

RESEARCH ARTICLE

Successful direct acting antiviral (DAA) treatment of HCV/HIV-coinfected patients before and after liver transplantation

Julia M. Grotenthaler^{1,2}, Christoph R. Werner^{1,2}, Martina Steurer^{1,2}, Ulrich Spengler^{2,3}, Thomas Berg⁴, Cornelius Engelmann⁴, Heiner Wedemeyer^{2,5}, Thomas von Hahn^{2,5}, Wolfgang Stremmel^{2,6}, Anita Pathil^{2,6}, Ulrich Seybold^{2,7}, Eckart Schott⁸, Usha Blessin⁸, Christoph Sarrazin⁹, Martin-Walter Welker⁹, Ellen Harrer¹⁰, Stefan Scholten¹¹, Clemens Hinterleitner^{2,12}, Ulrich M. Lauer^{2,13}, Nisar P. Malek^{1,2}, Christoph P. Berg^{1,2*}

1 Department of Gastroenterology, Hepatology, and Infectiology, University Hospital Tuebingen, Tuebingen, Germany, **2** German Center for Infection Research (DZIF) partner site, Tuebingen, Bonn, Hannover, Heidelberg, Munich, Germany, **3** Department of Internal Medicine I, University of Bonn, Bonn, Germany, **4** Division of Gastroenterology and Hepatology, University Hospital Leipzig, Leipzig, Germany, **5** Department of Gastroenterology, Hepatology, and Endocrinology, Medizinische Hochschule Hannover, Hannover, Germany, **6** Department of Internal Medicine IV, University Hospital Heidelberg, Heidelberg, Germany, **7** Division of Infectious Diseases, Medizinische Poliklinik-Innenstadt, University of Munich, Munich, Germany, **8** Department of Hepatology and Gastroenterology, Charité Universitätsmedizin Berlin, Berlin, Germany, **9** Department of Gastroenterology and Hepatology, University Hospital Frankfurt, Frankfurt, Germany, **10** Department of Internal Medicine 3, Institute of Clinical Immunology, University Hospital Erlangen, Erlangen, Germany, **11** Praxis Hohenstaufenring, Cologne, Germany, **12** Department of Medical Oncology, Haematology, Immunology, Rheumatology and Pulmology, University Hospital Tuebingen, Tuebingen, Germany, **13** Department of Clinical Tumor Biology, University Hospital Tuebingen, Tuebingen, Germany

* christoph.berg@med.uni-tuebingen.de



OPEN ACCESS

Citation: Grotenthaler JM, Werner CR, Steurer M, Spengler U, Berg T, Engelmann C, et al. (2018) Successful direct acting antiviral (DAA) treatment of HCV/HIV-coinfected patients before and after liver transplantation. PLoS ONE 13(6): e0197544. <https://doi.org/10.1371/journal.pone.0197544>

Editor: Chen-Hua Liu, National Taiwan University Hospital, TAIWAN

Received: March 12, 2018

Accepted: May 3, 2018

Published: June 6, 2018

Copyright: © 2018 Grotenthaler et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the paper.

Funding: No financial support was received in relation to this manuscript.

Competing interests: The authors have declared that no competing interests exist.

Abstract

Objectives

The aim of this multicenter retrospective study was to investigate safety and efficacy of direct acting antiviral (DAA) treatment in the rare subgroup of patients with HCV/HIV-coinfection and advanced liver cirrhosis on the liver transplant waiting list or after liver transplantation, respectively.

Methods

When contacting 54 German liver centers (including all 23 German liver transplant centers), 12 HCV/HIV-coinfected patients on antiretroviral combination therapy were reported having received additional DAA therapy while being on the waiting list for liver transplantation (patient characteristics: Child-Pugh A (n = 6), B (n = 5), C (n = 1); MELD range 7–21; HCC (n = 2); HCV genotype 1a (n = 8), 1b (n = 2), 4 (n = 2)). Furthermore, 2 HCV/HIV-coinfected patients were denoted having received DAA therapy after liver transplantation (characteristics: HCV genotype 1a (n = 1), 4 (n = 1)).

Results

Applied DAA regimens were SOF/DAC (n = 7), SOF/LDV/RBV (n = 3), SOF/RBV (n = 3), PTV/r/OBV/DSV (n = 1), or PTV/r/OBV/DSV/RBV (n = 1), respectively. All patients achieved

SVR 12, in the end. In one patient, HCV relapse occurred after 24 weeks of SOF/DAC therapy; subsequent treatment with 12 weeks PTV/r/OBV/DSV achieved SVR 12. One patient underwent liver transplantation while on DAA treatment. Analysis of liver function revealed either stable parameters or even significant improvement during DAA therapy and in follow-up. MELD scores were found to improve in 9/13 therapies in patients on the waiting list for liver transplantation; in only 2 patients a moderate increase of MELD scores persisted at the end of follow-up.

Conclusion

DAA treatment was safe and highly effective in this nation-wide cohort of patients with HCV/HIV-coinfection awaiting liver transplantation or being transplanted.

Introduction

Presumably 2.3 million Hepatitis C (HCV) positive patients worldwide are coinfecting with human immunodeficiency virus (HIV), of which about 100,000 are living in Western and Central Europe [1]. Coinfection with HIV is known to accelerate complications of chronic HCV infection [2], such as the development and decompensation of liver cirrhosis and emergence of hepatocellular carcinoma (HCC). With the development of direct acting antiviral agents (DAA), antiviral treatment has led to very high SVR (sustained virologic response) rates of 95–100% in the past few years [3–8].

By now, substantial experience exists for DAA therapy in a variety of different patient subgroups. In the special subgroup of HCV/HIV-coinfecting patients, DAA treatment shows safety profiles and SVR rates that are nearly identical to those of HCV-monoinfected patients [9–14], although drug-drug interactions (DDIs) with antiretroviral medication can be challenging in this cohort [15, 16]. There have also been a number of trials to evaluate DAA therapy in patients with compensated (Child-Pugh A) liver cirrhosis [17–22], demonstrating favorable safety and efficacy profiles (SVR rates 90–95%) in HCV-monoinfected as well as in HCV/HIV-coinfecting patients [11, 12, 23]. Similar SVR rates were demonstrated for HCV-monoinfected patients after liver transplantation [22, 24–31]. In contrast, SVR rates are less impressive in patients with decompensated liver cirrhosis, mainly in the range of 80–85% [3, 4, 17, 22, 26, 27, 32, 33]. Furthermore, the potential of severe deterioration of liver function under DAA therapy in patients with advanced liver cirrhosis [17, 22, 24, 27, 32, 34] has led to the recommendation of very careful usage or even refusal of DAA therapy in patients with MELD (model for end-stage liver disease) scores exceeding 18–20 points [3, 35].

In this context, so far only few data exist concerning safety and efficacy of DAA therapy in HCV/HIV-coinfecting patients (i) exhibiting advanced stages of liver cirrhosis while waiting for liver transplantation or (ii) undergoing DAA therapy after liver transplantation. Therefore, we performed a retrospective multicenter analysis throughout Germany, focusing on patients with either of these two rare conditions.

Patients and methods

For this retrospective cross-sectional multicenter analysis, 54 specialized liver centers in Germany were contacted, including (i) all 23 German university hospitals performing liver transplantations, (ii) 2 additional non-transplanting university hospitals, and (iii) 29 medical

practices specialized in hepatology or infectious diseases. Responses were obtained from 22 university hospitals and 10 practices. Notably, 9 university hospitals and 1 medical practice were able to contribute eligible patients to this study. The other institutions reported to have no suitable patients. Data acquisition was carried out pseudonymously by use of a precast Excel chart to ensure structured and standardized data collection. Collected data contained basic patient characteristics, stage of liver disease, specifications of HCV and HIV disease, course of DAA therapy, as well as laboratory results. Recorded time spans encompassed initiation of DAA therapy (baseline) until end of follow-up (12 or 24 weeks after end of treatment).

Complete data sets were obtained for 14 patients. One patient (Pt. 6) received a second DAA therapy, so that a total of 15 DAA therapies were recorded as shown in [Table 1](#). Twelve patients were on the waiting list for liver transplantation at the initiation of DAA therapy with Child-Pugh stage A (n = 6), B (n = 5), C (n = 1); MELD scores: range 7–21, median 13; two patients with HCC; HCV genotypes 1a (n = 8), 1b (n = 2), 4 (n = 2); one patient underwent liver transplantation while on DAA therapy. The decision for listing the individual patients for liver transplantation was in the responsibility of the respective transplant center. Two patients with HCV genotype 1a or 4, respectively, had already been transplanted at the beginning of DAA treatment; one transplanted patient (Pt. 13) suffered from fibrosing cholestatic hepatitis following recurrence of hepatitis C, the other (Pt. 14) from re-cirrhosis of the liver graft. Nine patients had received previous treatment for HCV with Interferon-based therapies. All patients suffered from HIV-1 and were under stable antiretroviral therapy: HIV stadium A1-C3; CD4 cell count 50-1010/μl (CD4 cell count available for n = 11 patients). For more details see [Table 1](#).

Data analysis was performed using IBM SPSS Statistics (Version 24), GraphPad Prism (Version 7.03), and Microsoft Excel (Version 2010). Continuous variables in dependent samples were analyzed with Friedman's ANOVA. P values < 0.05 were considered significant. For post hoc analysis, Wilcoxon signed ranks test was used. Bonferroni-Holm correction was applied in case of multiple comparisons. Retrospective simulation of potential DDIs was performed by use of the website www.hep-druginteractions.org (University of Liverpool) [3]. HCV RNA negativity was defined as HCV RNA PCR below the lower limit of detection in a sensitive assay.

This study was approved by the Ethics Committee at the Medical Faculty of the Eberhard-Karls University and at the University Hospital Tuebingen (Project number: 805/2015BO2). The Committee waived the need for written informed consent for this retrospective analysis.

Results

DAA treatment regimens were chosen as shown in [Table 1](#). Regimen choices were based on the available options at the time of initiation of therapy. No patient died during treatment and there was no case, in which DAA treatment had to be discontinued (two discontinuations of Ribavirin). In five patients, complications were recorded as listed in [Table 1](#). One patient underwent liver transplantation while on DAA therapy. There were no transplant rejections during therapy and follow-up. The antiretroviral treatment regimen was modified in one patient (Pt. 13) prior to DAA therapy. Retrospective simulation yielded potential DDIs of DAAs with antiretroviral medication in 11/15 therapy regimens (73.3%). Serum levels of antiretroviral medication were monitored in one patient. HIV RNA PCR was performed in 12/14 patients with varying frequency at non-standardized time-points. No significant HIV viremia or viral blips were detected during DAA therapy. In the follow-up phase, only one transient episode of low level HIV viremia was reported (Pt. 1, 89 copies/ml).

Table 1. Individual listing of patient characteristics.

Patient	Pt. 1	Pt. 2	Pt. 3	Pt. 4	Pt. 5	Pt. 6a	Pt. 6b ^a	Pt. 7	Pt. 8	Pt. 9	Pt. 10	Pt. 11	Pt. 12	Pt. 13	Pt. 14
LTx-Status	pre LTx	pre LTx	pre LTx	pre LTx	pre LTx	pre LTx	pre LTx	pre LTx	pre LTx	pre LTx	pre LTx	pre LTx	pre LTx	post LTx	post LTx ^b
General data															
Age (years)	45	57	49	56	48	64	64	39	49	53	48	54	38	45	49
Sex	m	f	f	m	m	m	m	m	m	m	m	m	m	m	m
BMI (kg/m ²)	33	19	23	26	25	25	25	21	23	35	21	17	21	22	23
Child-Pugh	C	A	B	B	B	B	B	A	A	A	A	A	B	n/a	un- known
MELD	18	9	9	10	13	16	14	21	13	12	7	14	17	12	13
HCC	no	yes	no	no	no	no	no	no	no	no	no	no	yes	no	no
Time since LTx (months)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0 ^c	35	58
Immuno- suppressants	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	TAC MMF Pred	CSA MMF Pred	TAC MMF -
HCV															
Genotype	4	1a	1a	1b	4	1b	1b	1a	1a	1a	1a	1a	1a	4	1a
First diagnosed (... years ago)	8	31	18	32	30	18	18	35	21	21	un- known	21	~30	9	11
Pretreatment with IFN-based regimen or DAA therapy	no	no	no	yes	no	yes	yes	yes	yes	yes	no	yes	yes	yes	yes
Outcome of previous treatment	n/a	n/a	n/a	NR	n/a	discontinuation	relapse after DAA therapy	relapse	relapse	relapse	NR	n/a	NR	NR	NR
HIV															
HIV type	HIV-1	HIV-1	HIV-1	HIV-1	HIV-1	HIV-1	HIV-1	HIV-1	HIV-1	HIV-1	HIV-1	HIV-1	HIV-1	HIV-1	HIV-1
First diagnosed (... years ago)	18	31	30	32	30	17	17	35	26	27	26	27	~30	11	15
Stadium	A2	A1	B3	C2	B3	B2	B2	C3	B3	A1	C2	C3	B3	A1	A2
HIV-Medication	FTC/ TDF/ RPV	FTC/ TDF/ ATV/ RTV	3TC/ FPV/ RTV	FTC/ TDF/ LPV/ RTV	ATV	FTC/TDF/FPV/ RTV	FTC/ TDF/ FPV/ RTV	DRV/ RTV	FTC/ TDF/ RAL	FTC/ TDF/ RAL	DRV/ RAL/ RTV	LPV/ RTV/ 3TC/ ABC/ RAL	FTC/ TDF/ RAL	3TC/ ABC/ RAL	TDF/ 3TC/ RAL
DAA therapy															
HCV-Medication	SOF/ DAC	SOF/ DAC	SOF/ LDV/ RBV	SOF/ DAC	SOF/ DAC	SOF/DAC	PTV/r/ OBV/ DSV	PTV/r/ OBV/ DSV/ RBV	SOF/ RBV	SOF/ DAC	SOF/ LDV/ RBV	SOF/ LDV/ RBV	SOF/ RBV	SOF/ DAC	SOF/ RBV
Duration (weeks)	24	24	12	12	24	24	12	24	24	24	24	24	27	40 ^d	24
HCV-RNA-PCR first negative (weeks)	4	8	2	12	8	4	4	8	12	12	24	24	6	27	8
Outcome	SVR 12	SVR 12	SVR 12	SVR 12	SVR 12	relapse	SVR 12	SVR 12	SVR 12	SVR 12	SVR 12	SVR 12	SVR 12	SVR 12	SVR 12
Complications	yes ^e	no	no	no	no	no	no	no	no	no	no	yes ^f	yes ^g	yes ^h	yes ⁱ

(Continued)

Table 1. (Continued)

Patient	Pt. 1	Pt. 2	Pt. 3	Pt. 4	Pt. 5	Pt. 6a	Pt. 6b ^a	Pt. 7	Pt. 8	Pt. 9	Pt. 10	Pt. 11	Pt. 12	Pt. 13	Pt. 14
Transplant rejection during DAA therapy	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	no	no	no

Pt. 1–14 = Patients 1–14; LTx = liver transplantation; pre LTx = patient on liver transplant waiting list at initiation of DAA therapy; post LTx = DAA therapy was initiated after liver transplantation; m = male; f = female; BMI = body mass index; n/a = not applicable; MELD = model for end-stage liver disease; HCC = hepatocellular carcinoma; TAC = Tacrolimus; MMF = Mycophenolate mofetil; Pred = Prednisolone; CSA = Ciclosporin; IFN = Interferon; NR = nonresponse; FTC = Emtricitabine; TDF = Tenofovir; RPV = Rilpivirine; ATV = Atazanavir; RTV = Ritonavir; 3TC = Lamivudine; FPV = Fosamprenavir; LPV = Lopinavir; DRV = Darunavir; RAL = Raltegravir; ABC = Abacavir; SOF = Sofosbuvir; DAC = Daclatasvir; LDV = Ledipasvir; RBV = Ribavirin; PTV = Paritaprevir; r = Ritonavir; OBV = Ombitasvir; DSV = Dasabuvir; PCR = polymerase chain reaction; SVR 12 = sustained virologic response 12 weeks after end of treatment.

^a relapse after SOF/DAC (24 weeks), SVR 12 achieved after second therapy with PTV/r/OBV/DSV (12 weeks);

^b re-cirrhosis in transplanted liver;

^c LTx three weeks after initiation of DAA therapy, initial immunosuppressive therapy with TAC/MMF/Pred, TAC switched to Sirolimus during DAA therapy;

^d 40 weeks of therapy, addition of RBV after three months (discontinuation after 14 days due to worsening of renal function), and SMV after four months, respectively, due to a delayed drop in HCV RNA levels;

^e biliary stent occlusion with cholangitis;

^f hemolytic anemia, resulting in discontinuation of RBV;

^g HCC recurrence after LTx;

^h fibrosing cholestatic hepatitis, renal insufficiency, incisional hernia;

ⁱ abdominal pain.

<https://doi.org/10.1371/journal.pone.0197544.t001>

Notably, 13/14 patients achieved SVR 12 following the first DAA therapy (92.9%; 11 patients on the transplant waiting list and both patients after liver transplantation). HCV RNA negativity was reached after a median of 8 weeks during DAA therapy (range 2–27 weeks; see Fig 1). One patient (No. 6a) suffered from a relapse following 24 weeks of therapy with Sofosbuvir / Daclatasvir; subsequently, this patient achieved SVR 12 under a modified DAA therapy with Paritaprevir / Ritonavir / Ombitasvir / Dasabuvir, administered over 12 weeks (see Pt. 6b).

For safety analysis, we monitored the course of liver function tests and MELD scores under DAA therapy and during follow-up. Statistical analysis was performed on the results of the patients on the transplant waiting list (see Table 2 and Fig 2). In all evaluable cases, significant and persistent improvements of serum alanine transaminase ($p < 0.001$) and thrombocyte levels ($p = 0.002$) could be observed. INR (international normalized ratio), bilirubin, and albumin displayed a trend towards improvement without reaching levels of significance. Creatinine levels ($p = 0.002$) and eGFR (estimated glomerular filtration rate; $p = 0.013$) showed minimal changes of the mean, however, we could demonstrate a transient, statistically significant worsening under DAA therapy. These changes remained significant even when excluding the one patient (Pt. 7) with a markedly impaired and fluctuating renal function from analysis on a trial basis. The two transplanted patients showed stable liver function tests under DAA therapy and during follow-up. Especially the patient suffering from fibrosing cholestatic hepatitis (Pt. 13) displayed a pronounced improvement in bilirubin levels, albumin, and thrombocytes.

As shown in Fig 3A, initial individual MELD scores improved in 9 patients on the transplant waiting list compared to baseline: 7 patients showed sustained improvement from the DAA treatment period until the end of follow-up, while 2 patients started to improve only when reaching the follow-up period. One of these patients' (Pt. 7) MELD score was mainly driven by an impaired and fluctuating renal function. In contrast, 2 patients showed worsening of their MELD scores persisting throughout treatment and follow-up. MELD scores in another

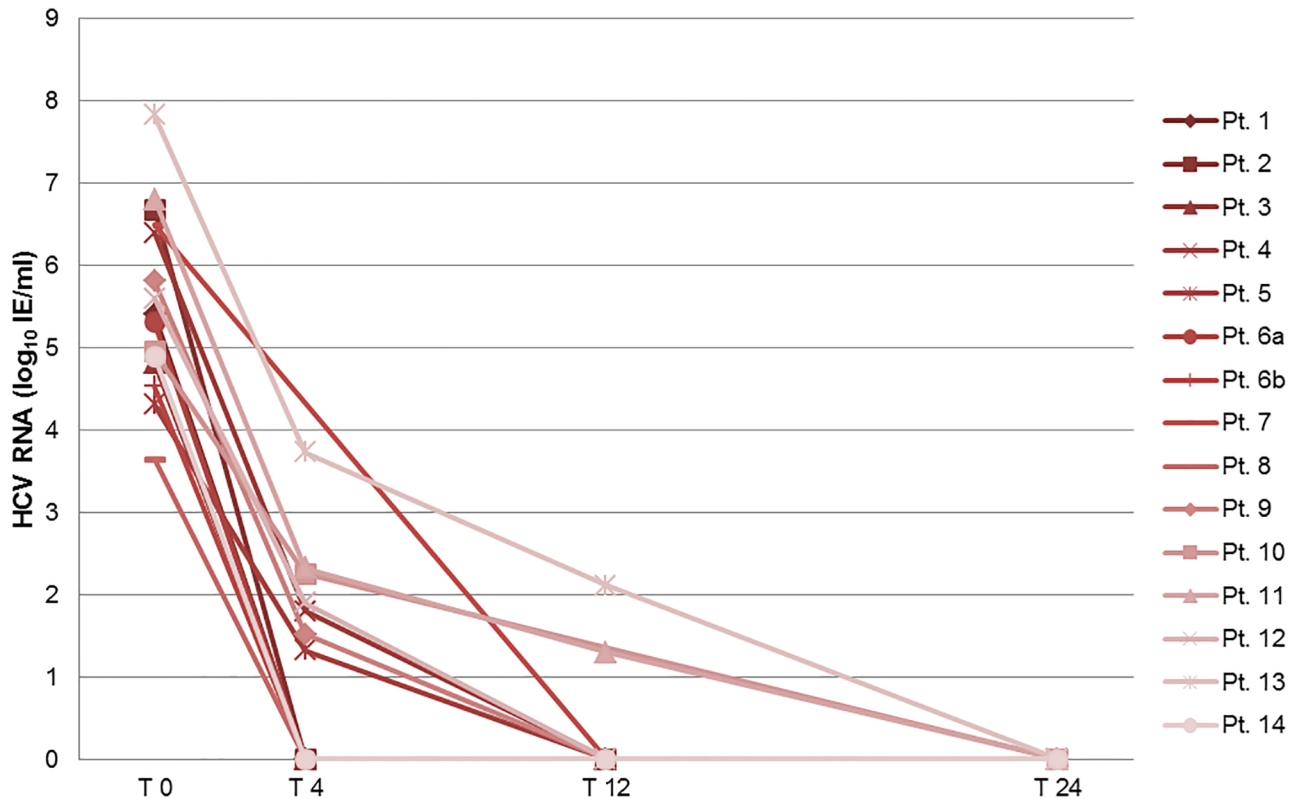


Fig 1. Course of HCV RNA under DAA therapy. Pt. 1–14: individual patients. T 0 = initiation of DAA therapy; T 4/12/24 = 4/12/24 weeks after initiation of DAA treatment (T24 only if treatment course was long enough). Undetectable HCV RNA was set to zero in the otherwise logarithmized data.

<https://doi.org/10.1371/journal.pone.0197544.g001>

2 patients returned to baseline at the follow-up period after initial worsening under DAA therapy. Overall, changes in MELD scores did not reach a level of significance (see Table 2 and Fig 3B).

Discussion

In this retrospective German multicenter study, data on safety and efficacy of DAA therapy in patients with HCV/HIV-coinfection on the liver transplant waiting list or after liver transplantation, respectively, were analyzed. SVR rates in this rare patient subgroup were encouragingly high: Although a substantial number of patients with decompensated liver cirrhosis (50% Child-Pugh B/C) were included, all chronic HCV infections were cured, including the one patient who achieved SVR only after a second, modified DAA treatment. Our results seem to slightly exceed SVR rates in the one and only case series including HCV/HIV-coinfected patients on the liver transplant waiting list, which has yet been published [37]. This study reported an overall SVR rate of 85.4% (79.2% pre liver transplantation) while not discussing the possibility for re-treatment in case of failure. Our data are also slightly exceeding results for DAA treatment in advanced liver disease for HCV-monoinfected patients in prospective trials such as SOLAR-1 [26], SOLAR-2 [27], ASTRAL-4 [32], CUP [17], ALLY-1 [22], as well as in larger real-world cohort analyses [4, 17]. This may be due to the small sample size and highly selected patients in our study. Furthermore, DAA treatment was solely performed in highly specialized and experienced liver centers, which might have contributed to these optimal outcomes.

Table 2. Changes in laboratory results under DAA therapy and during follow-up in patients on the liver transplant waiting list.

Parameter		N	Baseline	EOT	EO FU	p-value
ALT (U/l)	Mean ± SEM	13	70 ± 14.7	24 ± 2.9	27 ± 2.6	<0.001
	Range		21–212	8–43	17–52	
Thrombocytes (1,000/ μ l)	Mean ± SEM	12	60 ± 10.0	84 ± 14.0	92 ± 15.5	0.002
	Range		25–135	29–187	27–175	
MELD	Mean ± SEM	11	14 ± 1.2	13 ± 1.7	11 ± 1.4	0.307
	Range		7–21	6–27	5–22	
Bilirubin (total) (mg/dl)	Mean ± SEM	13	2.6 ± 0.4	2.5 ± 0.5	1.9 ± 0.3	0.101
	Range		0.5–6.0	0.6–6.8	0.4–4.2	
INR	Mean ± SEM	13	1.2 ± 0.05	1.2 ± 0.02	1.2 ± 0.02	0.832
	Range		1.1–1.6	1.0–1.3	1.1–1.3	
Albumin (g/dl)	Mean ± SEM	9	3.4 ± 0.2	3.9 ± 0.2	4.0 ± 0.2	0.169
	Range		2.6–4.2	3.2–4.8	2.7–5.1	
Creatinine (mg/dl)	Mean ± SEM	13	1.3 ± 0.3	1.5 ± 0.5	1.2 ± 0.3	0.002
	Range		0.6–4.8	0.6–7.1	0.6–4.3	
eGFR (ml/min/1.73m ²)	Mean ± SEM	13	84 ± 27.6	79 ± 27.9	86 ± 25.7	0.013
	Range		14–119	9–116	16–119	

Analysis was only possible for data sets, in which values for all three time points (baseline, end of treatment (EOT), end of follow-up (EO FU)) were given. Significant p-values (Friedman’s ANOVA) are printed in bold. Mean, standard error of the mean (SEM), and range are indicated for the three time points. N = number of data sets of DAA therapies which could be analyzed per parameter; ALT = alanine transaminase; MELD = model for end-stage liver disease; INR = international normalized ratio; eGFR = estimated glomerular filtration rate. Calculation of eGFR by use of the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation [36].

<https://doi.org/10.1371/journal.pone.0197544.t002>

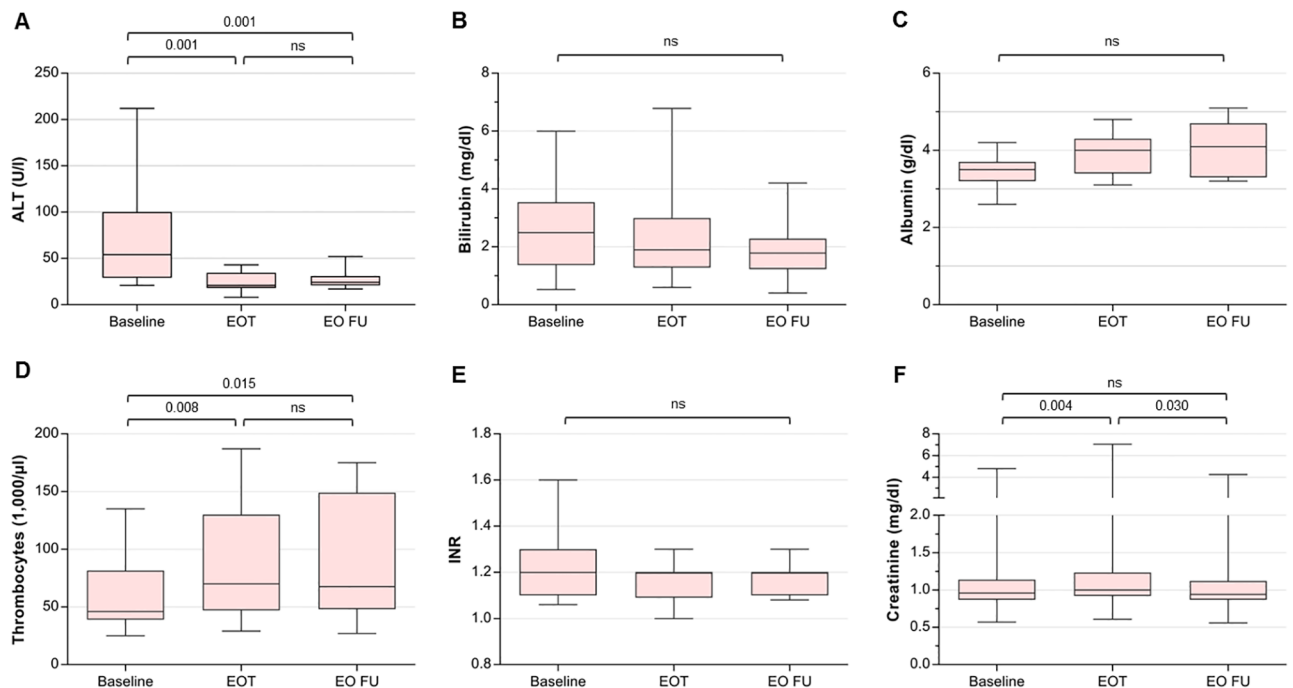


Fig 2. Changes of (A) alanine transaminase (ALT), (B) bilirubin, (C) albumin, (D) thrombocytes, (E) INR (international normalized ratio), and (F) creatinine in patients on the liver transplant waiting list. Box plots: median and interquartile ranges; whiskers: minimum to maximum. P-values from post hoc analysis (Wilcoxon signed ranks test, Bonferroni-Holm correction); ns = not significant, EOT = end of treatment, EO FU = end of follow-up.

<https://doi.org/10.1371/journal.pone.0197544.g002>

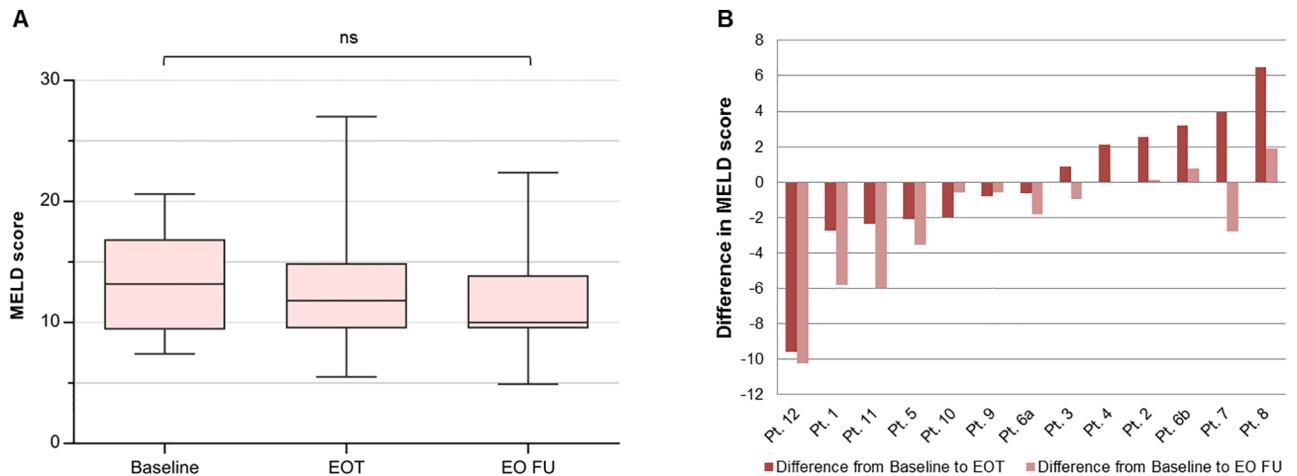


Fig 3. (A) Changes of MELD scores in patients on the liver transplant waiting list. Changes did not reach significance levels; ns = not significant, EOT = end of treatment, EO FU = end of follow-up. **(B) Changes of individual MELD scores in patients on the liver transplant waiting list.** Pt. 1–12: individual patients. EOT = end of treatment, EO FU = end of follow-up.

<https://doi.org/10.1371/journal.pone.0197544.g003>

In addition to the remarkable SVR rates, our data demonstrate a tolerable safety profile of DAA therapy in this special cohort. Most recorded complications show no clear association to antiviral therapy. Moreover, we could demonstrate an overall stability of liver function during DAA therapy and in follow-up. Statistical analysis revealed transient significant worsening of creatinine levels and eGFR under DAA therapy. However, changes of the mean were very small and most patients had normal or nearly normal renal function throughout observation. This caused a pronounced floor effect impairing the impact of this result. Furthermore, in all patients receiving antiretroviral regimens containing Tenofovir, eGFR did not fall below the threshold associated with a risk of accumulation. MELD score changes with approximately half of the patients showing improvement are consistent with data for HCV-monoinfected patients with decompensated liver cirrhosis [32]. Furthermore, the significant and sustained improvement of thrombocyte levels could be taken as an indicator for reduction in portal hypertension. Our findings are in line with data on long-term outcome in HCV-monoinfected patients on the liver transplant waiting list, in which successful DAA therapy can lead to significant improvement and stabilization of liver function, even enabling patients to be removed from the transplant waiting list [33, 35]. Interestingly, there were no reports on any clinically relevant adverse drug effects, although retrospective screening for DDIs of DAAs with the antiretroviral medication yielded potential interactions in 73% of the patients.

There are three reports in the literature [38–40] dealing with the subject of DAA therapy in altogether 15 HCV/HIV-coinfected patients after liver transplantation. High SVR rates, but also several complications, especially one rejection and one case of death [38], were reported. Our two liver transplant patients undergoing DAA therapy both achieved SVR 12 and did not suffer from any severe complication.

Considering the high response rate of the specialized centers, the relatively small number of patients that were detected in our study probably comes close to the actual size of this very rare subgroup of patients in Germany. Our data correspond to different cohort studies stating a prevalence of 2.6–3.0% [41, 42] for HCV/HIV-coinfected patients on the liver transplant waiting list, and a prevalence of 0.2–0.3% [43, 44] for HCV/HIV-coinfected patients after liver transplantation.

Many questions remain to be answered for this special patient collective: Besides providing further proof for safety and efficacy of DAA treatment, future studies should focus on the choice of DAA regimens, the clinical relevance of potential DDIs, as well as the patients' long-term outcome. Given the low prevalence of HCV/HIV-coinfected patients on the liver transplant waiting list and after liver transplantation, respectively, international studies are required to recruit a sufficient number of patients.

In summary, our data strongly suggest that DAA treatment can be performed with excellent efficacy and tolerable safety in patients with HCV/HIV-coinfection and advanced liver cirrhosis on the liver transplant waiting list as well as in HCV/HIV-coinfected patients after liver transplantation. However, considering this challenging patient population, DAA therapy should preferably be performed in specialized liver centers comprising particular knowledge in managing patients with HIV-infection.

Acknowledgments

We would like to thank all centers that participated in this study and supported the effort to assemble the individual experiences of DAA therapy in this rare patient collective.

Author Contributions

Conceptualization: Julia M. Grottenthaler, Nisar P. Malek, Christoph P. Berg.

Data curation: Julia M. Grottenthaler, Christoph R. Werner, Martina Steurer, Ulrich Spengler, Thomas Berg, Cornelius Engelmann, Heiner Wedemeyer, Thomas von Hahn, Wolfgang Stremmel, Anita Pathil, Ulrich Seybold, Eckart Schott, Usha Blessin, Christoph Sarrazin, Martin-Walter Welker, Ellen Harrer, Stefan Scholten, Ulrich M. Lauer, Christoph P. Berg.

Formal analysis: Julia M. Grottenthaler, Christoph R. Werner, Martina Steurer, Ulrich Spengler, Thomas Berg, Cornelius Engelmann, Heiner Wedemeyer, Thomas von Hahn, Wolfgang Stremmel, Anita Pathil, Ulrich Seybold, Eckart Schott, Usha Blessin, Christoph Sarrazin, Martin-Walter Welker, Ellen Harrer, Stefan Scholten, Clemens Hinterleitner, Ulrich M. Lauer, Christoph P. Berg.

Supervision: Nisar P. Malek, Christoph P. Berg.

Writing – original draft: Julia M. Grottenthaler, Christoph R. Werner, Christoph P. Berg.

Writing – review & editing: Julia M. Grottenthaler, Christoph R. Werner, Martina Steurer, Ulrich Spengler, Thomas Berg, Cornelius Engelmann, Heiner Wedemeyer, Thomas von Hahn, Wolfgang Stremmel, Anita Pathil, Ulrich Seybold, Eckart Schott, Usha Blessin, Christoph Sarrazin, Martin-Walter Welker, Ellen Harrer, Stefan Scholten, Clemens Hinterleitner, Ulrich M. Lauer, Nisar P. Malek, Christoph P. Berg.

References

1. Platt L, Easterbrook P, Gower E, McDonald B, Sabin K, McGowan C, et al. Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. *The Lancet Infectious diseases*. 2016; 16(7):797–808. [https://doi.org/10.1016/S1473-3099\(15\)00485-5](https://doi.org/10.1016/S1473-3099(15)00485-5) PMID: 26922272.
2. Koziel MJ, Peters MG. Viral hepatitis in HIV infection. *The New England journal of medicine*. 2007; 356(14):1445–54. <https://doi.org/10.1056/NEJMra065142> PMID: 17409326.
3. European Association for the Study of the Liver. Electronic address eee. EASL Recommendations on Treatment of Hepatitis C 2016. *Journal of hepatology*. 2017; 66(1):153–94. <https://doi.org/10.1016/j.jhep.2016.09.001> PMID: 27667367.

4. Werner CR, Schwarz JM, Egetemeyr DP, Beck R, Malek NP, Lauer UM, et al. Second-generation direct-acting-antiviral hepatitis C virus treatment: Efficacy, safety, and predictors of SVR12. *World journal of gastroenterology*. 2016; 22(35):8050–9. <https://doi.org/10.3748/wjg.v22.i35.8050> PMID: [27672299](https://pubmed.ncbi.nlm.nih.gov/27672299/).
5. Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *The New England journal of medicine*. 2014; 370(16):1483–93. <https://doi.org/10.1056/NEJMoa1316366> PMID: [24725238](https://pubmed.ncbi.nlm.nih.gov/24725238/).
6. Feld JJ, Jacobson IM, Hezode C, Asselah T, Ruane PJ, Gruener N, et al. Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection. *The New England journal of medicine*. 2015; 373(27):2599–607. <https://doi.org/10.1056/NEJMoa1512610> PMID: [26571066](https://pubmed.ncbi.nlm.nih.gov/26571066/).
7. Ferenci P, Bernstein D, Lalezari J, Cohen D, Luo Y, Cooper C, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. *The New England journal of medicine*. 2014; 370(21):1983–92. <https://doi.org/10.1056/NEJMoa1402338> PMID: [24795200](https://pubmed.ncbi.nlm.nih.gov/24795200/).
8. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *The New England journal of medicine*. 2014; 370(3):211–21. <https://doi.org/10.1056/NEJMoa1306218> PMID: [24428467](https://pubmed.ncbi.nlm.nih.gov/24428467/).
9. Del Bello D, Ita Nagy F, Hand J, Khedemi R, Lecluse-Barth J, Dieterich D, et al. Direct-acting antiviral-based therapy for chronic hepatitis C virus in HIV-infected patients. *Current opinion in HIV and AIDS*. 2015; 10(5):337–47.
10. Sulkowski MS, Eron JJ, Wyles D, Trinh R, Lalezari J, Wang C, et al. Ombitasvir, paritaprevir co-dosed with ritonavir, dasabuvir, and ribavirin for hepatitis C in patients co-infected with HIV-1: a randomized trial. *Jama*. 2015; 313(12):1223–31. <https://doi.org/10.1001/jama.2015.1328> PMID: [25706092](https://pubmed.ncbi.nlm.nih.gov/25706092/).
11. Rockstroh JK, Nelson M, Katlama C, Lalezari J, Mallolas J, Bloch M, et al. Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a non-randomised, open-label trial. *The lancet HIV*. 2015; 2(8):e319–27. [https://doi.org/10.1016/S2352-3018\(15\)00114-9](https://doi.org/10.1016/S2352-3018(15)00114-9) PMID: [26423374](https://pubmed.ncbi.nlm.nih.gov/26423374/).
12. Naggie S, Cooper C, Saag M, Workowski K, Ruane P, Towner WJ, et al. Ledipasvir and Sofosbuvir for HCV in Patients Coinfected with HIV-1. *The New England journal of medicine*. 2015; 373(8):705–13. <https://doi.org/10.1056/NEJMoa1501315> PMID: [26196665](https://pubmed.ncbi.nlm.nih.gov/26196665/).
13. Wyles DL, Ruane PJ, Sulkowski MS, Dieterich D, Luetkemeyer A, Morgan TR, et al. Daclatasvir plus Sofosbuvir for HCV in Patients Coinfected with HIV-1. *The New England journal of medicine*. 2015; 373(8):714–25. <https://doi.org/10.1056/NEJMoa1503153> PMID: [26196502](https://pubmed.ncbi.nlm.nih.gov/26196502/).
14. Luetkemeyer AF, McDonald C, Ramgopal M, Noviello S, Bhole R, Ackerman P. 12 Weeks of Daclatasvir in Combination With Sofosbuvir for HIV-HCV Coinfection (ALLY-2 Study): Efficacy and Safety by HIV Combination Antiretroviral Regimens. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 2016; 62(12):1489–96. <https://doi.org/10.1093/cid/ciw163> PMID: [27025835](https://pubmed.ncbi.nlm.nih.gov/27025835/).
15. El-Sherif O, Khoo S, Solas C. Key drug-drug interactions with direct-acting antiviral in HIV-HCV coinfection. *Current opinion in HIV and AIDS*. 2015; 10(5):348–54.
16. Martinello M, Dore GJ, Skurowski J, Bopage RI, Finlayson R, Baker D, et al. Antiretroviral Use in the CEASE Cohort Study and Implications for Direct-Acting Antiviral Therapy in Human Immunodeficiency Virus/Hepatitis C Virus Coinfection. *Open forum infectious diseases*. 2016; 3(2):ofw105. Epub 2016/07/16. <https://doi.org/10.1093/ofid/ofw105> PMID: [27419177](https://pubmed.ncbi.nlm.nih.gov/27419177/)
17. Foster GR, Irving WL, Cheung MC, Walker AJ, Hudson BE, Verma S, et al. Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. *Journal of hepatology*. 2016; 64(6):1224–31. <https://doi.org/10.1016/j.jhep.2016.01.029> PMID: [26829205](https://pubmed.ncbi.nlm.nih.gov/26829205/).
18. Reddy KR, Bourliere M, Sulkowski M, Omata M, Zeuzem S, Feld JJ, et al. Ledipasvir and sofosbuvir in patients with genotype 1 hepatitis C virus infection and compensated cirrhosis: An integrated safety and efficacy analysis. *Hepatology*. 2015; 62(1):79–86. <https://doi.org/10.1002/hep.27826> PMID: [25846144](https://pubmed.ncbi.nlm.nih.gov/25846144/).
19. Bourliere M, Bronowicki JP, de Ledinghen V, Hezode C, Zoulim F, Mathurin P, et al. Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS). *The Lancet Infectious diseases*. 2015; 15(4):397–404. [https://doi.org/10.1016/S1473-3099\(15\)70050-2](https://doi.org/10.1016/S1473-3099(15)70050-2) PMID: [25773757](https://pubmed.ncbi.nlm.nih.gov/25773757/).
20. Feld JJ, Moreno C, Trinh R, Tam E, Bourgeois S, Horsmans Y, et al. Sustained virologic response of 100% in HCV genotype 1b patients with cirrhosis receiving ombitasvir/paritaprevir/r and dasabuvir for 12 weeks. *Journal of hepatology*. 2016; 64(2):301–7. <https://doi.org/10.1016/j.jhep.2015.10.005> PMID: [26476290](https://pubmed.ncbi.nlm.nih.gov/26476290/).
21. Lawitz E, Gane E, Pearlman B, Tam E, Ghesquiere W, Guyader D, et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without

- ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. *Lancet*. 2015; 385(9973):1075–86. [https://doi.org/10.1016/S0140-6736\(14\)61795-5](https://doi.org/10.1016/S0140-6736(14)61795-5) PMID: 25467591.
22. Poordad F, Schiff ER, Vierling JM, Landis C, Fontana RJ, Yang R, et al. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. *Hepatology*. 2016; 63(5):1493–505. <https://doi.org/10.1002/hep.28446> PMID: 26754432.
 23. Sulkowski M, Hezode C, Gerstoft J, Vierling JM, Mallolas J, Pol S, et al. Efficacy and safety of 8 weeks versus 12 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin in patients with hepatitis C virus genotype 1 mono-infection and HIV/hepatitis C virus co-infection (C-WORTHY): a randomised, open-label phase 2 trial. *Lancet*. 2015; 385(9973):1087–97. [https://doi.org/10.1016/S0140-6736\(14\)61793-1](https://doi.org/10.1016/S0140-6736(14)61793-1) PMID: 25467560.
 24. Zopf S, Kremer AE, Neurath MF, Siebler J. Advances in hepatitis C therapy: What is the current state—what come's next? *World journal of hepatology*. 2016; 8(3):139–47. <https://doi.org/10.4254/wjh.v8.i3.139> PMID: 26839638.
 25. Righi E, Londero A, Carnelutti A, Bacarani U, Bassetti M. Impact of new treatment options for hepatitis C virus infection in liver transplantation. *World journal of gastroenterology*. 2015; 21(38):10760–75. <https://doi.org/10.3748/wjg.v21.i38.10760> PMID: 26478668.
 26. Charlton M, Everson GT, Flamm SL, Kumar P, Landis C, Brown RS Jr., et al. Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease. *Gastroenterology*. 2015; 149(3):649–59. <https://doi.org/10.1053/j.gastro.2015.05.010> PMID: 25985734.
 27. Manns M, Samuel D, Gane EJ, Mutimer D, McCaughan G, Buti M, et al. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multi-centre, open-label, randomised, phase 2 trial. *The Lancet Infectious diseases*. 2016; 16(6):685–97. [https://doi.org/10.1016/S1473-3099\(16\)00052-9](https://doi.org/10.1016/S1473-3099(16)00052-9) PMID: 26907736.
 28. Charlton M, Gane E, Manns MP, Brown RS Jr., Curry MP, Kwo PY, et al. Sofosbuvir and ribavirin for treatment of compensated recurrent hepatitis C virus infection after liver transplantation. *Gastroenterology*. 2015; 148(1):108–17. <https://doi.org/10.1053/j.gastro.2014.10.001> PMID: 25304641.
 29. Forns X, Charlton M, Denning J, McHutchison JG, Symonds WT, Brainard D, et al. Sofosbuvir compassionate use program for patients with severe recurrent hepatitis C after liver transplantation. *Hepatology*. 2015; 61(5):1485–94. <https://doi.org/10.1002/hep.27681> PMID: 25557906.
 30. Ciesek S, Proske V, Otto B, Pischke S, Costa R, Luthgehetmann M, et al. Efficacy and safety of sofosbuvir/ledipasvir for the treatment of patients with hepatitis C virus re-infection after liver transplantation. *Transplant infectious disease: an official journal of the Transplantation Society*. 2016; 18(3):326–32. <https://doi.org/10.1111/tid.12524> PMID: 26988272.
 31. Coilly A, Fougereou-Leurent C, de Ledinghen V, Houssel-Debry P, Duvoux C, Di Martino V, et al. Multi-centre experience using daclatasvir and sofosbuvir to treat hepatitis C recurrence—The ANRS CUPILT study. *Journal of hepatology*. 2016; 65(4):711–8. <https://doi.org/10.1016/j.jhep.2016.05.039> PMID: 27262758.
 32. Curry MP, O'Leary JG, Bzowej N, Muir AJ, Korenblat KM, Fenkel JM, et al. Sofosbuvir and Velpatasvir for HCV in Patients with Decompensated Cirrhosis. *The New England journal of medicine*. 2015; 373(27):2618–28. <https://doi.org/10.1056/NEJMoa1512614> PMID: 26569658.
 33. Belli LS, Berenguer M, Cortesi PA, Strazzabosco M, Rockenschaub SR, Martini S, et al. Delisting of liver transplant candidates with chronic hepatitis C after viral eradication: A European study. *Journal of hepatology*. 2016; 65(3):524–31. <https://doi.org/10.1016/j.jhep.2016.05.010> PMID: 27212241.
 34. Bunchorntavakul C, Reddy KR. Treat chronic hepatitis C virus infection in decompensated cirrhosis—pre- or post-liver transplantation? the ironic conundrum in the era of effective and well-tolerated therapy. *Journal of viral hepatitis*. 2016; 23(6):408–18. <https://doi.org/10.1111/jvh.12534> PMID: 27018088.
 35. van der Meer AJ, Berenguer M. Reversion of disease manifestations after HCV eradication. *Journal of hepatology*. 2016; 65(1 Suppl):S95–S108. <https://doi.org/10.1016/j.jhep.2016.07.039> PMID: 27641991.
 36. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Annals of internal medicine*. 2009; 150(9):604–12. PMID: 19414839.
 37. Guaraldi G, Rossotti R, Verucchi G, Tavio M, Pasulo L, Beghetto B, et al. Successful Pre- and Post-transplant Sofosbuvir-Based Anti-Hepatitis C Virus Treatment in Persons Living With Human Immunodeficiency Virus Infection. *Open forum infectious diseases*. 2017; 4(2):ofx065. <https://doi.org/10.1093/ofid/ofx065> PMID: 28584851.
 38. Grant JL, Hawkins C, Brooks H, Palella FJ Jr., Koppe SW, Abecassis MM, et al. Successful sofosbuvir-based therapy in HIV/hepatitis C virus coinfecting liver transplant recipients with recurrent hepatitis C virus infection. *Aids*. 2016; 30(1):93–8.

39. Castells L, Llaneras J, Campos-Varela I, Bilbao I, Crespo M, Len O, et al. Sofosbuvir and daclatasvir in mono- and HIV-coinfected patients with recurrent hepatitis C after liver transplant. *Annals of hepatology*. 2017; 16(1):86–93. <https://doi.org/10.5604/16652681.1226819> PMID: 28051797.
40. Borentain P, Colson P, Dhiver C, Gregoire E, Hardwigsen J, Botta-Fridlund D, et al. Successful treatment with sofosbuvir of fibrosing cholestatic hepatitis C after liver transplantation in an HIV-HCV-coinfected patient. *Antiviral therapy*. 2015; 20(3):353–6. <https://doi.org/10.3851/IMP2841> PMID: 25105441.
41. Araiz JJ, Serrano MT, Garcia-Gil FA, Lacruz EM, Lorente S, Sanchez JI, et al. Intention-to-treat survival analysis of hepatitis C virus/human immunodeficiency virus coinfecting liver transplant: Is it the waiting list? *Liver transplantation: official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society*. 2016; 22(9):1186–96. <https://doi.org/10.1002/lt.24474> PMID: 27114030.
42. Martel-Laferriere V, Michel A, Schaefer S, Bindal S, Bichoupan K, Branch AD, et al. Clinical characteristics of human immunodeficiency virus patients being referred for liver transplant evaluation: a descriptive cohort study. *Transplant infectious disease: an official journal of the Transplantation Society*. 2015; 17(4):527–35. <https://doi.org/10.1111/tid.12395> PMID: 25929731.
43. Mindikoglu AL, Regev A, Magder LS. Impact of human immunodeficiency virus on survival after liver transplantation: analysis of United Network for Organ Sharing database. *Transplantation*. 2008; 85(3):359–68. <https://doi.org/10.1097/TP.0b013e3181605fda> PMID: 18301332.
44. Locke JE, Durand C, Reed RD, MacLennan PA, Mehta S, Massie A, et al. Long-term Outcomes After Liver Transplantation Among Human Immunodeficiency Virus-Infected Recipients. *Transplantation*. 2016; 100(1):141–6.