. Careful attention by the clinician to ARV-DAA interactions is important before starting and while treating HCV in HIV-infected patients.

Role of liver transplantation secondary to ESLD from HCV in HIV/HCV

The first solid organ transplants in HIV-positive patients occurred almost 20 years ago [68]. Since that time, liver and kidney transplantation in HIV-infected patients has become more common. To further assess utility of liver transplantation in this cohort, a prospective

multicenter study compared patient and graft survival in liver transplantation between HIV/HCV co-infected patients and HCV mono-infected patients. Three-year graft and patient survival rates were 60 and 53% (HIV/HCV) versus 79 and 74% (BCV only). HIV was the only covariate significantly associated with reduced patient and graft survival. Further analysis of transplant recipients showed that survival rates in HIV/HCV patients approached the HCV mono-infected cohort if HCV-positive donors, combined liver-kidney transplantation, and BMI > 21 kg/m² were avoided [69]. Additionally, SVR rates were low and tolerability poor in HIV/HCV co-infected patients receiving an HCV-positive donor liver [70].

Presently, liver transplantation secondary to HCV is a viable option for carefully selected candidates and confers a benefit to patients with careful selection of donor livers. Liver transplantation in HIV/HCV co-infected patients should only be performed in centers with a multidisciplinary team that can manage complex interactions between cART and immunosuppressive regimens [71].

HCC surveillance in HIV/HCV

HIV/BCV co-infected patients are not a target population for HCC surveillance in the guidelines of the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), or the Asian Pacific Association for the Study of the Liver (APASL) [72]. The standard surveillance method of ultrasonography every 6 months (all major societies) or ultrasonography plus alpha-fetoprotein testing (APASL only) would apply to HIV/HCV patients when they become cirrhotic. The European AIDS Clinical Society (EACS) guidelines suggest ultrasonography every 6 months for HIV-infected patients, commenting that “persons with liver cirrhosis and persons with HBV co-infection are at high risk of HCC [73].

Concluding remarks

Across multiple phase three trials, efficacy rates of HCV treatment are nearly identical between HCV mono-infected and HIV/HCV co-infected patients. HIV/HCV co-infected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with ARVs. DCV + SOF ± RBV is a recommended regimen when ARVs cannot be changed to accommodate alternative HCV treatment combinations. Shortened course therapy (8 weeks) with LDV/SOF is not recommended for HIV/HCV co-infected patients but may be acceptable for G/P. ARV treatment interruption for HCV therapy should never occur, and effective HIV treatment with cART is a key component of management. HCV treatment should never be prioritized over viral suppression of HIV, except in the rare case when the CD4 is greater than 500 cells/mm³.

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Fig. 1.

Causes of liver disease in HIV infection. *HCV* hepatitis C virus, *HEV* hepatitis E virus, *HBV* hepatitis B virus, *HDV* hepatitis D virus, *HAV* hepatitis A virus, *EtOH* alcohol, *IDU* IV drug use, *NRTI* nucleoside reverse transcriptase inhibitor, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *PI* protease inhibitor

Fig. 2. Liver-mediated injury of HIV/HCV co-infection. *HIV* human immunodeficiency virus, *HCV* hepatitis C virus, *IP-10* interferon-gamma induced protein 10, *IL-1 β* interleukin-1 β , *TGF- β* transforming growth factor- β , *TNF- α* tumor necrosis factor- α .

Fig. 3. Change in SVR with evolution of HCV treatment options across ART eras. *HCV* Hepatitis C virus, *IFN* interferon, *PEG* pegylated, *RBV* ribavirin, *FDC* fixed-dose combination, *DAA* direct-acting antiviral, *SVR 40% [75], **SVR 60–80% [76], ***SVR 80–100% [54, 55, 57, 60, 62, 74]

Table 1
Major HCV treatment trials in HIV/HCV co-infected patients, their characteristics and main study comparators

Refs	Study	Regimen	HCV characteristics	Comparators
[51]	C-212	PEG-IFN + RBV + SMV	GT-1 ± cirrhosis	Tx naïve vs. Tx experience
[52]	PHOTON-1	SOF + RBV	GT 1-3	GT-1 vs. GT 2,3 Tx naïve vs. Tx experience
[53]	PHOTON-2	SOF + RBV	GT 1-4 ± cirrhosis	Tx 12wks vs. Tx 24 wks Tx naïve vs. Tx experience
[54]	ERADICATE	LDV/SOF	GT-1 Tx naïve	None
[55]	ION-4	LDV/SOF	GT-1 ± cirrhosis	None
[56]	C-WORTHY	GZR/EBR ± RBV	GT-1 Tx naïve	RBV vs. no RBV Tx 8 wks vs. Tx 12 wks
[57]	C-EDGE	GZR/EBR	GT-1,4,6 Tx naïve	None
[58]	ALLY-2	SOF + DCV	GT 1-4	Tx 8 wks vs. Tx 12 wks Tx naïve vs. Tx experience
[59]	TURQUOISE-1	OMB/PTV/r + DSV + RBV	GT-1 ± cirrhosis	Tx 12 wks vs. Tx 24 wks. Tx naïve vs. Tx experience
[61]	ASTRAL-5	SOFNEL	GT 1-4 ± cirrhosis	None
[62]	EXPEDITION-2	GLE/PIB	GT 1-6 ± cirrhosis	Tx 8 wks vs Tx 12 wks Cirrhosis vs. no cirrhosis
[74]	ENDURANCE-1	GLE/PIB	GT-1	Tx 8 wks vs. Tx 12 wks

PEG-IFN pegylated interferon, RBV ribavirin, SMV simeprevir, SOF sofosbuvir, LDV ledipasvir, GZR grazoprevir, EBR elbasvir, DCV daclatasvir, OMB ombitasvir, PTV paritaprevir, rritonavir, DSV dasabuvir, VEL velpatasvir, GLE glecaprevir, PIB pibrentasvir, GT genotype, Tx treatment, wks weeks

Table 2

Drug-drug interactions between HIV antiretrovirals and HCV DAA

	SMV + SOF	SOF	LDV/SOF or SOF/VEL	SOF + DCV	OMV/PTV/r + DSV	GZR/EBR	GLE/PIB
Atazanavir + ritonavir	x	+	–	–	–	x	x
Darunavir + ritonavir	x	+	–	+	x	x	x
Lopinavir + ritonavir	x	+	+	+	x	x	x
Tipranavir + ritonavir	x	–	x	x	x	x	x
Efavirenz	x	+	–	–	x	x	x
Rilpivirine	+	+	+	+	x	+	+
Etravirine	x	+	+	+	x	x	x
Raltegravir	+	+	+	+	+	+	+
Elvitegravir + cobicistat	x	+	x	x	x	x	+
Dolutegravir	+	+	+	+	+	+	+
Maraviroc	+	+	+	+	–	+	+
Tenofovir DF	+	+	–/*	+	+	+	+
Tenofovir AF	+	+	+	+	+	+	+

Adapted from AASLD/IDSA/IAS-USA, recommendations for testing, managing, and treating hepatitis C. *SMV* simeprevir, *SOF* sofosbuvir, *LDV* ledipasvir, *DCV* daclatasvir, *OMV* ombitasvir, *PTV* paritaprevir, *r* ritonavir, *DSV* dasabuvir, *GZR* grazoprevir, *EBR* elbasvir, *GLE* glecaprevir, *PIB* pibrentasvir, + Okay to co-administer, – Potential interaction, consider dose adjustment and/or additional monitoring, x Do not coadminister

* Monitor for nephrotoxicity