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CO-INFECTIONS AND COMORBIDITY (S NAGGIE, SECTION EDITOR)

Drug Interactions of Hepatitis C Direct-Acting Antivirals in the HIV-Infected Person

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Abstract The development of direct-acting antivirals for hepatitis C has occurred at a rapid pace. Up to recently, HCV therapy has been limited to pegylated-interferon and ribavirin, but now physicians have several highly efficacious and well-tolerated interferon-free direct-acting antiviral agent (DAA) regimens available. In order to minimise patient harm and maximise the response to therapy, physicians must remain cognisant of the potential DAA drug-drug interactions in patients with HIV/HCV co-infection. HCV clearance needs to be achieved while maintaining HIV suppression and not compromising future antiretroviral options. CYP450 enzyme induction or inhibition accounts for many of the pharmacokinetic interactions between HCV DAA and HIV antiretrovirals, although an increasing number of transporter-mediated interactions are now recognised. DAA interactions in the HIV/HCV co-infected patient are largely extrapolated from drug-drug interaction studies with commonly used antiretrovirals. These studies then inform the selection of permitted antiretroviral regimens in phase II and III DAA clinical studies in HIV/HCV co-infection. We review the recently reported drug-drug interaction studies of HCV DAA therapy in the HIV-infected person and the HIV antiretroviral combinations in HCV DAA clinical trials.

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Introduction

The era of highly active antiretroviral therapy (HAART) has resulted in a reduction in AIDS-related deaths. This trend has occurred in parallel with an increase in liver-related mortality in HIV-infected individuals largely driven by hepatitis C infection in high-income countries [1, 2]. HIV and HCV share similar modes of acquisition. As a result, up to one third of patients with HIV are co-infected with HCV, while the rates of co-infection rise to more than 50 % in people who inject drugs (PWID) [3, 4].

Patients with HIV/HCV co-infection are at increased risk of accelerated fibrosis, cirrhosis, hepatic decompensation and hepatocellular carcinoma compared to HCV mono-infection [5]. European and American guidelines advocate prioritisation of HCV therapy in patients with HIV/HCV co-infection because of these increased risks [6••, 7••]. Studies from the interferon era have demonstrated that successful hepatitis C therapy in mono-infected and co-infected patients reduces liver-related complications and mortality [8, 9]. However, the benefits of successful treatment have only been realised in a minority of patients, as therapy with pegylated-interferon and ribavirin produces a sustained virological response (SVR) in <30 % of HIV patients co-infected with HCV genotype 1 [9, 10].

The addition of the first HCV direct-acting antiviral agents (DAA) in 2011, telaprevir and boceprevir, to standard of care therapy resulted in increased sustained virologic response rates of 63–74 % in HIV/HCV co-infection [10, 11]. These first in class NS3/4A protease inhibitors had a significant side effect profile resulting in high treatment discontinuation rates and numerous drug-drug interactions with antiretrovirals

(ARVs) [12] Additionally, these drugs were never approved in HIV-infected patients, limiting access in many parts of the world. The advent of highly efficacious interferon-free DAA therapy for HCV, associated with minimal side effects, represents a real turning point in the management of HIV/HCV co-infection. However, drug-drug interactions (DDIs) remain highly relevant in this cohort, with all of these HCV-DAA regimens possessing drug interaction potential.

This article aims to review the relevant drug-drug interaction data between interferon-free HCV DAAs and ARVs. General approaches for the management of clinically significant DDIs will also be discussed as well as areas of uncertainty where DDI data is lacking. This review will focus primarily on interferon-free DAA regimens, as the first generation protease inhibitors are no longer recommended for the treatment of hepatitis C by either the European or American guidelines.

Drug-Drug Interactions

Drug-drug interactions remain an important consideration in HIV/HCV co-infection [13]. Pharmacokinetic interactions occur when drug A results in a change in drug concentrations of drug B. A clinically relevant pharmacokinetic interaction occurs when this change in drug concentration shifts the concentration of a drug outside its therapeutic range. A reduction in drug concentrations can reduce the efficacy of an antiviral, with the associated risk of antiviral resistance. Conversely, an increase in drug concentrations can increase the risk of drug toxicity. Pharmacokinetic interactions can occur at the level of drug absorption, metabolism, distribution or elimination. Human CYP450 isoform CYP3A is responsible for the oxidative metabolism of more than 40 % of the drugs in clinical use [14]. Many drug-drug interactions are attributable to CYP450 enzyme inhibition or induction. Membrane transporter proteins are also increasingly recognised as an important site for drug-drug interactions [15].

DAA Pharmacology and Drug Interactions With Antiretrovirals in Healthy Volunteers

Ledipasvir/Sofosbuvir

Ledipasvir (90 mg) and sofosbuvir (400 mg) are co-formulated in a fixed-dose combination that is administered once daily. Sofosbuvir is converted to an active triphosphate in hepatocytes, and its major inactive plasma metabolite (GS-331007) is primarily excreted in the urine [16]. Neither sofosbuvir nor ledipasvir are metabolised by CYP450 enzymes. Ledipasvir is primarily excreted in bile as unchanged part drug. Sofosbuvir is a P-glycoprotein (P-gp) substrate, and ledipasvir is a weak inhibitor of P-gp and breast cancer resistance protein (BCRP) [17].

In the majority of drug interaction studies between ledipasvir/sofosbuvir and antiretrovirals, a non-nucleoside reverse transcriptase (NNRTI) backbone of emtricitabine/tenofovir (FTC/TDF) was included as part of a combination ARV regimen. A phase I study in healthy volunteers evaluated the co-administration of ledipasvir/sofosbuvir with FTC/TDF/efavirenz or FTC/TDF/rilpivirine [17]. Tenofovir exposure was increased by 98 and 40 %, respectively, with FTC/TDF/efavirenz and with FTC/TDF/rilpivirine when given with ledipasvir/sofosbuvir when compared to antiretroviral therapy alone. The safety of increased tenofovir levels in these regimens with ledipasvir/sofosbuvir were assessed in the ION-4 phase III trial [18••], and only 1 % of patients were noted to have a treatment emergent rise in baseline creatinine ≥0.4 mg/dl.

The effects of sofosbuvir and ledipasvir on raltegravir exposure were investigated separately [17, 19]. Raltegravir area under the curve (AUC) was modestly reduced when given with ledipasvir (15–18 %) and sofosbuvir (27 %). The combined effect of the fixed-dose combination of ledipasvir/sofosbuvir on raltegravir was not studied, although this combination was safe and effective in 146 patients with HIV/HCV infection [18••].

The effect of ledipasvir/sofosbuvir on tenofovir pharmacokinetics when given within a boosted HIV protease inhibitor regimen has recently been reported [20]. Healthy volunteers received ledipasvir/sofosbuvir with FTC/TDF/atazanavir/ritonavir or FTC/TDF/darunavir/ritonavir. Tenofovir trough levels were moderately increased (~40–60 %) with ledipasvir/sofosbuvir in combination with a boosted protease inhibitor (PI). The effect of staggered administration was similar. There are no safety data of increased tenofovir levels in this setting. Given that tenofovir levels are already increased (20–30 %) when given with a boosted protease inhibitor, co-administration of ledipasvir/sofosbuvir with TDF and a boosted HIV protease inhibitor should therefore be avoided if possible, particularly in patients with low baseline eGFR (<50 ml/min), with close monitoring for renal toxicity required if this combination is used.

Atazanavir (given with FTC/TDF and ritonavir [r]) trough concentrations are increased by 63 % with ledipasvir/sofosbuvir, and this combination is associated with indirect hyperbilirubinaemia [20]. Ledipasvir AUC and C_{min} are increased by 90 and 134 %, respectively, with atazanavir/r, although this magnitude of ledipasvir exposure was not associated with any safety signals in phase III trials of HCV mono-infected patients. There is no significant interaction between ledipasvir/sofosbuvir and darunavir/r [20]. This data supports the co-administration of ledipasvir/sofosbuvir with boosted HIV protease inhibitors, provided they are not combined with TDF.

A multiple-dose crossover DDI study to assess the interaction potential of ledipasvir/sofosbuvir with elvitegravir/cobicistat and dolutegravir has also recently been reported [21]. Healthy volunteers received ledipasvir/sofosbuvir with

elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate (E/C/F/TAF) (n=30) or FTC/TDF/dolutegravir (n=30). Ledipasvir and GS-331007 exposure were increased by 79 and 48 %, respectively, when co-administered with E/C/F/TAF. This increased exposure is most likely as a result of intestinal P-gp and/or BCRP inhibition by cobicistat and is not considered clinically relevant based on safety-exposure data. Cobicistat AUC was increased by 53 %, although this increased exposure was not associated with common adverse events from phase II/III studies and is deemed not clinically relevant by the investigators. Ledipasvir/sofosbuvir increased tenofovir exposure within FTC/TDF/dolutegravir (consistent with previous DDI studies) but not within E/C/F/TAF. There was no significant interaction between ledipasvir/sofosbuvir and dolutegravir or FTC.

Simeprevir

Simeprevir is an NS3/4A protease inhibitor that is licenced in combination with sofosbuvir for HCV genotype 1 and 4 infections, and administered at a dose of 150 mg once daily. Simeprevir is metabolised by CYP3A and is a mild inhibitor of intestinal CYP3A and CYP1A2 [22].

Efavirenz reduced simeprevir exposure by 71 % in healthy volunteers; thus, this combination is not recommended [23]. Simeprevir is also not recommended with boosted HIV protease inhibitors or elvitegravir/cobicistat, as simeprevir concentrations are significantly increased with CYP3A inhibitors. Dose reduction of simeprevir is not sufficient to mitigate this interaction—simeprevir exposure was increased 2.59-fold when administered at a dose of 50 mg once daily with darunavir/r [23].

There is no significant interaction between simeprevir and rilpivirine, raltegravir and TDF [23]. Although the combination of simeprevir with FTC, lamivudine and/or abacavir has not been studied, no specific drug-drug interactions are expected. There is no anticipated interaction between simeprevir and dolutegravir (dolutegravir is primarily metabolised through glucuronidation via UGT1A1), although co-administration has been studied.

Daclatasvir

Daclatasvir (60 mg once daily) is an NS5A inhibitor that is licenced in Europe as part of an interferon-free combination with sofosbuvir and is currently under review by the Food and Drug Administration (FDA). Daclatasvir is a substrate of CYP3A4 and P-gp, and an inhibitor of OATP1B1, P-gp and BCRP [24].

Daclatasvir levels are increased when administered with strong CYP3A inhibitors (e.g., atazanavir/r and cobicistat-boosted regimens). Atazanavir/r increased daclatasvir AUC ~2.1-fold in healthy volunteers. The magnitude of increase in daclatasvir exposure is not as high with darunavir/r (1.4-fold) or lopinavir/r (1.15-fold). Daclatasvir dose reduction to 30 mg once daily is recommended when used with atazanavir/r or cobicistat-boosted antiretrovirals [24].

Daclatasvir exposure is reduced when used with CYP3A inducers such as efavirenz. In healthy volunteers, daclatasvir AUC was reduced by 32 % when co-administered with efavirenz. An increase in daclatasvir dose to 90 mg once daily is recommended to overcome this interaction [23]. No dose modification is required with rilpivirine. Co-administration of daclatasvir with etravirine and nevirapine is not recommended, due to the lack of data and the expected decrease in daclatasvir concentrations mediated by CYP3A4 induction. There is no significant interaction between daclatasvir and dolutegravir [25], and there is no anticipated interaction between daclatasvir and raltegravir.

Ritonavir-Boosted Paritaprevir, Ombitasvir Plus Dasabuvir

This triple DAA regimen combines a ritonavir (r)-boosted NS3/4A protease inhibitor (paritaprevir) with an NS5A inhibitor (ombitasvir) and a non-nucleoside NS5B polymerase inhibitor (dasabuvir) (P/r/O+D). Paritaprevir/r is co-formulated as a fixed-dose combination with ombitasvir and administered once as two tablets daily, while dasabuvir is administered as a single tablet twice daily.

Paritaprevir is metabolised by CYP3A and is given with low-dose ritonavir, a potent CYP3A inhibitor to optimise paritaprevir exposure and to allow for once daily dosing. Ombitasvir is metabolised via amide hydrolysis followed by oxidative metabolism. Dasabuvir is primarily metabolised by CYP2C8 but also undergoes metabolism by CYP3A. This combination has the potential for numerous drug-drug interactions. Ritonavir is a potent hepatic and intestinal CYP3A inhibitor, a modest inducer of glucuronidation and an inhibitor of P-glycoprotein (P-gp) and BCRP. Protein transporters play an important role in the metabolic pathways of these agents. Paritaprevir is a substrate and inhibitor of OATP-1B1/1B3 and is an inhibitor of P-gp and BCRP. Dasabuvir is also an inhibitor of BCRP and P-gp [26–30].

A comprehensive drug-drug interaction phase I study programme has been undertaken in healthy volunteers to investigate the interaction profile of P/r/O+D with ARVs. Based on the safety/efficacy exposure data of the regimen from phase II clinical trials, an increase in exposure by ≤100 % or a decrease in exposure by ≤50 % for the 3 DAA were deemed not clinically significant [31].

There was no significant interaction observed between P/r/O+D and emtricitabine/tenofovir (FTC/TDF) in healthy volunteers [32]. FTC/TDF can be safely co-administered without any dose modification. The P/r/O+D combination and abacavir/lamivudine has not been studied. Although there is the potential for increased abacavir exposure mediated by ritonavir inhibition of UDP-glucuronyl transferase, abacavir

and lamivudine can be administered with P/r/O+D without any dose modification.

Efavirenz should not be administered with P/r/O+D. The co-administration of P/r/O+D with efavirenz (as part of fixed-dose combination with FTC/TDF) resulted in premature study discontinuation due to adverse events (nausea/vomiting and transaminase elevations) [32]. Rilpivirine exposure is increased 3.25-fold when administered with P/r/O+D, and evening administration of rilpivirine (with food or 4 h after dinner) did not mitigate this interaction [32]. This interaction is attributable to ritonavir CYP3A inhibition and is associated with the potential for QT prolongation. Co-administration of rilpivirine and P/r/O+D is not recommended. The interaction between P/r/O+D and etravirine or nevirapine has not been studied, but co-administration is not recommended based on the expected reduction in paritaprevir levels through CYP3A induction.

Since the P/r/O+D regimen includes 100 mg of ritonavir, it should not be administered with HIV regimens containing ritonavir or cobicistat. A phase I study in healthy volunteers evaluated the interaction between two dosing strategies of atazanavir with P/r/O+D. Atazanavir was administered as either a morning dose (without ritonavir) or evening dose of 300 mg (with 100 mg ritonavir) with P/r/O+D dosed with the P/r/O component in the morning [31]. Paritaprevir AUC and C_{max} were increased by 94 and 46 %, respectively, with no significant effect on the exposure of atazanavir, ombitasvir or dasabuvir when atazanavir was given in the morning. Paritaprevir exposure was significantly higher when atazanavir/ritonavir was dosed in the evening.

The recommended dose of darunavir when given with P/r/O+D is 800 mg as a morning dose without ritonavir or cobicistat. Darunavir AUC and C_{min} were reduced by 24 and 48 %, respectively, in this dosing scenario [31]. Darunavir should therefore not be administered with P/r/O+D in patients with extensive PI resistance or in patients who do not have optimal suppression of HIV replication prior to instituting HCV therapy. Other protease inhibitors such as lopinavir and saquinavir are contraindicated with P/r/O+D. Raltegravir exposure is increased 2.3-fold when given with P/r/O+D, but this combination can safely be co-administered based on safety data from phase II and III studies in HIV/HCV co-infection. Although not studied, no significant interaction between P/r/O+D and dolutegravir is anticipated.

Ritonavir-Boosted Paritaprevir and Ombitasvir Without Dasabuvir

The dual combination of ritonavir-boosted paritaprevir and ombitasvir (P/r/O, without dasabuvir) is licenced in Europe for hepatitis C genotype 4 infection. The interaction profile of P/r/O+D and P/r/O are broadly similar, although darunavir and atazanavir are not recommended in combination with P/r/O [28].

HCV Drugs in the Pipeline

Grazoprevir (MK-5172) is an NS3/4A protease inhibitor that in co-formulated with the NS5A inhibitor elbasvir (MK-8742) and is currently in phase III development as a single tablet, fixed-dose combination tablet dosed once daily.

A phase I DDI study evaluated the potential interaction between dolutegravir and grazoprevir/elbasvir in 12 healthy volunteers. There was no significant change in elbasvir or dolutegravir exposure in this combination. Grazoprevir AUC and C_{max} were reduced by 19 and 36 %, respectively, although this exposure is within the therapeutic window for grazoprevir [33]. There are no significant interactions between grazoprevir or elbasvir and raltegravir or tenofovir [34].

Grazoprevir and elbasvir are sensitive to the effects of CYP3A inhibition and induction. The pharmacokinetic interactions between grazoprevir- and ritonavir-boosted protease inhibitors were assessed in healthy volunteers. Grazoprevir AUC was increased by 958 % with atazanavir/r, 650 % with darunavir/r and 1186 % with lopinavir/r [35]. Another open-label study was performed to investigate the co-administration of elbasvir with ritonavir-boosted HIV protease inhibitors [36]. Elbasvir exposure was increased by 376 % with atazanavir/r, 66 % with darunavir/r and 271 % with lopinavir/r. Grazoprevir and elbasvir AUC are reduced by 84 and 54 %, respectively, when co-administered with efavirenz [37, 38]. Thus, boosted HIV protease inhibitors and efavirenz should not be given in combination with the grazoprevir/elbasvir combination.

Clinical Trial Data in HIV/HCV Co-infected Persons

Several phase II and III clinical trials have been conducted to assess the safety and efficacy of interferon-free DAA combinations for HCV in patients with HIV/HCV infection. This is in contrast to the first generation protease inhibitor trials, where phase III trials were significantly delayed in patients with HIV/HCV co-infection excluding this patient population from the initial regulatory approvals. Permitted HIV ARV regimens were guided by the available data from phase drug-drug interaction studies in healthy volunteers and phase II and III clinical trial data, and are listed in Table 1.

Ledipasvir/Sofosbuvir

The ION-4 phase III trial assessed the safety and efficacy of the combination of ledipasvir/sofosbuvir for 12 weeks in 335

Table 1 Antiretroviral regimens permitted in phase II and III trials of HCV direct-acting antivirals in HIV/HCV co-infection

HCV DAA trial	HIV antiretrovirals
ION-4[18] phase III	
Ledipasvir/sofosbuvir (90 mg/400 mg once daily FDC)	FTC/TDF/efavirenz (n=160) FTC/TDF/Raltegravir (n=146) FTC/TDF/Rilpivirine (n=29)
ALLY-2[39] phase III	
Daclatasvir+sofosbuvir (60 mg+400 mg once daily)	Patients were receiving 2 NRTIs with a protease inhibitor, NNRTI or integrase inhibitor Protease inhibitors: darunavir/r (n=51), atazanavir/r (n=36), lopinavir/r (n=12) NNRTIs: efavirenz (n=34), nevirapine (n=9), rilpivirine (n=7) Integrase inhibitors: raltegravir (n=40), dolutegravir (n=8) *dose of daclatasvir adjusted based on ARV: standard dose (60 mg) for all except increase dose to 90 mg for efavirenz or nevirapine regimens and decrease dose to 30 mg for atazanavir/ritonavir regimen
TURQUOISE-1[40] phase II	
Paritaprevir/ritonavir/ombitasvir Two FDC tablets once daily (75 mg/50 mg/12.5 mg per tablet)+dasabuvir (250 mg twice daily)	Patients received 2 NRTIs (from FTC, TDF and lamivudine) plus either atazanavir (without ritonavir, dosed in morning with the FDC tablet) [n=28] or raltegravir [n=35]
C-EDGE co-infection[41] phase III	
Grazoprevir/elbasvir (100 mg/50 mg once daily FDC)	Patients were receiving an NRTI backbone with raltegravir, dolutegravir or rilpivirine NRTI: abacavir containing (n=47) or tenofovir containing (n=164) NNRTI: rilpivirine (n=38) Integrase inhibitors: raltegravir (n=113) or dolutegravir (n=59)

FDC fixed-dose combination, *FTC* emtricitabine, *TDF* tenofovir, *r* ritonavir, *NRTI* nucleoside reverse transcriptase inhibitor, *NNRTI* non-nucleoside reverse transcriptase inhibitor

patients with HIV/HCV co-infection [18••]. Patients were receiving FTC/TDF/efavirenz (n=160), FTC/TDF/rilpivirine (n=29) or FTC/TDF/raltegravir (n=146). There was no HIV viral breakthrough observed on treatment, and population pharmacokinetic analysis demonstrated similar ledipasvir and sofosbuvir exposure across all three ARV regimens [18••]. Mean serum AUC for tenofovir was not different based on antiretroviral regimen and was not associated with change in serum creatinine from baseline [18••]. There were no treatment discontinuations related to adverse events. Renal monitoring was performed throughout, and four patients (1 %) were noted to have a rise in serum creatinine ≥0.4 mg/dl, and two patients required TDF dose reduction or discontinuation because of a rise in creatinine from baseline. Only one of these patients had evidence of tubular toxicity, which was evident at baseline [18••].

Daclatasvir+ Sofosbuvir

The ALLY-2 phase III trial assessed the safety and efficacy of daclatasvir and sofosbuvir for 12 weeks in 203 patients with HIV/HCV co-infection [39]. The majority of patients were receiving ARV therapy at baseline, and these regimens included ritonavir-boosted protease inhibitors (n=99), NNRTIs (n=50) and integrase inhibitors (n=48) (specific ARVs provided in Table 1). Patients on a boosted PI regimen received 30 mg of daclatasvir, and those on efavirenz or etravirine received 90 mg of daclatasvir. Treatment-naïve patients were randomised 2:1 to 12 or 8 weeks, whereas treatment-experienced patients were all treated for 12 weeks. Patients with cirrhosis were allowed in all arms. There was a higher relapse rate in patients treated for 8 weeks, and this group included significantly more patients on darunavir-based therapy than the 12-week groups, although no ARV regimen achieved SVR >90 % in the 8-week group. At the time, a comparable increased in daclatasvir exposure with darunavir/r and atazanavir/r was assumed, and the daclatasvir dosage was reduced in all patients on a boosted PI regimen in this trial to 30 mg daily. However, follow-up healthy volunteer studies confirmed that daclatasvir exposure is suboptimal when dose reduced with darunavir/r or lopinavir/r. Accordingly, dose modification is only recommended when atazanavir/r is co-administered with daclatasvir. The majority of adverse events were mild, and no serious adverse events were related to treatment. The majority of patients maintained HIV-virological suppression on treatment, with only two patients noted to have a HIV viral load >50 copies/ml at the end of treatment.

Paritaprevir/r/Ombitasvir+ Dasabuvir

The combination of paritaprevir/r, ombitasvir and dasabuvir (P/r/O+D) with weight-based ribavirin in HIV/HIV co-infection is currently being evaluated in a multicentre phase

II/III trial [40•]. An interim analysis of the pilot portion of the phase II trial has been reported (TURQUOISE-1 part 1a). Patients received P/r/O+D for 12 weeks (n=31) or 24 weeks (n=32). Patients were on stable atazanavir- or raltegravir-based regimens (n=28 and n=35, respectively) with two NNRTIs (from FTC, TDF, lamivudine). A rise in HIV viral load (HIV RNA ≥40 copies/ml) was observed in eight patients (13 %) during the treatment period. However, all these patients achieved HIV re-suppression without changing ARV therapy. Adverse events were common and largely mild, and there were no serious adverse events resulting in treatment discontinuation. Part 1b assessing safety and efficacy of dosing P/r/O+D with darunavir/r is ongoing and the phase III component is pending.

Grazoprevir/Elbasvir

The efficacy and safety of grazoprevir and elbasvir for 12 weeks in HIV/HCV co-infection was assessed in a phase III trial that included 218 patients [41•]. Permitted ARV regimens included abacavir- or tenofovir-based NRTI backbones with raltegravir, dolutegravir or rilpivirine. The most common side effects were fatigue, headache and nausea. There were no treatment discontinuations related to side effects. Two patients (<1 %) were noted to have transient HIV viraemia during the 12-week treatment course, although both patients achieved HIV re-suppression without requiring a change of ARV regimen. Boosted HIV protease inhibitor regimens and efavirenz-based regimens were not allowed due to previously reported drug interactions.

Discussion

The vast majority of drug-drug interaction studies are performed in healthy volunteers. This is the standard approach in assessing pharmacokinetic interactions in order to avoid potential harm to patients. Extrapolating these data to judge the clinical significance of interactions in patients with HIV/HCV infection and/or cirrhosis can be difficult, as both HCV infection and cirrhosis impair cytochrome P450 enzyme activity and alter drug disposition [42, 43]. For this reason, phase III trials in HIV/HCV co-infection, cirrhosis, decompensated liver disease, renal disease and transplant remain a critical need for all development programmes.

Interpreting the clinical significance of drug-drug interactions requires a clear understanding of the therapeutic window for each drug. Individual concentration-response relationships for HCV DAAs are not well established. Safety data on potentially significant DAA-ARV interactions in HIV/HCV-infected patients are also largely limited to the drug combinations permitted in phase II and III trials.

Interactions between HCV DAA and other co-medications also warrant special attention in HIV/HCV-infected patients. Ledipasvir absorption is pH dependent and may be reduced when co-administered with acid-suppressing agents or proton-pump inhibitors (PPI) [44]. It is recommended to separate antacids and ledipasvir/sofosbuvir administration by 4 h. PPI doses comparable to omeprazole 20 mg can be administered with ledipasvir/sofosbuvir, but they should not be taken before ledipasvir/sofosbuvir. P/r/O+D is expected to decrease concentrations of omeprazole, esomeprazole and lansoprazole, mediated by ritonavir [28]. Increased PPI dosage may be required if clinically indicated. All HCV DAA combinations have potential interactions with statins and lipid-lowering agents. Dexamethasone is contraindicated with daclatasvir, and the exposure of steroids that are CYP3A4 substrates (dexamethasone, fludrocortisone and fluticasone) may be significantly increased in ritonavir-containing regimens [25, 28]. There are no clinically significant interactions between methadone and daclatasvir, sofosbuvir, P/r/O+D or simeprevir [16, 25, 28, 29], and no interaction is expected with ledipasvir. There is also a potential for interactions between opiates that are primarily metabolised by CYP3A (such as oxycodone, tramadol and fentanyl) and HCV DAA regimens that include ritonavir or simeprevir, and additional monitoring may be required. Co-administration of amiodarone with sofosbuvir alone or in combination with daclatasvir, simeprevir or ledipasvir is contraindicated, due to the risk of life-threatening bradycardia, with one fatal case reported [45]. The mechanism for this interaction is not clear.

With the realisation of high SVR rates in all patient populations, the European Association for the Study of the Liver (EASL) recommendations and the American Association of the Study of Liver Diseases/Infectious Diseases Society of America (AASLD/IDSA) guidelines recommend that patients with HIV/HCV co-infection be treated the same as patients with HCV mono-infection, after recognition and management of drug-drug interactions between HCV DAAs and HIV antiretrovirals. Before instituting HCV therapy, a detailed drug history (including recreational and over the counter drugs) should be sought from the patient. Dedicated electronic resources such as the University of Liverpool drug interactions website (http://hep-druginteractions.org) and guideline documents provide useful interaction charts in assessing for potential interactions between a patient's antiretroviral regimen and any chosen HCV DAA combination.

Some interactions can be managed with dose modification of the HCV DAA (e.g. dose reduction of daclatasvir when given with atazanavir/r). If an antiretroviral regimen switch or alteration is required, this should be done in consultation with the patient's HIV practitioner. The goal of therapy should be to safely achieve a sustained virological response for HCV, while maintaining HIV suppression without compromising future antiretroviral therapeutic options. The AASLD/IDSA

guidelines and the EASL recommendations on the management of hepatitis C also include a guidance section on assessing and managing drug-drug interactions in practice [6••, 7••].

Conclusions

Hepatitis C infection remains a major source of co-morbidity in patients with HIV infection. The advances in therapy and the availability of all oral interferon-free HCV DAA therapy provides an opportunity to reverse the trend of increasing liver-related mortality in HIV-infected patients. HCV infection can be safely and successfully treated in HIV-infected patients provided drug-drug interactions are recognised and managed.

Compliance with Ethics Guidelines

Conflicts of Interest Omar El-Sherif has received conference travel and accommodation support from AbbVie, Janssen and MSD.

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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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