Interferon-free treatment with sofosbuvir/daclatasvir achieves sustained virologic response in 100% of HIV/HCV-coinfected patients with advanced liver disease

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Abstract

Aim
We aimed to investigate the safety and efficacy of interferon (IFN)- and ribavirin (RBV)-free therapy with of sofosbuvir plus daclatasvir (SOF/DCV) in HIV/HCV-coinfected patients (HIV/HCV), who have an urgent need for effective antiviral therapy. We also assessed its impact on liver stiffness and liver enzymes.

Design
Thirty-one thoroughly documented HIV/HCV with advanced liver disease (advanced liver fibrosis and/or portal hypertension) who were treated with SOF/DCV were retrospectively studied.

Methods
The following treatment durations were applied: HCV-genotype (HCV-GT)1/4 without cirrhosis:12weeks; HCV-GT1/4 with cirrhosis:24weeks; HCV-GT3:24weeks; if HCV-RNA was detectable 4weeks before the end of treatment, treatment was extended by 4weeks at a time.

Results
Fifty-two percent of patients were treatment-experienced. The majority of patients had HCV-GT1 (68%), while HCV-GT3 and HCV-GT4 were observed in 23% and 10% of patients, respectively. Ninety-four percent had liver stiffness>9.5kPa or METAVIR>F2 and 45% had liver stiffness>12.5kPa or METAVIR F4. Portal hypertension (HVPG≥6mmHg) and clinically
significant portal hypertension (HVPG≥10mmHg) were observed in 67%(18/27) and 26%(7/27) of patients, respectively. Sustained virologic response 12 weeks after the end of treatment (SVR12) was achieved in 100%(31/31). Treatment with SOF/DCV was generally well-tolerated and there were no treatment discontinuations. HCV eradication improved liver stiffness from 11.8 (interquartile range [IQR]:11.5kPa to 6.9 (IQR:8.2)kPa (median change:-3.6[IQR:5.2]kPa;P<0.001) and decreased liver enzymes. The mean time period between treatment initiation and follow-up liver stiffness measurement was 32.7±1.2 weeks.

Conclusions
IFN- and RBV-free treatment with SOF/DCV was well-tolerated and achieved SVR12 in all HIV/HCV with advanced liver disease. It also significantly improved liver stiffness, suggesting anti-fibrotic and anti-portal hypertensive effects.

Keywords: Hepatitis C; antiviral therapy; liver stiffness; liver fibrosis; cirrhosis; portal hypertension
Introduction

Chronic hepatitis C (CHC) is exhibited by 25%-30% of European and US-American HIV-positive patients [1]. While AIDS-related mortality is decreasing, hepatitis C virus (HCV) coinfection has emerged as a major cause of morbidity and mortality in HIV-positive patients [2]. When compared to HCV monoinfection, HIV/HCV coinfection has been found to be associated with faster liver fibrosis progression [3] and markedly higher risk of developing cirrhosis [4]. HCV eradication prevents end-stage liver disease, hepatocellular carcinoma, and death, with an even greater impact in HIV-positive than HIV-negative patients [5]. The efficacy of dual-therapy with pegylated interferon plus ribavirin (PEGIFN/RBV) has improved as a result of treatment individualization over the last decade. However, it still remains unsatisfactory, especially in HIV-positive patients [6]. With the availability of first-generation direct-acting antiviral agents (DAAs), sustained virologic response (SVR) rates comparable to those in HCV-monoinfected patients were demonstrated [7-10]. However, serious adverse events are of particular concern in HIV-positive patients, as this patients group is highly susceptible to severe infectious complications during triple-therapy, even in the absence of cirrhosis [9]. As a consequence, treatment uptake rates with IFN-based regimens have been much lower in this patient population [11, 12]. The approval of IFN-free regimens has ushered in a new era in the treatment of CHC. Studies investigating the safety and efficacy of sofosbuvir (SOF)/RBV [13, 14], SOF/daclatasvir (DCV) [15], SOF/ledipasvir (LDV) [16, 17], as well as ritonavir boosted paritaprevir, ombitasvir, and dasabuvir (3D) [18] in HIV/HCV-coinfected patients have shown promising results. Treatment is
therefore indicated in all HIV-positive patients with chronic hepatitis C. Moreover, current European Association for the Study of the Liver (EASL) [19] and American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) [20] guidelines recommend prioritization of HIV/HCV-coinfected patients.

Due to its pangenotypic efficacy and its favorable drug-drug interaction (DDI) profile, SOF/DCV can be used in nearly all patients with HIV/HCV coinfection [21]. In the phase 3 ALLY-2 study [15], excellent SVR rates were observed among both treatment-naïve (96%) and treatment-experienced (98%) HIV/HCV-genotype (GT) 1-coinfected patients who received 12 weeks of SOF/DCV. However, only a small number of non-HIV/HCV-GT 1-coinfected patients were included in the ALLY-2 study and patients with cirrhosis were underrepresented (16%) [15]. However, as patients with advanced liver disease are at considerable risk for hepatic decompensation and death [22], they have an urgent need for effective treatment options.

Liver stiffness, assessed by transient elastography, is an accurate non-invasive marker of liver fibrosis and commonly used in HIV/HCV-coinfected patients [23]. Importantly, it also predicts the development of hepatic decompensation and hepatocellular carcinoma, as well as liver-related and overall mortality [24-26]. SVR to IFN-based therapies has been shown to induce liver stiffness regression in this special population [27]. However, the effect of HCV eradication with IFN-free therapies has yet to be investigated.

The aim of our study was to investigate the safety and efficacy of SOF/DCV in HIV/HCV-coinfected patients with advanced liver disease. We also assessed the changes in liver stiffness and liver enzymes after HCV-therapy.
Patients and methods

Study design

Thirty-one HIV/HCV-coinfected patients with advanced liver disease treated with SOF/DCV at the Medical University of Vienna were studied retrospectively.

Assessed parameters

Epidemiological, HIV, and HCV characteristics were assessed from patients’ medical history. Interleukin 28B rs12979860 SNP (IL28B) genotyping was performed in house using the StepOnePlus Real Time PCR System and a Custom TaqMan SNP Genotyping Assay (Applied Biosystems, Carlsbad, CA, USA) as previously described [28]. HCV-genotype (HCV-GT) was determined using the VERSANT HCV Genotype 2.0 Assay Line Probe Assay (LiPA) (Siemens Healthcare Diagnostics, Tarrytown, NY, USA). HCV-RNA was assessed using the Abbott RealTime HCV assay (Abbott Molecular, Des Plaines, IL, USA) with a lower limit of quantification (LLOQ) and detection of 12 IU x mL\(^{-1}\). SVR4 and SVR12 were defined as undetectable HCV-RNA 4 and 12 weeks after the end of therapy, respectively. Aspartate (AST) and alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), as well as CD4+ T-lymphocyte (CD4+) count were assessed using standard laboratory methods.

HCV therapy

SOF (Sovaldi [Gilead, Cambridge, UK] 400 mg once daily) was covered by the Austrian health insurance and provided by the local pharmacy. Bristol-Myers Squibb provided DCV (30-90 mg once daily) within a named patient program. After the approval by the European Medicines
Agency, DCV was also provided by the local pharmacy (Daklinza [Bristol-Myers Squibb, Uxbidge, UK] 30-90 mg once daily). Similar to the ALLY-2 study [15], adjusted DCV doses of 30 mg or 90 mg were used in patients who were treated with ritonavir-boosted protease inhibitors (PIs) or non-nucleoside reverse-transcriptase inhibitors (NNRTIs), respectively. The patient who was on both a NNRTI and a ritonavir-boosted PI was treated with a daily DCV dose of 60 mg. None of the patients received RBV. The following treatment durations were applied: HCV-GT 1/4 without cirrhosis: 12 weeks; HCV-GT 1/4 with cirrhosis: 24 weeks; HCV-GT 3: 24 weeks; if HCV-RNA was detectable 4 weeks before the end of treatment, treatment duration was extended by 4 weeks at a time.

Similarly to the ALLY-2 study [15], AEs and laboratory abnormalities were graded according to the criteria of the Division of AIDS of the National Institute of Allergy and Infectious Diseases.

Liver stiffness and HVPG measurement

Measurement of liver stiffness was performed by transient elastography (Fibroscan, Echosens, Paris, France), as previously described [29]. Liver stiffness was assessed before (baseline [BL]) and after HCV treatment (follow-up [FU]).

The Vienna Hepatic Hemodynamic Lab at the Medical University of Vienna performed the HVPG measurements in accordance with a standardized operating procedure [30]. At our center, measurement of HVPG is a routine procedure in patients with evidence of advanced chronic liver disease, as recommended by current guidelines [31, 32]. Concomitant medications known to have an effect on HVPG, including but not limited to beta blockers and nitrates were paused 5 days prior to HVPG measurements. Portal hypertension and clinically significant portal hypertension were defined as HVPG ≥6mmHg and ≥10mmHg [31, 32], respectively.
Advanced liver disease and cirrhosis were diagnosed by transient elastography (BL liver stiffness >9.5 kPa and >12.5 kPa [33], respectively), liver biopsy (METAVIR >F2 and F4, respectively), or HVPG measurement (portal hypertension and clinically significant portal hypertension, respectively).

Statistics

Statistical analyses were performed using IBM SPSS Statistics 23 (IBM, Armonk, NY, USA) and GraphPad Prism 6 (GraphPad Software, La Jolla, CA, USA). Continuous variables were reported as mean ± standard error of the mean or median (interquartile range), while categorical variables were reported as number of patients with (proportion of patients with) the certain characteristic. Confidence intervals of proportions were calculated using the modified Wald method. Student’s t-test was used for group comparisons of continuous variables when applicable. Otherwise, Mann-Whitney U test was applied. Group comparisons of categorical variables were performed using Chi squared or Fisher’s Exact test. Intraindividual comparisons were performed using Wilcoxon matched-pairs signed rank test, or McNemar’s test. Spearman’s rank correlation coefficient was calculated for correlation analyses. A $P$ value ≤0.05 was considered as statistically significant.

Ethics

This study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee of the Medical University of Vienna (No. 1814/2015).
Results

Patient characteristics

The mean BL CD4+ T-lymphocyte (CD4+) count was 495 ±46 cells x μL⁻¹ (Table 1). Almost all patients (97% [30/31]) were currently on antiretroviral therapy. Although the majority of patients were on an integrase inhibitor-based regimen (68% [21/31]), there was a wide range of concomitant antiretroviral therapy. Eighty-one percent (25/31) of patients had suppressed HIV-RNA (<50 copies/mL) at BL.

Fifty-two percent (16/31) of patients were treatment-experienced, including patients with previous first-generation DAA failure (6% [2/31]). The majority of patients was infected with HCV-GT 1 (68% [21/31]), while HCV-GT 3 and HCV-GT 4 were observed in 23% (7/34) and 10% (3/34) of patients, respectively. Seventy-four percent (23/31) of patients had the IL28B non-C/C genotype.

Ninety-four percent (29/31) had liver stiffness >9.5 kPa or METAVIR >F2 and 45% (14/31) had liver stiffness >12.5 kPa or METAVIR F4. Among 27 patients with information on HVPG, portal hypertension and clinically significant portal hypertension were observed in 67% (18/27) and 26% (7/27) of patients, respectively. All patients had advanced liver disease and 52% (16/31) of patients had cirrhosis.

Virologic response

At treatment week (W)4, 17% (5/29) and 52% (15/32) had undetectable HCV-RNA and HCV-RNA<LLOQ, respectively (Figure 1). At W8, HCV-RNA was detectable in 31% (4/13) of HCV-GT 1/4 patients without cirrhosis. In these patients, treatment duration was extended by 4 weeks
at a time to 16 (n=2), 20 (n=1), or 24 weeks (n=1). Only 77% (24/31) achieved undetectable HCV-RNA at W12, while HCV-RNA<LLOQ was observed in 97% (30/31) of patients.

HCV-RNA was undetectable in all patients (100% [31/31]) at the end of treatment and all patients (100% [31/31]) achieved SVR4 and SVR12.

Safety

Twenty-seven (79%) patients had at least one AE during HCV-therapy and FU (Table 2). Grade 3/4 AEs occurred in 4 (13%) patients. These were influenza (fever grade 3), gastroenteritis (fever grade 3), ulcer bleeding (hemorrhage grade 3), and acute myocardial infarction (grade 4). Serious AEs were observed in only 2 (6%) patients (ulcer bleeding and acute myocardial infarction). Grade 3/4 AEs and serious AEs were not considered to be treatment-related and there were no treatment discontinuations.

Grade 3/4 laboratory abnormalities were observed in 8 (26%) patients. At BL (before the first administration of SOF/DCV), 3 (10%) patients had CD4+ counts <200 cells x μL\(^{-1}\) (grade 3), 3 (10%) patients had platelet counts <50 G x L\(^{-1}\) (grade 3), and one patient had an AST elevation >5 x upper limit of normal (grade 3). One additional patient developed a CD4+ count <200 cells x μL\(^{-1}\) (grade 3) during HCV-therapy. To exclude a potential detrimental effect of SOF/DCV on CD4+ and platelet counts, we assessed the course of CD4+ and platelet count during HCV-therapy and FU (Supplementary figure 2).
Changes in liver stiffness and liver enzymes

The mean time periods between BL liver stiffness measurement and treatment initiation as well as BL and FU liver stiffness measurement were 10 ±2.2 and 42.7 ±2.8 weeks, respectively. Thus, the mean time period between treatment initiation and FU liver stiffness measurement was 32.7 ±1.2 weeks.

Liver stiffness decreased in 90% (28/31) of patients, while it increased in 10% (3/31) of patients (Figure 1). There was a decrease in liver stiffness between BL and FU (11.8 [11.5] vs. 6.9 [8.2] kPa; median change: -3.6 [5.2] kPa; P<0.001). The median relative change in liver stiffness was -33 (26)%.

The proportion of patients with liver stiffness values >9.5 kPa decreased significantly (BL: 71% [22/31] vs. FU: 35% [11/31]; P<0.001). Moreover, there was a trend toward a decrease in the proportion of patients with liver stiffness values >12.5 kPa (BL: 42% [13/31] vs. FU: 26% [8/31]; P=0.059).

Liver enzyme levels decreased statistically significantly after HCV-therapy: AST: 44 (34) vs. 29 (20) U x L⁻¹; median change: -16 (23) U x L⁻¹; P<0.001, ALT: 47 (41) vs. 22 (19) U x L⁻¹; median change: -22 (27) U x L⁻¹; P<0.001, and GGT: 81 (97) vs. 23 (23) U x L⁻¹; median change: -54 [67] U x L⁻¹; P<0.001 (Figure 1).

Determinants of the change in liver stiffness

There was a statistically significant inverse correlation between the relative changes in liver stiffness and BL liver stiffness (ρ=-0.462; P=0.009), indicating more pronounced relative decreases among patients with higher BL liver stiffness. We did not observe a correlation between the relative changes in liver stiffness and BL liver enzyme levels (AST [ρ=0.154;
\[ P=0.409 \], ALT [\( \rho=0.088; \ P=0.64 \)], and GGT [\( \rho=0.131; \ P=0.483 \)], or their change after HCV-therapy (AST [\( \rho=-0.05; \ P=0.788 \)], ALT [\( \rho=-0.079; \ P=0.672 \)], and GGT [\( \rho=-0.077; \ P=0.679 \)]).
Discussion

Our real-life cohort comprises thoroughly characterized HIV/HCV-coinfected patients with an urgent need for effective HCV-therapy. Several IFN-free regimens have been studied in HIV/HCV-coinfected patients. However, none of these studies aimed to investigate the use of IFN-free regimens in patients with advanced liver disease. The proportions of patients with cirrhosis and clinically significant portal hypertension were 52%, and 26%, respectively, which underlines the difficult-to-treat character of our study population. Moreover, more than half of them were treatment-experienced, including patients with previous first-generation DAA failure (6%), and 23% had HIV/HCV-GT 3 coinfection.

Two large phase 3 trials investigated the use of 24 weeks of SOF/RBV in HIV-positive patients [13, 14]. Combining the HIV/HCV-GT 1/4 arms of both studies, SVR was observed in only 81% of patients, although all patients were treatment-naïve. The rates of SVR may further decline in treatment-experienced patients and real-life cohorts comprising a higher proportion of patients with cirrhosis. Due to the unprecedented advances in the field of HCV-therapy, these SVR rates are no longer satisfactory and more potent regimens, such as SOF/DCV, should be used for patients with HIV/HCV-GT 1/4 coinfection [19, 20].

The majority of patients included in the phase 3 ALLY-2 study had HIV/HCV-GT 1 coinfection. In patients treated for 12 weeks, the presence of previous negative predictive factors, such as liver cirrhosis, did not affect SVR rates. Although the association between cirrhosis and treatment failure did not attain statistical significance, due to limited statistical power (only 16% of patients had cirrhosis), a clinically relevant impact cannot be ruled out. Thus, current EASL guidelines [19] recommend either the addition of RBV, or 24 weeks of treatment in patients with
In our study, we adopted the latter approach, which resulted in SVR in all HIV/HCV-GT 1/4 patients with cirrhosis (n=11), despite the high proportion of patients with clinically significant portal hypertension. This is in line with our previous observation [34], that IFN-free regimens overcome the negative effect of portal hypertension on virologic response.

In HIV/HCV-GT 1/4-coinfected patients without cirrhosis, response-guided therapy was used. The concept of response-guided therapy has been validated for PEGIFN/RBV [6] and first-generation DAAs, such as boceprevir [9]. Although some authors have proposed response-guided algorithms for individualization of IFN-free treatment [35, 36], a final appraisal of its practicability has not yet been made. In our study, the adaption of response-guided treatment durations for HIV/HCV-GT 1/4 patients without cirrhosis might have led to an overtreatment of 4 out of 13 patients. Treatment duration was extended to 16-24 weeks in these patients, although according to the excellent results of the ALLY-2 study, 12 weeks might have been sufficient.

Two studies investigated the use of SOF/LDV in HIV-positive patients [16, 17], which is another NS5B/NS5A inhibitor combination with a favorable DDI profile. The NIAID ERADICATE study [16] was restricted to treatment-naïve, HIV/HCV-GT 1 patients without cirrhosis, which precludes direct comparisons with our study. The second study (ION-4 study [17]), included a significant proportion of difficult-to-treat HCV-GT 1/4 patients, such as patients with cirrhosis (20%), as well as first-generation DAA (29%) and SOF/RBV failures (4%). Patients were treated for 12 weeks, resulting in SVR rates of 95% and 97% among treatment-naïve and treatment-experienced patients, respectively. Moreover, the combination of the 3D regimen and RBV has been investigated in the TURQUOISE-1 study [18] in HIV/HCV-GT 1-coinfected patients, including 10% of patients with cirrhosis. Patients were randomized into two arms comparing 12 and 24 weeks of treatment, achieving SVR rates of 94% and 91%, respectively.
However, the 3D regimen is only effective against HCV-GT 1/4 and even SOF/LDV is not a pangenotypic regimen, as its efficacy against HCV-GT 3 largely relies on the addition of RBV [37]. Accordingly, EASL [19] and AASLD [20] guidelines recommend against the use of SOF/LDV in patients with HCV-GT 3 and suggest the use of SOF/PEGIFN/RBV, SOF/RBV, or SOF/DCV ±RBV.

HIV/HCV-GT 3 coinfection is common in Europe and other parts of the world [12]. The prevalence of liver cirrhosis among HIV/HCV-coinfected patients is more than 20% [2], and might be even higher among HIV/HCV-GT 3 patients, as HCV-GT 3 accelerates liver fibrosis progression [38]. Thus, both patients with HIV/HCV-GT 3 (7%) and with cirrhosis (16%) were underrepresented in the phase 3 ALLY-2 study [15]. Based on the results of the ALLY-3 study [39], which investigated the same regimen in HCV monoinfection, these patients are considered as one of the remaining difficult-to-treat populations. Current EASL guidelines recommend both the addition of RBV and extended SOF/DCV treatment duration of 24 weeks in patients with HCV-GT 3 and cirrhosis [19], although the currently available evidence for this recommendation is very limited. In our study, all HIV/HCV-GT 3-coinfected patients (5 out of 7 patients had cirrhosis) were treated without RBV for 24 weeks and all patients achieved SVR. Nevertheless, larger studies investigating the optimal treatment strategy for patients with HIV/HCV-GT 3 coinfection and cirrhosis are needed.

DDIs were of major concern when first-generation DAAs were used [12]. Even with second-generation DAAs, such as simeprevir or the 3D regimen, drug-drug interactions with antiretroviral therapy complicate management in the majority of patients [21]. Similar to the phase 3 ALLY-2 study [15], patients with ritonavir-boosted PIs received a reduced DCV dose of 30 mg in our study. Patients with ritonavir-boosted darunavir containing antiretroviral therapy
were overrepresented among patients who had a relapse in the ALLY-2 study. Moreover, recent pharmacokinetic data suggests that 60 mg is more appropriate for patients on ritonavir-boosted darunavir or lopinavir containing antiretroviral therapy [40]. Since all patients achieved SVR in our study, we did not observe a detrimental effect. Nevertheless, the daily DCV dose should not be reduced to 30 mg in patients on ritonavir-boosted darunavir, as the low number of patients (n=4) included in our study limits the significance of this finding.

As patients with advanced liver disease are at considerable risk for hepatic decompensation and death [22], they represent the frontline in the use of IFN-free regimens. Combining treatment-naïve and treatment-experienced patients receiving 12 weeks of SOF/DCV in the ALLY-2 study, the SVR rate among patients with advanced liver fibrosis treated for 12 weeks was 97%. Although our study included patients with even more advanced liver disease who would have been excluded from the ALLY-2 study (decompensated cirrhosis; platelet count <50 G x L⁻¹), SVR was achieved in all patients. However, we can only speculate whether this was by chance or as a result of the use of longer treatment durations.

While the proportion of patients with at least one AE during HCV-therapy and FU (79%) was comparable to the ALLY-2 study (69%), we observed numerically higher proportions of patients with grade 3/4 (13% vs. 4%) and serious AEs (6% vs. 2%), which might be explained by the multimorbidity of our study population. Importantly, none of the grade 3/4 or serious AEs was considered to be treatment-related and there were no treatment discontinuations. Moreover, the majority of grade 3/4 laboratory abnormalities were observed at BL, before the first administration of SOF/DCV. Low absolute CD4+ and platelet counts at BL are secondary to portal hypertension [41] and underline the difficult-to-treat character of our study population.
Importantly, both parameters remained stable during HCV-therapy. Thus, SOF/DCV is well-tolerated, even in HIV/HCV-coinfected patients with advanced liver disease.

With increasing availability of highly effective and well-tolerated regimens, the focus of attention will shift from liver disease progression [38] to the regression of liver fibrosis and portal hypertension after HCV eradication [21, 42]. Achieving SVR with IFN-based therapies has been shown to decrease liver stiffness in HIV/HCV coinfected patients. In the ANRS CO13 HEPAVIH cohort [27], the probability of achieving a 30% decrease in liver stiffness among patients with SVR was 51% and 74% at 1 and 2 years after the end of treatment, respectively. In a previous study in HCV-monoinfected patients with cirrhosis under IFN-free treatment, we also observed a decrease in liver stiffness, paralleled by an increase in platelet count shortly after HCV eradication, suggesting an anti-portal hypertensive effect [34].

This is the first study to provide information on changes in liver stiffness after HCV eradication with IFN-free therapies in the setting of HIV/HCV-coinfection. In our study, the median relative change in liver stiffness between BL and FU was -33%, indicating a rapid, clinically significant effect. We observed more pronounced relative decreases among patients with higher BL liver stiffness. These findings have strong implications for the long-term management of patients with cirrhosis at BL, as a decrease in liver stiffness might abolish the need for HCC surveillance and screening endoscopies [32].

Potential mechanisms for the decrease in liver stiffness after HCV eradication include changes in tissue contraction/relaxation, hepatic necroinflammation, liver fibrosis, and cholestasis [29, 42]. Although the improvement in liver stiffness was paralleled by a decrease in liver enzymes, there was no correlation between liver enzymes as a marker of necroinflammation and the relative change in liver stiffness. Moreover, the expected dynamics of liver fibrosis and cholestasis after
HCV eradication may rather explain long-term, than short-term changes. Further studies investigating short- and long-term changes in liver fibrosis and portal hypertension after IFN-free treatments in HIV/HCV-coinfected patients are highly encouraged, due to their strong clinical implications (e.g. HCC surveillance, screening endoscopies, and prevention of variceal hemorrhage).

The main limitations of our study arise from its retrospective design and the limited number of patients. Firstly, although our results are promising, we cannot draw definite conclusion on the utility of response-guided therapy in the era of IFN-free regimens, or the optimal treatment strategy for patients with HIV/HCV-GT 3 and cirrhosis. Secondly, since we do not have information on changes in liver histology and portal hypertension, the mechanism by which HCV eradication lowers liver stiffness in this short time period remains unclear.

In conclusion, IFN- and RBV-free treatment with SOF/DCV was well-tolerated and achieved SVR in all difficult-to-treat HIV/HCV-coinfected patients, including those with HIV/HCV-GT 3 coinfection, cirrhosis, and/or portal hypertension. It also improved liver stiffness, suggesting anti-fibrotic and anti-portal hypertensive effects. As IFN-free regimens achieve comparable rates of SVR in HIV-negative and HIV-positive patients, HIV/HCV-coinfected patients should from now on be referred to as a special, rather than a difficult-to-treat population.
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Contributions
References

genotype 1 in patients with HIV: a randomised, double-blind, controlled phase 2 trial. 


populations including genotype-3 patients, decompensated genotype-1 patients, and genotype-1 patients with prior sofosbuvir treatment experience. *J Hepatol*, **60**:S3-S4.


### Table 1

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<thead>
<tr>
<th>Patient and treatment characteristics</th>
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<tr>
<td><strong>Epidemiological characteristics</strong></td>
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<td><strong>HIV infection parameters</strong></td>
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<td>HIV-RNA &lt;50 copies/mL</td>
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<tr>
<td>NRTIs plus NNRTI</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>NNRTI plus ritonavir-boosted PI</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Ritonavir-boosted PI plus II</td>
<td>1 (3%)</td>
</tr>
<tr>
<td><strong>HCV infection parameters</strong></td>
<td></td>
</tr>
<tr>
<td>Previous HCV treatment</td>
<td>16 (52%)</td>
</tr>
<tr>
<td>Pegylated interferon plus ribavirin</td>
<td>14 (45%)</td>
</tr>
<tr>
<td>First-generation direct-acting antiviral</td>
<td>2 (6%)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>1</td>
<td>21 (68%)</td>
</tr>
<tr>
<td>1a</td>
<td>17 (55%)</td>
</tr>
<tr>
<td>1b</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>3</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>4</td>
<td>3 (10%)</td>
</tr>
</tbody>
</table>

**HCV-RNA levels (log IU/mL)**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6.01 (0.12)</td>
</tr>
</tbody>
</table>

**Interleukin 28B rs12979860 SNP non-C/C**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>23 (74%)</td>
</tr>
</tbody>
</table>

**Liver disease severity**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver stiffness $&gt;9.5$ kPa or METAVIR $&gt;F2$</td>
<td>29 (94%)</td>
</tr>
<tr>
<td>Liver stiffness $&gt;12.5$ kPa or METAVIR $F4$</td>
<td>14 (45%)</td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>18 (67%)*</td>
</tr>
<tr>
<td>Clinically significant portal hypertension</td>
<td>7 (26%)*</td>
</tr>
<tr>
<td>Advanced liver disease</td>
<td>31 (100%)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>16 (52%)</td>
</tr>
</tbody>
</table>

*Information available in 27 patients.

**Table 1.** Patient and treatment characteristics.

**Abbreviations:**

- NRTI nucleoside/nucleotide reverse-transcriptase inhibitor
- PI protease inhibitor
- II integrase inhibitor
- NNRTI non-nucleoside reverse-transcriptase inhibitor
### Table 2

<table>
<thead>
<tr>
<th>Description</th>
<th>n=31</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any adverse event</strong></td>
<td>27 (79%)</td>
</tr>
<tr>
<td><strong>Common adverse events</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (42%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>10 (32%)</td>
</tr>
<tr>
<td>Cough</td>
<td>8 (26%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (26%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>Depression</td>
<td>6 (19%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>5 (16%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (16%)</td>
</tr>
<tr>
<td>Rash</td>
<td>5 (16%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Tendinitis</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (6%)</td>
</tr>
<tr>
<td><strong>Grade 3/4 adverse events</strong></td>
<td>4 (13%)</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>2 (6%)</td>
</tr>
</tbody>
</table>
Grade 3/4 laboratory abnormality  8 (26%)
AST >5 x upper limit of normal  1 (3%)
CD4+ count <200 cells x μL⁻¹  4 (13%)
Platelet count <50 G x L⁻¹  3 (10%)

**Table 2.** Adverse events during HCV-therapy and follow-up.

Abbreviations:  
AST aspartate aminotransferase  
CD4+ CD4+ T-lymphocyte
Figure 1. A Liver stiffness before (baseline [BL]) and after HCV-therapy (follow-up [FU]). Patients with a decrease in liver stiffness (n=28) are shown in blue, while patients in whom liver stiffness increased (n=3) are shown in red. Panels B, C, and D show the changes in aspartate (AST) and alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT) after HCV-therapy, respectively.

* One data point is outside the axis (AST: -249 U x mL\(^{-1}\) and ALT: -476 U x mL\(^{-1}\)).
** Three data points are outside the axis (GGT: -281, -325, and -396 U x mL⁻¹).

Statistics: In panel A, symbols indicate median liver stiffness at BL, liver stiffness of individual patients, and median liver stiffness at FU, from left to right. The error bars show the interquartile range (IQR). In panels B, C, and D the bold line and error bar represent the median of differences and its IQR, respectively. Wilcoxon matched-pairs signed rank test was used for intraindividual comparisons.