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Treatment of Chronic HCV Genotype 1 Coinfection

Christoph Boesecke[1] · **Jürgen K. Rockstroh**[1]

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Abstract Several all-oral direct-acting antiviral (DAA) combination therapies including two fixed-dose combinations (FDCs) have been recently licensed for treatment of hepatitis C virus (HCV) genotype 1 infection. Results of pivotal trials with these new compounds are now also available in human immunodeficiency virus (HIV)/HCV-coinfected patients, highlighting that, in the DAA era, differences no longer do exist in efficacy between HCV-monoinfected and HIV/HCV-coinfected patients. This review will give an overview of the key DAA-containing studies in HIV/HCV genotype 1 coinfection and give guidance on how and when these should be used in clinical practice. Simplified DAA-based and potentially interferon-free HCV therapy regimens are characterized by smaller pill burden, better tolerability, shorter treatment durations, and higher cure rates. With first pilot studies in HCV treatment-naive and treatment-experienced persons with HCV/HIV coinfection demonstrating sustained virological response rates above 95 %, interferon (IFN)-free DAA combinations should be considered the new standard of care for chronic HCV. Per both European and US treatment guidelines, HCV treatment indications and DAA drug selection in HIV-coinfected patients are no longer different from HCV-monoinfected patients as cure rates in HCV-monoinfected and HCV-coinfected patients are superimposable. Drug-drug interactions with the new DAAs and concomitant antiretroviral therapy, however, have to be checked carefully prior to selecting DAAs due to commonly shared metabolization pathways. In countries with access to the new DAAs, interferon-free DAA combination therapy for HCV genotype 1 infection is strongly recommended. Agents should be selected based upon HCV genotype and according to current guidelines. Potential drug-drug interactions between HIV antiretrovirals and HCV therapy need to be checked, and if necessary, combination antiretroviral therapy (cART) has to be adapted to the respective HCV therapy.

Key Points

- *HCV treatment in HIV-coinfected patients is the same as in HCV-monoinfected patients as response rates under DAA in the setting of HIV coinfection have been as good as in HCV-monoinfected patients.*
- *IFN-free DAA combinations should be considered standard of care for chronic HCV genotype 1 coinfection.*
- *Drug-drug interactions with the new DAAs and concomitant antiretroviral therapy have to be accounted for due to shared metabolic pathways via the cytochrome p450 system and drug transporters.*
- *Major limitations in treatment uptake are access to DAA which is increasingly driven by the cost of the medications.*

Keywords Chronic hepatitis C · HCV · Genotype 1 · Interferon-free · HIV

Introduction

Of all patient populations worldwide, it is the human immunodeficiency virus (HIV)-infected patient population which has been fortunate to benefit from two revolutionary treatment discoveries within just two decades. The first being the

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✉ Jürgen K. Rockstroh
juergen.rockstroh@ukb.uni-bonn.de

[1] Department of Medicine I, Bonn University Hospital, Sigmund-Freud-Str. 25, 53127 Bonn, Germany

introduction of highly active antiretroviral therapy (HAART) in 1996, combining three individual antiretroviral drugs which significantly reduced mortality and morbidity among HIV-infected persons worldwide and the second being the licensing of hepatitis C virus (HCV) direct-acting antivirals (DAAs) in 2011, again with the potential to significantly alter not only liver-related diseases but also overall mortality and morbidity in HIV/HCV-coinfected persons worldwide. For coinfected patients in countries with access to the new DAAs, HCV treatment recommendations have changed dramatically. Several DAA regimens, including two fixed-dose combinations (FDCs), have been licensed so far, all of which can be used in HCV genotype 1 infection. These simplified DAA-based and interferon-free HCV therapy regimens are characterized by a smaller pill burden, better tolerability, shorter treatment duration, and high efficacy with sustained virologic response (SVR) rates ≥95 % [1•]. With these dramatic improvements, all-oral DAA combination therapies have now become the new gold standard of HCV therapy regardless of HIV status. However, as treatment with the new DAAs is expensive, access to these drugs is not guaranteed for all in most health-care systems. As a consequence, interferon-containing regimens may still play a role in the treatment of HCV genotype 1 coinfection. Fortunately, HCV treatment in HIV-coinfected patients is no longer different from HCV-monoinfected patients which streamlines the approach to care and lowers historical barriers to access for this high-risk population [2••, 3••, 4••]. Only drug-drug interactions with the new DAAs and concomitant antiretroviral therapy have to be accounted for due to shared metabolization pathways [3••].

This review will give an overview of the key DAA-containing studies in HIV/HCV genotype 1 coinfection and give guidance on how and when these should be used in clinical practice.

Interferon-Containing DAA Regimens

Telaprevir or Boceprevir Plus Peginterferon/Ribavirin

Already first studies using the first-generation HCV protease inhibitors (PIs) boceprevir or telaprevir in HCV/HIV genotype 1-coinfected individuals have clearly demonstrated substantial higher HCV treatment cure rates under triple therapy compared to just pegylated interferon/ribavirin (PR) combination therapy alone allowing for cure of hepatitis C in about two thirds of treated patients [5, 6]. The first-generation HCV protease inhibitors, boceprevir and telaprevir in combination with pegylated interferon and ribavirin (pegIFN/RBV), were approved in 2011 for the treatment of HCV genotype 1 infection. There was significant delay in phase 3 trials in HIV/HCV-coinfected patients resulting in the exclusion of HIV from the approvals and limitations to access for this population in many parts of the world. Due to significant side effects and regimen complexity related to this first generation of regimens, they were quickly surpassed by less complex regimens. Therefore, we will review only agents currently recommended by the European Association for the Study of the Liver (EASL) and/or US treatment guidelines (see Table 2) [2••].

Simeprevir Plus Peginterferon/Ribavirin

Simeprevir (SIM), a second wave protease inhibitor, came along with significant advantages: it is administered once daily, has a more favorable adverse event profile, and has considerable in vitro genotype 4 activity. Similar to most other single DAA regimens, simeprevir required the addition of pegIFN/RBV to decrease the risk of treatment-emergent resistance. Simeprevir triple therapy was evaluated in HIV/HCV-coinfected patients in the C212 study [7]. Interestingly, a response-guided therapy design was used which allowed for the shortening of the treatment of 12 weeks of SIM with 48 weeks of pegIFN/RBV to only 12 weeks of SIM with 24 weeks of pegIFN/RBV in patients with HCV RNA <25 IU/mL at week 4 and undetectable HCV RNA at week 12. Overall, 106 treatment-naive and treatment-experienced genotype 1 patients received simeprevir (150 mg daily) plus pegIFN/RBV, resulting in highly sustained virologic response at week 12 (SVR12) rates, in particular for treatment-naive patients (79 %) and prior pegIFN/RBV relapsers (87 %) [7]. In previous null responders, however, overall lower cure rates of 57 % were observed, emphasizing that more difficult-to-treat patients may require more potent strategies. As simeprevir has a high potential for drug-drug interactions, only the following antiretroviral therapy (ART) agents were allowed in the study: abacavir, lamivudine, emtricitabine, tenofovir, rilpivirine, enfuvirtide, raltegravir, and maraviroc. The safety profile was similar to that observed in HCV-monoinfected patients. Hyperbilirubinemia—a known side effect of simeprevir—occurred in five cases (in two cases of grade 3 elevation). Overall, only four patients discontinued simeprevir due to adverse events. Due to the rapid movement of the HCV therapeutic field, this regimen is no longer recommended by the US HCV treatment guidelines. However, this regimen is still an option for genotype 1-infected patients in the EASL guidelines for patients who can tolerate interferon. If SMP is used with pegIFN/RBV, resistance testing prior to HCV treatment initiation is recommended to rule out the presence of a Q80K mutation which is associated which lower SVR rates.

Sofosbuvir Plus Peginterferon/Ribavirin

Similar to the NEUTRINO study in HCV monoinfection, a combination of the oral HCV NS5B inhibitor sofosbuvir (SOF) plus pegIFN/RBV was examined in a small study of

12 weeks of treatment in 23 HIV-infected patients with genotype 1 (n=19), 2 (n=1), 3 (n=2), and 4 (n=1) coinfection [8]. The majority of patients were male (78 %) and had high CD4 cell counts (mean 563 cells/mm^3). Similar to the findings in HIV-uninfected patients, the overall SVR rate was 91 % and, in patients with genotype 1 infection, the SVR rate was 89 %. Two patients stopped HCV treatment due to adverse events (anemia and altered mood); no serious adverse events were reported. Similarly, although no longer recommended by the US HCV treatment guidelines, this regimen is recommended as an option for the treatment of genotype 1 infection in the EASL guidelines in patients who can tolerate interferon. This regimen does remain in the US guidelines as the first-line treatment for genotype 3 infection and as an option for treatment and retreatment of genotype 4–6 infection. It has negligible risk of resistance and has limited drug interaction risk with antiretrovirals.

Interferon-Free DAA Regimens

The ultimate goal in treatment of hepatitis C is to use interferon-free DAA regimens which result in cure in the majority of patients with limited toxicity and shortened treatment durations (see Table 1). Although interferon-free regimens have largely been realized, ribavirin-free DAA combinations, while available, are less universal. The use of ribavirin remains especially challenging in patients with cirrhosis and concomitant renal disease and adds both side effects and the need for monitoring to any regimen.

Sofosbuvir Plus Ribavirin

The PHOTON-1 and PHOTON-2 phase 3 trials studied the combination of sofosbuvir and ribavirin of 12- or 24-week duration in treatment-naive (genotypes 1–4) and treatment-experienced (genotypes 2 and 3) patients [9]. Broad inclusion criteria were applied within the trial, permitting the inclusion of patients with compensated cirrhosis, including those with significant portal hypertension. A wide range of antiretrovirals was allowed including the non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz and rilpivirine as well as the boosted HIV protease inhibitors atazanavir/ritonavir and darunavir/ritonavir. Baseline CD4 count had to be >200 cells/μL in ART-treated patients and >500 cells/μL in ART-untreated patients. Treatment duration for genotype 1 treatment-naive patients was 24 weeks. Overall SVR rate in genotype 1 treatment-naive patients was 81 % (182/226), and relapse occurred in 17 % (19/226); there was viral breakthrough in only one patient. The relatively high relapse rate and availability of interferon-free DAA combinations resulted in limited use of this regimen in genotype 1 patients (Table 2). In addition, subanalysis showed that SVR rate was lower for genotype 1 in the presence of cirrhosis [64 % (14/22) vs. 82 % (168/204) without cirrhosis], again suggesting that more potent strategies are needed for these more challenging patients. Safety in this large trial overall was excellent with only 8 % of patients developing a grade 3 or 4 adverse event (AE) and only 2.5 % had an adverse event resulting in early SOF discontinuation. This regimen performed well in patients with genotype 2, 3, and 4 infection and remains a recommended or alternative regimen for these genotypes.

Table 1 Current recommended interferon-free DAA treatment options for HCV genotype 1 (modified from [3••])

HCV GT	Treatment	Treatment duration
1	SIM+SOF	12 weeks without cirrhosis, 24 weeks with compensated cirrhotics with consideration of adding RBV
	LDV/SOF	12 weeks in non-cirrhotics[a], 24 weeks in P/R or PI+P/R treatment-experienced compensated cirrhotics[b] or in decompensated cirrhosis where RBV is contraindicated
	LDV/SOF+RBV	12 weeks in treatment-experienced compensated cirrhotics or in decompensated cirrhosis (recommended starting dose in this case is 600 mg with titration as tolerated)
	DCV+SOF	12 weeks without cirrhosis, 24 weeks with compensated cirrhosis
	OBV/PTV/r+DSV	12 weeks in subtype 1b without cirrhosis
	OBV/PTV/r+DSV+RBV	12 weeks in subtype 1b with compensated cirrhosis and subtype 1a without cirrhosis, 24 weeks in subtype 1a with compensated cirrhosis

RBV ribavirin, *SOF* sofosbuvir, *SIM* simeprevir, *DCV* daclatasvir, *LDV* ledipasvir, *OBV* ombitasvir, *PTV/r* paritaprevir/ritonavir, *DSV* dasabuvir

[a] Possible shortening to 8 weeks in GT 1 treatment-naive patients and possible extension to 24 weeks in treatment-experienced patients with uncertain options for retreatment

[b] Possible shortening to 12 weeks in slow progressors with options for retreatment

Table 2 Completed interferon-free DAA trials for HCV genotype 1 coinfection

Study acronym	DAA	RBV	Treatment duration (weeks)	Genotypes studied	Total study population (*n*)	Cirrhotic GT1 pts, *n* (%)	Overall SVR (%)	SVR GT1 TN (%)	SVR GT1 cirrhotics only (%)	Ref
PHOTON-1+PHOTON-2	Sofosbuvir	Yes	24	1–4	497	22 (10)	83	81	64	[9]
ALLY-2	Sofosbuvir+daclatasvir	No	8/12	1–4	203	24 (14)	76/97	96 (12-week am)	60/92	[13]
ION-4	Sofosbuvir/ledipasvir	No	12	1.4	335	65 (20)	96	95	94	[16]
TURQUOISE-I	Paritaprevir/r/ ombitasvir+dasabuvir	Yes	12/24	1	63	12 (19)	94/91	Not reported	Not reported	[17]
C-WORTHY	Grazoprevir+elbasvir	No/yes	12	1	59	0	87/97	87/97	n/a	[21]
C-EDGE	Grazoprevir/elbasvir	No	12	1, 4, 6	218	35 (16)	95	95	100	[22]

Sofosbuvir Plus Simeprevir

The safety and efficacy of the combination DAA regimen of simeprevir (150 mg) and sofosbuvir (400 mg) is supported by the OPTIMIST-1 and OPTIMIST-2 studies in HCV-monoinfected patients [10, 11]. The phase 3, randomized, open-label study OPTIMIST-1 study evaluated the efficacy and safety of 12- and 8-week treatment of simeprevir (SMV)+SOF, in treatment-naive or treatment-experienced HCV genotype 1 (GT1)-infected patients without cirrhosis. SMV+SOF for 12 weeks was superior to historic control (overall SVR 97 and 95 %, respectively), whereas SMV+SOF for 8 weeks did not achieve superiority versus historic control in treatment-naive and treatment-experienced HCV GT1-infected patients without cirrhosis (overall SVR 85 and 77 %, respectively). Clearly, these results help to strengthen the data for this DAA combination and also propose 12 weeks as the in general optimal treatment duration. In addition, as seen from other data sets, the presence of the Q80K mutation at baseline seems to lose its impact in DAA combination therapy. The OPTIMIST-2 study aimed to demonstrate superiority of 12 weeks of SMV+SOF in treatment-naive or treatment-experienced (including interferon-intolerant) HCV GT1-infected patients with cirrhosis compared with a historical control. SMV+SOF for 12 weeks achieved superiority in SVR12 rates versus the historical control (overall SVR 88 and 79 %, respectively). In comparison to the treatment-naive and treatment-experienced patients without cirrhosis, however, lower cure rates were observed which were as low as 74 % in cirrhotics with GT1a infection with baseline Q80K mutation.

Data on the use of the sofosbuvir and simeprevir-containing regimen for HIV-infected patients with chronic HCV genotype 1 coinfection have so far only been generated in cohort settings. The largest cohort to date came from interim results from an ongoing German multicenter cohort. Of 395 patients enrolled, 288 were HCV monoinfected and 107 HCV/HIV coinfected [12•]. Genotype 1 was detected in 64 % (254/395). Liver cirrhosis was present in 38 % (152/395) of the patients. Fifty percent of the patients had previously failed interferon-based therapy. Overall SVR rates for the 3 treatment regimens analyzed (SOF/PR, SIM/SOF, SOF/daclatasvir (DCV)) ranged from 86 to 91 %; to date, no SVR rates per genotype exist. Lower SVR12 rates (15 % less) were seen in patients with cirrhosis. Premature discontinuation or lost to follow-up was observed in <5 % of patients counted as treatment failure, whereas relapse occurred in 5 %.

Sofosbuvir+Daclatasvir

ALLY-2 is the phase 3 study of sofosbuvir+the oral NS5A inhibitor DCV in patients with HIV/HCV coinfection [13]. This randomized, open-label study enrolled HCV treatment-

naive (N=151) or treatment-experienced (N=52) adults coinfected with HIV and HCV. The distribution of genotype included 83 % genotype 1, 9 % genotype 2, 6 % genotype 3, and 2 % genotype 4 infection. Naive patients were randomly assigned (2:1), with stratification by cirrhosis status and HCV genotype, to receive 12 or 8 weeks of once-daily SOF 400 mg+DCV 60 mg (dose adjusted for concomitant antiretrovirals, 30 mg with ritonavir-boosted PIs, 90 mg with NNRTIs except rilpivirine). The study allowed a large variety of antiretroviral therapies (ARVs) with 49, 25, and 25 % patients, respectively, received PI-based, NNRTI-based, or other (primarily INI-based) combination antiretroviral therapy (cART); 4 patients were not on cART. Overall, 199/203 (98 %) patients completed therapy; 1 patient discontinued early for incarceration. Overall, SVR12 was achieved by 96 and 98 % of naive and experienced genotype 1 patients, respectively, after 12 weeks of therapy, but only 76 % of naive genotype 1 patients after 8 weeks. Among the patients treated for 12 weeks, SVR12 rates were similar regardless of prior treatment experience, HCV genotype or genotype 1 subtype, cirrhosis status, concurrent cART regimen, or race. There were no virologic breakthroughs; 2/153 patients (1 %) in the 12-week group and 10/50 (20 %) in the 8-week group had post-treatment relapse. The observed higher relapse rate in the 8-week arm raises the question whether 8 weeks are too short. One difficulty in analyzing the data is that over 40 % of the patients from the 8-week arm were on concomitant darunavir/r-containing ART and therefore only dosed with 30 mg of daclatasvir, which is no longer the recommended adjustment and may have resulted in lower daclatasvir exposures, increasing the risk of relapse. Healthy volunteer drug-drug interaction studies with atazanavir/r reported significantly increased daclatasvir levels resulting in the recommendation to reduce the dose of daclatasvir from 60 to 30 mg daily. However, more recent data reported that daclatasvir had fewer interactions with boosted darunavir or lopinavir so dose reduction is not recommended (see Table 3) [14]. Regardless, no ARV regimen achieved an SVR >90 % with 8 weeks of therapy, suggesting that this is a suboptimal length of treatment and increases the risk of relapse. There were no treatment-related adverse events leading to treatment discontinuation. It should be noted that few patients with cirrhosis were included in this study, thus limiting the ability to draw conclusions on efficacy in this more difficult-to-treat subgroup. Compassionate use programs have reported higher SVR with 24 weeks of daclatasvir and sofosbuvir in patients with cirrhosis, suggesting that there is at least a subpopulation who will benefit from extension of therapy [15]. The European HCV treatment guidelines currently recommend 24 weeks of this regimen for patients with genotype 1, 3, or 4 infection with cirrhosis, while only 12 weeks is recommended for genotype 3-infected patients without cirrhosis.

Ledipasvir/Sofosbuvir

The first available HCV DAA FDC consisting of sofosbuvir and the oral NS5A inhibitor ledipasvir was examined in the ION-4 study. ION-4 was a phase 3, multicenter, open-label study conducted in the USA, Canada, and New Zealand and included genotype 1 or 4 patients who were either HCV treatment naive or treatment experienced [16•]. Twenty percent of patients were allowed to have compensated liver cirrhosis upon inclusion. HIV patients had to be well controlled for HIV with an HIV-RNA <50 copies/mL and a CD4 cell count above 100 cells/mm^3. Patients could either be on rilpivirine, efavirenz, or raltegravir in combination with tenofovir (TDF)/FTC. No boosted HIV PIs were allowed into the study as PK interaction studies had not been completed upon initiation of the trial. Three hundred thirty-five patients with genotype 1a (75 %), genotype 1b (23 %), and genotype 4 (2 %) were enrolled, 82 % were male, 61 % were white, mean age was 52 (range 26–72), mean baseline HCV RNA was 6.7 log10 IU/mL (range 4.1–7.8), 20 % had cirrhosis, 24 % had IL28B CC genotype, and 55 % had not responded to prior HCV treatment. Patients were taking efavirenz (48 %) or raltegravir (44 %) or rilpivirine (9 %). The overall SVR12 rate was 96 % (321/335) after 12 weeks of SOF/ledipasvir (LDV); no difference was seen in patients with cirrhosis (N=67) or treatment failure (N=185) underlying the robustness of this regimen. Although 98 % (46/47) of treatment-experienced patients with cirrhosis achieved SVR12 in this study, this is not the recommended regimen for this difficult-to-treat subgroup. Extending treatment to 24 weeks or using 12 weeks with the addition of weight-based ribavirin is recommended to decrease the risk of relapse. Only 2 patients had on-treatment virologic failure most likely due to non-compliance, and 10 had virologic relapse after discontinuing treatment. In a multivariate analysis, black race emerged as the only predictive factor associated with a lower SVR rate. So far, no clear reason for this difference can be provided. Adherence and/or drug levels were not different between black patients and other study participants. Also, no racial impact was found in any of the other ION studies. Therefore, pharmacogenomic investigations are being planned to further explore this finding. No patient discontinued therapy because of adverse events. Although there were few patients with genotype 4 infection in this study, several studies of this regimen in genotype 4 infection support its use as a recommended regimen for this genotype.

As ledipasvir may increase tenofovir exposure (potentially because of persistent inhibition of efflux drug transporters), careful renal monitoring was carried out during the trial. Indeed, 4 patients (1 %) within the trial had changes in creatinine ≥0.4 mg/dL of whom 2 completed treatment with no ART change, 1 had a dose reduction of TDF, and 1 was switched off of TDF. Even more increases in tenofovir levels can be

Table 3 Potential drug-drug interactions between DAA and ART (modified from [3••])

Drug-drug Interactions between ARVs and DAAs

	HCV drugs	ATV/r	DRV/c	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c	RAL	ABC	FTC	3TC	TDF	ZDV
DAAs	boceprevir	D35%	↓D	↓32%D44%	↓45%D34%	↓19%E20%	↑10%D23%	↓E	↓6%E39%	E	↔	↓D	↔	↔	↔	↔	↔	↔[i]
	daclatasvir	↑110%[ii]	↑	↑40%	↑15%	↓32%[iii]	↓	↓	↔	↔	↔	↑[ii]	↔	↔	↔	↔	↑10%E10%	↔
	ombitasvir/paritaprevir/r/dasabuvir	↑[iv]	↑	D[v]	↑	[vii]	↓E?	↓E?	E[viii]	E	E	↑	E134%	↔	↔	↔	↔	↔
	ombitasvir/paritaprevir/r	↑[iv]	↑	↑[vi]	↑	[vii]	↓E?	↓E?	E[viii]	E	↔	↑	E20%	↔	↔	↔	↔	↔
	simeprevir	↑	↑	↑	↑	↓71%	↓	↓	↑6%E12%	↔	↔	↑	↓11%E8%	↔	↔	↔	↓14%E18%	↔
	sofosbuvir/ledipasvir	↑8/113%[ix]	↑E[ix]	↑34/39%[ix]	↔[ix]	↓-/34%	↔	↔	↔	E?	↔	↑36/78%E[ix]	D=20%	↔	↔	↔	E[ix]	↔
	sofosbuvir	↔	↑	↑34%	↔	↓6%D4%	↔	↔	↑9%E6%	↔	↔	↔	↓5%D27%	↔	↓6%	↔	↓6%	↔
	telaprevir	↓20%E17%	↓D	↓35%D40%	↓54%	↓26%D7%	↓16%	↓?	↓5%E	E	E25%	↑13%D16%	E31%	↔	↔	↔	E30%[ix]	↔[i]

Legend:

↑ = potential elevated exposure of DAA; ↓ = potential decreased exposure of DAA; ↔= no significant effect

E = potential elevated exposure of ARV; D = potential decreased exposure of ARV

Numbers refer to decreased/increased AUC of DAAs and ARVs as observed in drug interactions studies. Sofosbuvir/ledipasvir: first/second numbers refer to changes AUC sofosbuvir/ledipasvir.

DRV/c = darunavir coformulated with cobicistat (800/150 mg QD)

i = potential hematological toxicity; ii = daclatasvir should be reduced to 30 mg once daily with ATV/r or EVG/c. No dose reduction with unboosted ATV; iii = daclatasvir should be increased to 90 mg once daily; iv = use only with unboosted ATV and in patients without significant HIV PI mutations (ATV increased paritaprevir exposure due to CYP3A4 and OATP1B1/3 inhibition, not recommended without dasabuvir); v = coadministration is not recommended due to decreased darunavir Ctrough by 50% when DRV administered 800 mg or 600 mg BID (second dose given with additional RTV) ; vi = increase in paritepravir exposure when coadministered with DRV 800 mg given with Viekirax; vii = severe tolerability issues; viii = frequent ECG monitoring for QT prolongation;

ix = TDF containing regimens with either ritonavir or cobicistat are not recommended but if no other option then close monitoring of kidney function due to increase of tenofovir

Color legend:

no clinically significant interaction expected.

these drugs should not be coadministered.

potential interaction which may require a dosage adjustment or close monitoring.

Note: the symbol (green, amber, red) used to rank the clinical significance of the drug interaction is based on **www.hep-druginteractions.org.**

expected when ledipasvir/sofosbuvir is co-administered with boosted HIV protease inhibitors as they themselves can further increase TDF exposure (see Table 3). This is important to keep in mind when selecting HIV therapy and planning ledipasvir/sofosbuvir FDC therapy.

Paritaprevir/r/Ombitasvir Plus Dasabuvir

The first interferon-free DAA regimen containing three different DAAs was examined in the TURQUOISE-I study, a phase 2, randomized, open-label study evaluating the combination of paritaprevir (NS3 protease inhibitor) with ritonavir-boosting, ombitasvir (NS5A inhibitor), and dasabuvir (non-nucleoside NS5B polymerase inhibitor)+RBV regimen for 12 or 24 weeks [17•]. HCV treatment-naive or pegIFN/RBV-experienced patients, with or without Child-Pugh class A cirrhosis, CD4+ count ≥200 cells/mm^3 or CD4+ % ≥14 %, and plasma HIV-1 RNA suppressed on a stable atazanavir- or raltegravir-inclusive ART regimen, were included. Twelve out 63 patients had cirrhosis at baseline, and 21/63 were treatment experienced. Overall SVR rates were 93 %, and showed no difference between 12 and 24 weeks of therapy, although this small phase 2 trial is not powered to determine if there is a subgroup of patients that would benefit from the longer course of therapy. Relapse rates were low in this trial (1.6 %), but there were two HCV reinfections occurring after successful end of treatment (EOT) highlighting that reinfection with HCV can occur at any time if risk behavior leading to HCV transmission is not addressed. Adverse events were generally mild, and no serious adverse events or discontinuations due to an adverse event were reported. The most common adverse events were fatigue, insomnia, and nausea. Elevation in total bilirubin was the most common laboratory abnormality, occurring predominantly in pts receiving atazanavir/r. Of clinical importance is the ritonavir-boosted paritaprevir as this limits co-administration with certain HIV PIs (see Table 3). The phase 3 TURQUOISE-I trial will address many of the remaining questions regarding approach to therapy for HIV/HCV patients, although it is not expected to differ from that seen in the phase 3 trials in HCV monoinfection. Drug interactions exclude the use of all NNRTI and some boosted HIV protease inhibitors.

Difficult-to-Treat Patient Populations and Future Treatment Challenges

Although SVR rates across DAA regimens on average are above 95 %, special difficult-to-treat patient populations can be identified which remain more challenging. So far, little data is available from randomized trials on treatment in decompensated cirrhotics but some trials have been completed recently in HCV-monoinfected patients. In a phase 2, open-label study, the treatment with the NS5A inhibitor ledipasvir, the nucleotide polymerase inhibitor sofosbuvir, and ribavirin in patients infected with HCV genotypes 1 or 4 and advanced cirrhosis was assessed [18]. Cohort A enrolled patients with cirrhosis and moderate or severe hepatic impairment who had not undergone liver transplantation. Cohort B enrolled patients who had undergone liver transplantation: those without cirrhosis; those with cirrhosis and mild, moderate, or severe hepatic impairment; and those with fibrosing cholestatic hepatitis. Patients were randomly assigned (1:1) to receive 12 or 24 weeks of a fixed-dose combination tablet containing ledipasvir and sofosbuvir, once daily, plus ribavirin. In cohort A (non-transplant), SVR12 was achieved by 86 % of GT1 patients. In cohort B (transplant recipients), SVR12 was achieved by 96–98 % of patients without cirrhosis or with compensated cirrhosis, by 85–88 % of patients with moderate hepatic impairment, by 60–75 % of patients with severe hepatic

impairment, and by all 6 patients with fibrosing cholestatic hepatitis. Response rates in the 12- and 24-week groups were similar. Thirteen patients (4 %) discontinued the ledipasvir and sofosbuvir combination prematurely because of adverse events; 10 patients died, mainly from complications related to hepatic decompensation. These results clearly underline that HCV therapy appears feasible even in more advanced liver cirrhosis. It is important to highlight though that although the Model For End-Stage Liver Disease (MELD) score improved in the majority of patients in some individuals, worsening of the MELD score was observed and also 10 patients died, indicating that treatment may have had no benefit or simply came too late in a subset of patients. Clearly, no predictive factors exist to help to decide who to treat or not. It has also been discussed whether improvements in MELD score for patients on the transplant list may delay organ allocation and increase the risk for HCC development while being on the transplant waiting list. Although no controlled trial data is available for HIV/HCV-coinfected subjects with decompensated cirrhosis, some first findings from observational cohorts have been reported. Within the Mount Sinai cohort, 544 HCV-monoinfected patients on sofosbuvir and/or simeprevir were evaluated with regard to hepatic decompensation or serious adverse events (SAEs) in a real-life setting [19]. For data analysis, the study group was divided into patients who had not undergone liver transplantation (LT) (cohort 1, which included 499 patients) and patients who had already undergone LT (cohort 2, which included 45 patients). In cohort 1, 4.5 % of patients experienced liver decompensation or an SAE during treatment or within 1 month after EOT. Three cases died unexpectedly with no underlying conditions considered to be life-threatening. One patient had Child-Pugh class B who was prescribed with SOF/SMV. The overall mortality was 0.6 %. Of the 13 surviving patients, 4 relapsed after EOT, 1 was viral load undetectable at EOT, 2 were viral load detectable at the time of treatment discontinuation, and 6 achieved SVR 12. Liver decompensation or an SAE led to treatment discontinuation in 1.4 % (7/499). Risk factors for decompensation/SAE included low baseline albumin and high total bilirubin, but not fibrosis stage which may have been related to the overall high percentage of patients with more advanced liver disease or cirrhosis. Low hepatic reserve may have increased decompensation risk in the non-LT patients. In cohort 2, 28 % of patients experienced liver decompensation or an SAE during treatment or within 1 month after EOT. Liver decompensation or an SAE led to treatment discontinuation in 4.4 % (2/45) of patients. Low baseline hemoglobin was identified as a risk factor for hepatic decompensation/SAE. The underlying mechanisms leading to life-threatening adverse events or decompensation from SOF- and/or SMV-containing regimens need to be investigated further particularly in coinfection. Based on past and current data, SMV should not be used in Child-Pugh class B and C patients. Under consideration of the increased complication rate, management of HCV patients with decompensated cirrhosis should only take place in experienced centers with preferably access to liver transplantation services.

One additional future challenge for some DAAs could be the presence of baseline resistance-associated variants (RAVs) as well as the emergence of NS3 and NS5A resistance in patients who develop virological failure under all-oral DAA therapies. A more detailed discussion on resistance-related issues is beyond the scope of this review. However, it is important that whereas some baseline PI mutations such as the Q80K appears to impact SVR rates in GT1 patients in simeprevir- and interferon-containing regimens, this seems to be overcome by combination DAA therapy (please see "Simeprevir Plus Peginterferon/Ribavirin" section on simeprevir therapy above). Patients who fail on a HCV-PI tend to develop PI mutations which, however, tend to disappear or better are no longer detectable by population sequencing 1–2 years after virological failures. Retreatment of HIV/HCV-coinfected patients with prior PI resistance from HCV-PI/interferon/ribavirin therapy with sofosbuvir/simeprevir (after a median of 29 months since PI-based therapy) appeared to be successful with all patients except one achieving SVR12 [20]. Baseline NS5A resistance-associated variant mutations so far have not appeared to have a major impact on treatment outcome. Data from the treatment-naive trials with grazoprevir and elbasvir, however, have shown that presence of RAVS with >5-fold reduction in susceptibility to elbasvir which can only be found in a small number of patients (<5 %) have significantly reduced SVR rates in genotype 1a but not genotype 1b patients [21, 22]. Addition of ribavirin seems to overcome this issue and to increase SVR rates in this particular subset of patients. Interestingly, in a recent large subanalysis of cirrhotic genotype 1 patients receiving ledipasvir/sofosbuvir, numerically, SVR rates were slightly higher in patients without baseline RAVs [23]. Again, the addition of ribavirin and extension of treatment duration to 24 weeks led to HCV cure in all patients regardless of baseline RAVs. Retreatment of patients who failed on 8–12 weeks of ledipasvir/sofosbuvir with the same regimen for 24 weeks showed dramatically decreased SVR rates in the presence of the Y93H/N mutation (SVR12 33 %) and to a lesser extent for the L31M mutation (SVR12 80 %) [24]. Also, studies have demonstrated that NS5A mutations appear to persist after virological failure, making it very likely that they will continue to impact HCV retreatment with all-oral DAA therapies including NS5A inhibitors [25]. Therefore, at least in the setting of patients failing an all-oral DAA combination therapy, genotypic HCV resistance testing should be performed to guide possible subsequent treatment decisions.

Future DAA Regimens

The licensing of the first nucleot(s)ide interferon-free DAA regimen containing an NS3 PI and an NS5A inhibitor can be expected within the next 12 months. Very promising data from the phase 2 C-WORTHY trial and the phase 3 C-EDGE study confirms that this will be a useful regimen in HIV/HCV coinfection [21, 26]. The C-WORTHY study was a phase 2, multicenter, randomized controlled trial of grazoprevir (NS3 protease inhibitor) plus elbasvir (NS5A inhibitor) with or without ribavirin [21]. Of note, this was the first DAA study to include both HCV genotype 1-monoinfected or HCV genotype 1-coinfected patients in the same trial. Eligible patients were treatment-naive and non-cirrhotic. Fifty-nine coinfected patients were enrolled in part B of the study and randomized to grazoprevir (100 mg) plus elbasvir (50 mg) qd with or without ribavirin for 12 weeks. The only allowable ARV was raltegravir+ two NRTI analogues for at least 8 weeks prior to enrollment. CD4 cell count was required to be >300 cells/mm^3, and HIV-RNA was undetectable for 24 weeks. SVR12 rates in coinfected patients treated for 12 weeks were 87 % without ribavirin (95 % confidence interval (CI) 69–96; 26/30) and 97 % with ribavirin (95 % CI 82–100; 28/29). SVR rates in monoinfected patients treated for 12 weeks were 98 % without ribavirin (95 % CI 88–100; 43/44) and 93 % with ribavirin (95 % CI 85–97; 79/85). The safety profile of grazoprevir plus elbasvir with or without ribavirin was similar in monoinfected and coinfected patients. No patient discontinued due to an AE or laboratory abnormality. The most common AEs were fatigue, headache, nausea, insomnia, and asthenia. Coinfected pts maintained HIV suppression during therapy except for one who discontinued HIV medications.

In C-EDGE, an open-label, single-arm, multicenter study across Europe, the USA, and Australia, 218 treatment-naive patients with HCV genotype 1, 4, or 6 infection with or without cirrhosis were treated with the single daily pill for 12 weeks, fixed-dose combination of grazoprevir 100 mg/elbasvir 50 mg qd [26]. Allowable ARVs included tenofovir or abacavir and either emtricitabine or lamivudine plus raltegravir, dolutegravir, or rilpivirine, and other ARVs were excluded due to drug interactions. Eighty-seven percent (189/218) of patients were infected with genotype 1, 17 % were black, 16 % had cirrhosis, and 97 % received allowable ARVs. Overall, the SVR rate in genotype 1 was 95 %; relapse occurred in 5 patients (all non-cirrhotics), reinfection in 1, and discontinuation in 4 patients (none related to virological failure or adverse event). The high SVR rate as well as the good tolerability make this FDC an additional highly effective treatment option for patients with HCV/HIV coinfection.

When and How to Treat

Both European and US guidelines emphasize that all treatment-naive and treatment-experienced patients with compensated or decompensated chronic liver disease due to HCV should be considered for therapy and that treatment should be prioritized for patients with HIV coinfection regardless of the fibrosis stage or HCV genotype [2••, 3••, 4••]. Treatment should also be considered regardless of the fibrosis stage for individuals at risk of transmitting HCV, including active injection drug users and men who have sex with men (MSM) with high-risk sexual practices. We would recommend reading the companion article on acute HCV in MSM by [27]

Selection of DAA depends on local access to individual DAA and reimbursement policies within the respective health-care system as well as HCV genotype, prior treatment response (see Table 1), and potential drug-drug interactions especially with ART (see Table 3). Special attention needs to be paid in patients on HIV ritonavir-boosted PI-containing ART (e.g., atazanavir, lopinavir, darunavir) as co-administration with HCV PI-based DAA treatment is not recommended (e.g., simeprevir, grazoprevir) or requires cessation of HIV ritonavir boosting regimen (e.g., paritaprevir/r) during HCV therapy. In addition, prior to giving DAAs, ART-containing NNRTIs such as efavirenz or viramune or the cobicistat-boosted regimens (i.e., elvitegravir) also need to be checked for potential drug-drug interactions. We would recommend reading the companion review in this special edition on drug interactions by [27]. Approaches to complex drug interactions with DAA and ARV regimens in the HIV/HCV-coinfected patient can include (1) choice of compatible DAA regimen based on ARVs or (2) switch to compatible ARV regimen when a specific DAA regimen is desired.

Conclusion

In the era of several new DAA combination therapies, treatment response rates no longer differ between HIV/HCV-coinfected and HCV-monoinfected patients; HIV coinfection is no longer a risk factor for poorer response to HCV treatment. Therefore, in countries with access to the new DAAs, interferon-free DAA-containing treatment is strongly recommended especially in patients with advanced liver fibrosis/cirrhosis and/or with failed response to previous therapy. Agents should be selected based upon HCV genotype and according to current guidelines as drug-drug interactions between cART, ribavirin, and especially the new HCV protease inhibitors require careful selection of both HIV and HCV drugs as well as close monitoring.

Compliance with Ethics Guidelines

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