

ELITA consensus statements on the use of DAAs in liver transplant candidates and recipients

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Summary

The advent of safe and highly effective direct-acting antiviral agents (DAAs) has had huge implications for the hepatitis C virus (HCV) transplant field, and changed our management of both patients on the waiting list and those with HCV graft re-infection after liver transplantation (LT). When treating HCV infection before LT, HCV re-infection of the graft can be prevented in nearly all patients. In addition, some candidates show a remarkable clinical improvement and may be delisted.

Alternatively, HCV infection can be treated post-LT either soon after the transplant, taking advantage of the removal of the infected native liver, or at the time of disease recurrence, as was carried out in the past. In either case, some DAAs have a limited use because of their drug to drug interactions with various immunosuppressants as well as the many other drugs liver transplant recipients are often prescribed. In addition, some DAAs should be avoided in case of severe renal failure, which is not an unusual complication after LT.

The present document provides a series of consensus statements on the LT issues that have not been extensively addressed previously. These statements have been developed to support physicians and other stakeholders in charge of LT candidates and recipients when deciding to treat HCV, especially in difficult situations.

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Introduction

Chronic hepatitis C virus (HCV) infection related advanced liver disease is the most common indication for liver transplantation (LT), which accounts for about 10% to 50% of LTs performed in Northern and Southern Europe, respectively (www.ELTR.org). Until very recently, all HCV recipients who underwent LT had detectable viremia. Virtually all of them had HCV re-infection shortly after transplant. Between 10% to 30% developed cirrhosis within 5 years from LT and 40% presented signs of liver decompensation within 1 year from the diagnosis of recurrent cirrhosis.¹⁻³ The combination of pegylated interferon (PegIFN) and ribavirin (RBV) has been the only therapeutic option available for the last 20 years but it was rarely effective, particularly in patients with more advanced graft hepatitis. Due to the high risk of severe disease recurrence, re-transplantation was controversial because of the risk of HCV-induced graft failure. These fac-

tors clarify why HCV infected recipients had a reduced survival rate by at least 10% after 5 years of follow-up, compared to non-HCV infected individuals.⁴

The advent of safe and highly effective direct-acting antiviral agents (DAA) has had huge implications for the HCV transplant field, and changed the management of both patients on the waiting list and those with HCV graft re-infection after LT. When treating HCV infection before LT, some candidates show a remarkable clinical improvement and may be delisted. If not, HCV re-infection of the graft may be prevented in nearly all patients when a HCV RNA negative status is achieved by DAAs at least 4 weeks before transplantation (>95%).

Alternatively, HCV infection can be treated post-LT either soon after the transplant, taking advantage of the removal of the infected native liver, or at the time of disease recurrence, carried out in the past. In

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either case, some DAAs have a limited use due to their drug to drug interactions (DDI) with various immunosuppressants (IS), as well as the many other drugs often prescribed to liver transplant recipients. In addition, some DAAs should be avoided in cases of severe renal failure, which is not an unusual complication after LT.

Finally, anti-HCV positive donors with favourable histological features are likely to become an important additional resource for the donor pool, particularly in areas where anti-HCV positive donors are more prevalent. The potential recipients of these grafts should be selected beforehand and treated after LT.

In the middle of this therapeutic revolution, two monothematic European Liver and Intestine Transplant Association (ELITA) conferences were held in Milan in March 2015 and April 2016, where a selected number of European experts discussed the many unsolved issues regarding the use of DAAs before and after LT. The present document provides the conclusions of these conferences, which are presented as the ELITA statements.

Methods

These “Consensus statements” were elaborated following a slightly modified Appraisal of Guidelines for Research & Evaluation methodology.⁵ In brief, the promoter of this initiative was ELITA, whose governing body selected a scientific board of experts in charge of organizing the two conferences held in Milan and of writing this document. The two conferences were endorsed by the Italian Association for the study of the Liver (AISF) and by the European Association for the Study of the Liver (EASL). The scientific board defined the methodology used as well as the goals, and acted as developer and reviewer. The methodology chosen involved the following steps:

- The scientific board selected 13 topics of interest and relevant questions regarding both clinical practice and controversial areas.
- The scientific board also identified two working groups. The first addressed the issues related to “the management of the patient on the waiting list”, the second “the treatment of post-transplant HCV disease recurrence”. The two working groups were composed of five experts guided by a group leader. The members of the two working groups were selected based on competence, role, expertise and publications/research in the field of HCV and LT.
- The two group leaders together with the scientific board elaborated the provisional statements. All questions and provisional statements were circulated among the experts of each working group before the conferences

Table 1. GRADE system used in the EASL Clinical Practice Guidelines.

Grade evidence	
I	Randomized controlled trials
II-1	Controlled trials without randomization
II-2	Cohort or case-control analytic studies
II-3	Multiple time series, uncontrolled experiments
III	Opinions of respected authorities

were held in Milan. This policy allowed each expert to independently carry out a systematic literature search, using Medline/PubMed to support definitions and statements.

- The statements were discussed among the experts of the two working groups during two conferences held in Milan on 6th March 2015 and April 1st 2016, to improve the quality of the statements. The two conferences were videoed and all relevant comments were considered when preparing the final document.
- The scientific board prepared a draft of the “Consensus statements”, which incorporated the conclusions of the two Milan conferences, as well as the relevant data from existing publications and presentations at international meetings up to April 2016. For each of the 13 issues, a short background and a summary of the evidence was presented. The evidence and recommendations were graded according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system⁵ (Table 1).
- The first draft of the Consensus statements was eventually submitted to the experts of the working groups for corrections, comments and approval of the recommendations. Following a Delphi process, the experts were asked to specify whether they approved each recommendation and, if not, to justify their disagreement. Corrections and comments were considered in the final version of the Consensus statements. Agreement among experts was very high (96%).
- The promoter, and all members of the scientific board and working groups were asked to declare any potential conflict of interests.

The questions selected by the scientific board are listed below:

Pre-transplant phase

- Which DAAs should be used in patients with cirrhosis listed for LT?
- Which treatment schedules should be used in listed patients, and what are the expected sustained virological responses (SVR)?
- What is the impact of pre-LT DAAs on liver function and delisting?

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- Patients listed for decompensated cirrhosis (without hepatocellular carcinoma [HCC]): who should be treated or not treated before LT?
- Patients listed for HCC: who should be treated or not treated before LT?
- Is DAA therapy given across LT (“bridging therapy”) a valuable option?
- How should patients who fail DAA treatment be managed, and when is detection of resistance associated substitutions (RAS) a concern?

Post-transplant phase

- Which DAAs should be used after LT? The role of liver function, renal function and DDI.
- What rate of SVR is expected after treating patients for HCV disease recurrence?
- What is the best timing for DAA treatment after LT?
- Can HCV therapy be expected to have a beneficial impact on extra-hepatic manifestations of HCV?
- Is re-transplantation of HCV infected recipients a reliable option under DAA therapy?
- Can HCV positive donors be used more extensively?

Consensus statements

Which DAAs should be used in cirrhotic patients listed for LT?

Background. DAAs should be used with caution in LT candidates with severely impaired liver function (Child-Pugh B and C) or with severe renal dysfunction (estimated glomerular filtration rate [eGFR] <30 ml/min) as both conditions may affect the metabolism of some DAAs.

Facts.

- Impairment of liver function affects the exposure of various DAAs which is typically measured by the area under the curve (AUC) (Table 2). Simeprevir (SIM): AUC increased by 2.5-fold in Child-Pugh B and 5.2-fold in Child-Pugh C. Paritaprevir/r (ABT 450/r): AUC increased by almost tenfold in Child-Pugh C. Dasabuvir: AUC increased by 4-fold in Child-Pugh C but not in Child-Pugh B. Sofosbuvir (SOF): AUC increased by 2-fold both in Child-Pugh B and C. Grazoprevir (GZR): AUC increased by 2- to 3-fold in Child-Pugh B while there are no data to date for Child-Pugh C. Ledipasvir (LDV) and velpatasvir (VEL): AUC not affected by reduced liver function.
- Impairment of renal function impacts mainly the kinetics of the inactive metabolite of sofosbuvir, SOF007, which accumulates when the eGFR is below 60 ml/min (Table 2). In absence

of sufficient safety data, the SOF summary of product characteristics (SmPC) warns against its use if eGFR is below 30 ml/min.

- Some DAAs share transport and metabolic pathways with several other drugs, including calcineurin, mTOR inhibitors and anti-retrovirals, which can cause strong DDI. The potential risk of DDI should be carefully considered before deciding the most appropriate DAA regimen.
- In patients with decompensated cirrhosis, RBV can be started at 600 mg daily and subsequently adjusted, depending on tolerance. The dose of RBV should be lowered by 200 mg decrements if the haemoglobin level drops below 10 g/dl. RBV administration should be stopped if the haemoglobin levels drops below 8.5 g/dl.

Recommendations – pre-transplant phase

- SOF, LDV, velpatasvir (VEL) and daclatasvir (DCV) can be used in patients with cirrhosis with no need for dose adjustment, regardless of liver impairment. GRADE I
Comment: A note of caution is suggested when using DAAs in patients with severe liver disease (Child-Pugh C or model for end-stage liver disease (MELD) >20) because of limited data.
- The 3D combination (Paritaprevir/r, ombitasvir, dasabuvir) and the 2D combination (Paritaprevir/r, ombitasvir) should not be used in patients with decompensated cirrhosis (Child-Pugh B and C). SIM is not recommended in patients with moderate hepatic impairment (Child-Pugh B) and should be avoided in patients with Child-Pugh C cirrhosis. GRADE I.
The 3D, 2D combination, SIM and GZR/elbasvir (EBR) can be safely used only in patients with compensated cirrhosis (Child-Pugh A). GRADE II-2.
- In cases of pre-LT eGFR below 30 ml/min, SOF should be preferably planned after LT. GRADE III.
- DDI between a specific DAA and any other co-administered drug, should be carefully evaluated when planning any antiviral regimen. GRADE III.
Comment: Possible DDI should be checked on international websites (www.hepcdruginteractions.com) or discussed with a clinical pharmacologist.

Which treatment schedules are recommended for listed patients and what are the expected SVR?

Background. According to the guidelines released by EASL and American Association for the Study of Liver Diseases (AASLD),⁶⁻⁸ different DAA regimens result in very high SVR rates even in patients with decompensated cirrhosis. Currently, many of these patients are treated while on the waiting list for LT, although it is not entirely clear how many of

Table 2. Exposure of DAAs in cases of (A) liver function impairment or (B) kidney function impairment.

A				
Liver impairment (AUC fold-effect)				
	Mild^d	Moderate^e	Severe^e	Dosing guidelines (EMA)
Simeprevir		↑ 2.44	↑ 5.22	OLYSIO is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh class B or C)
Sofosbuvir		↑ 2.26	2.43	No dose adjustment is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, or C).
GS331007		(1.18 ^{***})	(1.09 ^{**})	
Ledipasvir	No adjustment	No adjustment	↔	No dose adjustment. Treatment with Harvoni should be guided by an assessment of the potential benefits and risks for the individual patient
Paritaprevir/r	↓ 0.52	↑ 1.62	↑ 10.23	Viekirax ± Exviera is not recommended in patients with moderate hepatic impairment (Child-Pugh B) and is contraindicated in patients with severe hepatic impairment (Child-Pugh C)
Ombitasvir	0.92	0.70	0.45	
Dasabuvir	1.17	0.84	4.19	No dose adjustment for Child-Pugh class A or B. Lower SVR rates were observed with Child-Pugh class C compared with Child-Pugh class A or B in ALLY-1, thus treatment for 24 weeks is recommended (EASL guidelines)
Daclatasvir	↓ 0.57	↓ 0.62 unbound	↓ 0.64 unbound	
Velpatasvir		↔	↔	No dose adjustment of Epclusa is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, or C). Safety and efficacy of Epclusa have been assessed in patients with Child-Pugh class B cirrhosis, but not in patients with Child-Pugh class C cirrhosis
Grazoprevir	↑ 1.66	↑ 4.82	↑ 11.68	No dose adjustment of ZEPATIER is required in patients with mild hepatic impairment (Child-Pugh A). ZEPATIER is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C)
Elbasvir	↓ 0.61	↓ 0.72	↓ 0.88	
B				
Renal impairment (AUC fold-effect)				
	Mild (eGFR 60–90^{***})	Moderate (eGFR 30–60^{***})	Severe (eGFR <30)	Haemodialysis
Simeprevir			↑1.62	n.d.
Sofosbuvir (GS331007)	↑1.61 ^{***} (↑1.55) ^{***}	↑2.07 ^{***} (↑1.88) ^{***}	↑2.71 ^{***} (↑5.51) ^{***}	↑1.28, 1.60 ^{**} (↑13.8, 21.7) ^{**}
Ledipasvir			↔	n.d.
Paritaprevir/r	↑1.19	↑1.33	↑1.45	n.d.
Ombitasvir	↔	↔	↔	n.d.
Dasabuvir	↑1.21	↑1.37	↑1.50	n.d.
Daclatasvir	↑1.18	↑1.39	↑1.51	↑1.27
Velpatasvir			↑1.50	n.d.
Grazoprevir			↑1.65	↔
Elbasvir			↑1.86	↔

↔, not modified; n.d., not determined.

^d Typically, Mild = CPT A, Moderate = CPT B, Severe = CPT C.^{**} Cmax reduced ↔.^{***} eGFR: Mild: typically in the range 50 or 60 ml/min to 80 or 90. Moderate: typically in the range 30 to 50 or 60 ml/min. Severe: <30 ml/min

Table 3. DAA treatments in patients with decompensated cirrhosis.

	Afdhal ¹⁰	Charlton ¹¹	Manns ¹²	Foster ¹³	Poordad ¹⁵	Curry ¹⁴
Patients, N	50	108	160	467	60	267
Therapy	SOF + R	SOF/LDV + rR	SOF/LDV + R	SOF/LDV + R SOF + DVC + R	SOF + DCV + R	SOF/VPV ± R
Treatment duration	48 wk	12 wk (53 patients) 24 wk (55 patients)	12 wk (78 patients) 24 wk (82 patients)	12 wk	12 wk	12 wk (180 patients) 24 wk (87 patients)
Child-Pugh A, N of patients	18	0	0	112	12	16
Child-Pugh B, N of patients	32	59	78	309	32	240
Child-Pugh C, N of patients		49	82	46	16	11
MELD	>15:4 patients		>15:41 patients	Mean (range) 11.9 (6–36)	>15:14 patients	>15:13 patients
Treatment-experienced %	80%		78%	47.1%	60%	80%
Genotype 1a-1b, %	38–30%		47.5–42.5%	GT1 50.3%	57–18%	78%
Genotype 2-3-4, %	32%		GT4: 10%	Other: 49.7%	8–17%	22%
SVR12, %						
Child-Pugh A, %	78%	88%	85–88%	SOF/LDV: 80%	92%	SOF/VPV: 83%
Child-Pugh B-C, %	68%			SOF + DCV: 74%	94–56%	SOF/VPV + RBV: 94%

them will achieve viral eradication post-LT. To date, this issue has been addressed by a single study,⁹ which enrolled patients with compensated cirrhosis who were treated with a single DAA (SOF) in combination with RBV.

Facts. Many studies have explored the efficacy of DAAs in terms of SVR in patients with various degrees of clinical decompensation (Table 3). Afdhal *et al.*¹⁰ found that the combination of SOF/RBV for 48 weeks given to 50 patients with Child-Pugh A or B cirrhosis and genotype 1 or 4 HCV, was associated with a 72% SVR overall (78% in Child-Pugh A and 68% in Child-Pugh B).

In the SOLAR 1 study,¹¹ the combination of SOF/LDV + RBV (600 mg, increased as tolerated) given to 108 patients with decompensated cirrhosis and infected with genotype 1 or 4 HCV, resulted in SVR12 rates between 85 and 89%, irrespective of Child-Pugh class (B or C) and of treatment duration (12 or 24 weeks). In the SOLAR 2 study,¹² the same combination of SOF/LDV + RBV (600 mg, increased as tolerated) given to 160 patients with cirrhosis for 12 or 24 weeks resulted in an SVR12 of 87–96% in Child-Pugh B patients and 72–80% in Child-Pugh C. The UK early access programme,¹³ which included 467 patients with Child-Pugh B or C cirrhosis, reported an overall SVR12 in 80% and 74% of patients treated with SOF/LDV ± RBV or SOF/DCV ± RBV (600 mg, increased as tolerated) for 12 weeks, respectively. Finally, the combination of SOF/VEL + RBV (1000–1200 mg) for 12 weeks in patients with decompensated cirrhosis (mainly Child-Pugh B), resulted in an 85% SVR rate, which was superior to the 50% SVR rate achieved by combining SOF/VEL without RBV for 12 weeks or 24 weeks.¹⁴

Looking at specific genotypes, the SVR12 was 80% in patients with HCV genotype 1 or 4, with slightly higher SVR12 rates when RBV was added. For patients infected with HCV genotype 3, the

SVR12 was approximately 60% in those treated with SOF/LDV, and 70% of those treated with SOF/DCV.¹³

The combination SOF + DCV + RBV (600 mg) for 12 weeks was also assessed in 113 pre- and post-LT patients with cirrhosis (any genotype) in the Ally1 study,¹⁵ which showed SVR12 rates of 92% in patients with Child-Pugh A cirrhosis, 94% (30/32) in Child-Pugh B and 56% (9/16) in Child-Pugh C. Finally, another study of 55 patients with genotype 1 HCV treated with SOF + SIM showed a SVR4 rate of 75%.¹⁶

In patients with HIV co-infection, efficacy and tolerability of DAA treatments was similar to that observed in HCV mono-infected patients.^{17,18}

The effects of DAAs given pre-LT on post-LT recurrence were explored in a single study by Curry *et al.*⁹ who treated 61 HCC patients with Child-Pugh A cirrhosis using SOF/RBV. All patients were infected with genotypes 1 or 4 and were treated for either 48 weeks or until LT. The “on treatment” response was very high (93% had HCV RNA less than the lower level of quantification (LLOQ) at week 4) and post-LT SVR12 was achieved in 70% of treated patients. In the same study, a “post hoc” analysis showed a dramatic post-LT SVR12 of 96% in the subgroup of 29 patients that had remained HCV RNA negative for at least 30 days before LT. Indeed, of the 29 patients who had HCV RNA below LLOQ for at least 30 days, only one (3%) suffered HCV recurrence after LT compared to 9 out of 14 patients (64%) of those who had HCV RNA below LLOQ for less than 30 days. These results suggest that the removal of the infected liver, once a viral clearance of at least 1 month duration has been achieved, is adequate for preventing HCV recurrence after LT, and it indicates that achievement of SVR is not a mandatory endpoint for all listed patients. To date, this is the only study addressing virologic response profiles or the kinetics required to prevent post-LT HCV recurrence.

Recommendations – pre-transplant phase

5. DAA therapy can be considered in patients who are listed for LT; virological response after DAA therapy is very high (around 90%) in patients with compensated cirrhosis (Child-Pugh A) and high (around 80%) in patients with decompensated cirrhosis (Child-Pugh B-C) and is not influenced by HIV co-infection. GRADE I.
6. The duration of DAA treatment should be as short as possible and DAA combinations achieving a SVR in 12 weeks should be preferred. GRADE III.
7. A serum HCV RNA negative status (LLOQ) for at least 1 month before LT seems to be a reliable virologic endpoint if prevention of HCV recurrence is the main treatment goal. Nevertheless, LT should not be postponed because of short ongoing pre-LT DAA therapy; if an organ becomes available, transplant should be carried out. GRADE III.
Comment: To date, this virologic endpoint has only been verified in patients with Child-Pugh A cirrhosis and therefore needs to be confirmed in patients with decompensated cirrhosis.
8. First line treatment options for listed patients according to specific genotypes are the following: Genotype 1/4: SOF/LDV + RBV (600 mg, increased as tolerated) or SOF + DCV + RBV for 12 weeks irrespective of liver function (Child-Pugh A, B and C). SOF/VEL without RBV for 12 weeks in patients with Child-Pugh A cirrhosis and with RBV (1,000–1,200 mg) in patients with Child-Pugh B and C. If patients do not tolerate RBV, the duration of SOF/VEL should be extended up to LT or to a maximum of 24 weeks. Other options for patients with Child-Pugh A cirrhosis and genotype 1 HCV are: SOF + SIM + RBV (600 mg, increased as tolerated) or 2D + RBV (600 mg, increased as tolerated) for 12 weeks or GZR/EBR for 12 weeks in patients with HCV G1b, or GZR/EBR + RBV for 16 weeks in patients with HCV G1a. Finally, in patients with Child-Pugh A cirrhosis and genotype 4 HCV, 3D with (600 mg increased as tolerated) or without RBV for 24 weeks are equally valuable options. GRADE I.
Genotype 2: SOF + DCV for 12 weeks or SOF/VEL for 12 weeks are the preferred regimen for any listed patient infected with genotype 2 due to its short duration. In patients with Child-Pugh B or C, RBV should be added. GRADE I.
Genotype 3: SOF/VEL + RBV (1,000–1,200 mg) for 12 weeks (Child-Pugh A, B) or SOF + DCV + RBV 1,000–1,200 mg for 12 weeks irrespective of liver function (Child-Pugh A, B and C). If patients do not tolerate RBV the duration of treatment of SOF/VEL or SOF + DCV can be extended up to LT or to a maximum of 24 weeks. GRADE II-2.

Genotype 5–6: The same regimens with SOF/VEL, SOF/LDV or SOF + DCV suggested for genotype 1 or 4 should be used for genotypes 5 and 6 although data are limited. GRADE II-1.

9. In HIV co-infected patients, the treatment options are identical to HCV mono-infected patients, provided that DDI with concurrent antiretroviral therapy are taken into account. GRADE II-2.

What is the impact of DAAs on liver function and de-listing?

Background. Up to one-third of patients with hepatitis B virus (HBV) and decompensated cirrhosis treated with nucleos(t)ides drugs while listed for LT, can be eventually delisted within 1 year due to clinical improvement. Once delisted, they maintain their clinical improvement for up to 5 years.¹⁹ A critical issue is therefore to determine whether DAA treatment can also achieve comparable results in HCV candidates with decompensated cirrhosis. The advantages of delisting HCV candidates are twofold: for the patient – as they no longer need a liver transplant, and for the donor pool – as demand for organs can be reduced.

Facts. Changes in liver function after DAA therapy given to patients with decompensated cirrhosis have been investigated in a limited number of studies,^{11–16} only two of which did not pool the pre- and post-transplant data together.^{12,16}

In the SOLAR 1 study,¹¹ the combination of SOF/LDV + RBV was given for 12 or 24 weeks to 108 patients with decompensated cirrhosis and with genotype 1 or 4 infection. A decrease in Child-Pugh score of at least two points from baseline to post-treatment week 4 was observed in about 40% of the patients. This result was not influenced by the length of the treatment. These findings were also confirmed by the SOLAR 2 study.¹²

In the ALLY 1 study,¹⁵ 48 patients with decompensated cirrhosis (32 Child-Pugh B and 16 Child-Pugh C) were treated with SOF + DCV + RBV for 12 weeks. All 48 patients but one had a MELD <25. Six of the 30 patients with Child-Pugh B cirrhosis (20%) showed a decrease greater than three points in MELD at SVR12. Among the 14 patients with Child-Pugh C cirrhosis, a similar rate of improvement was observed in three cases (3/14, 21%). The study did not consider possible predictors of improvement nor the possibility of delisting. Virtually no patients with MELD score >25 were considered eligible for DAA treatment in either study.

A study from France²⁰ explored delisting due to clinical improvement in 77 patients with decompensated cirrhosis from 18 centres. Patients were treated with various combinations of DAAs (SOF + DCV or LDV or SMV with or without RBV) for 12 or 24 weeks. Twelve patients (16%) were delisted due to clinical improvement. A similar delisting rate

(18%) was reported in another study from Spain, where 20 patients of the 110 treated with various combination of DAAs were delisted.²¹ A third European study promoted by ELITA²² found that 21 of 103 (20.4%) patients with decompensated cirrhosis could be delisted due to clinical improvement after a median period of 60 weeks. The probability of being delisted was very high in patients with a MELD <16 (about 35%) and minimal in those with a MELD >20 (about 5%). All delisted patients had either a complete regression or a dramatic improvement in signs of hepatic decompensation, such as ascites and/or hepatic encephalopathy. Improvement of the MELD score by at least three points and of albumin by at least 0.5 g/dl after 12 weeks of DAA, are useful independent dynamic predictors of inactivation on the waiting list (Fig. 1) and subsequent delisting. Despite these favourable results, caution is required for the following two reasons: 1) In candidates with high MELD score, a MELD decrease that is not sufficient for delisting may be a disadvantage for the patient who loses priority on the waiting list (MELD purgatory). 2) No data are available on how long clinical improvement will last and how many patients will develop HCC after delisting. However, a decrease of 2 to 3 MELD points may be beneficial for the LT candidate by reducing the risk of mortality on the waiting list, particularly in those with a medium/high MELD score and/or a prolonged waiting time.

Recommendations – pre-transplant phase

10. Patients with decompensated cirrhosis and a MELD score <20 on the LT waiting list should be considered for DAA therapy because around 20% of them will improve their liver function to the extent that they can be delisted. GRADE II-3.
Comment: The benefit of delisting would be twofold, for the patients themselves and for others on the LT waiting list, as demand for available organs may be reduced.
11. A minimal treatment period of 3 months should be considered before inactivation and delisting. The probability of being delisted due to clinical improvement depends not only on the MELD score before starting DAA therapy, but also on MELD score and albumin improvements after 12 weeks of therapy (details are given in recommendations 14 to 18). GRADE II-3.
12. In patients with high MELD scores (>20) and expected prolonged waiting time, the risk of a MELD purgatory effect should be balanced against the benefit of reducing the risk of death on the waiting list associated with MELD reduction. GRADE II-3

Comment: Caution is required concerning possible side effects in patients with very advanced disease (MELD >20) because experience in treating these patients using DAAs is very limited.

Patients listed for decompensated cirrhosis (without HCC): Who should be treated or not treated before LT?

Background. To establish whether pre-LT DAA therapy is justified, the following factors should be considered:

- The risk of death on the waiting list, which is proportional to the MELD score.
- The possibility of clinical improvement after DAA treatment, which may favour the delisting of some patients, typically those with low MELD scores.
- The awareness that a mild improvement in MELD score after DAA may not be enough for delisting and may work as a disadvantage for patients that lose priority on the waiting list. This MELD purgatory effect is typically observed in patients with high MELD scores.
- Cost-effectiveness considerations.
- Potential side effects as some case series show liver failure during DAA ± RBV.
- Local epidemiology and HCV positive donor policies Fig. 1.

Being aware of these factors will limit futile DAA treatment.

Facts. A significant decrease in either Child-Pugh or MELD score has been reported in 20% to 40% of patients with decompensated cirrhosis treated with DAAs. However, this improvement may not be sufficient for delisting, particularly in Child-Pugh C patients with high MELD scores, where the MELD purgatory effect is likely to be the highest. Factors associated with liver function improvement and further delisting while on treatment have been discussed above (question 3, facts).

Recommendations – pre-transplant phase

13. Patients with baseline MELD <16 (typically Child-Pugh B) have a high chance (35%) of being delisted because of clinical improvement and therefore should be treated while listed. GRADE II-3.
Comment: Currently, the follow-up of delisted patients is very short, therefore caution is needed regarding how long the clinical improvement will last and how many patients will develop HCC.
14. Patients with baseline MELD scores between 16 and 20 (mostly Child-Pugh C):
 - These patients have a chance of being delisted due to clinical improvement of about 12%. They should be started on DAAs while listed and the

- possible clinical improvement should be assessed after 12 weeks of therapy. GRADE II-3.
- Patients showing a significant improvement of MELD score >3 points and albumin >0.5 g/dl after 12 weeks on DAAs should be maintained on the waiting list but in inactive position, and considered for possible delisting during the follow-up.
 - Patients without a significant improvement in MELD and albumin after 12 weeks on DAAs should be maintained in active position on the waiting list. GRADE II-3.
15. Patients with baseline MELD between 21 and 25 (typically advanced Child-Pugh C):
- A minority of these patients, specifically those with acute-on-chronic liver failure, may undergo a substantial clinical improvement after DAA treatment which makes inactivation on the waiting list possible. For these patients, a case-by-case multidisciplinary decision is advised. GRADE II-3.
- Comment: Since a limited MELD improvement may hamper access to LT, patients should be maintained with their baseline MELD as assessed before DAA therapy, to counteract MELD purgatory. Such an exception should only be implemented after agreement with the Organizations for Organ Procurement. In addition, these candidates might benefit from receiving a graft from a suitable anti-HCV positive donor.
16. Patients with high MELD scores >25 :
- Based on current studies and practice, pre-LT DAA treatment of these candidates is not recommended because of their poor prognosis, significant risk of death pre- or post-LT, unknown probability of improvement, potential DAA toxicity and rapid access to LT. The option of post-LT treatment with DAAs is therefore preferable. GRADE III.
- Comment: In addition, these candidates might benefit from receiving a graft from a suitable anti-HCV positive donor.

Patients listed for HCC: Who should be treated or not before LT?

Background. Patients listed for HCC frequently have compensated liver cirrhosis and therefore can easily tolerate DAA treatment administered to prevent HCV recurrence after LT. This is particularly relevant in countries where old donors are preferentially given to HCC patients with relatively preserved liver function.

Facts. The 1-year rate of removal from the liver transplant waiting list due to tumour progression is estimated to be up to 10% in centres following the “Milan criteria”, and up to 20% in those following the “extended criteria”. Similarly, the risk of dying of HCC recurrence after LT is up to 10% in cen-

tres adopting the Milan criteria, and up to 20% in those adopting the extended criteria. The response to therapeutic interventions for HCC while the patient is on the waiting list further affects prognosis either pre- or post-LT. These competing risks should be considered to avoid futile DAA treatment (Fig. 1).

This scenario is further complicated by the recent alert regarding a possible increased risk of HCC recurrence in patients who cleared HCV with DAAs after achieving a complete HCC eradication following resection or local ablation. As the available data are conflicting, properly designed studies are urgently needed to address this issue.^{23–26}

Recommendations – pre-transplant phase

17. In patients listed for HCC, pre-LT treatment should be restricted to those with the following features: a) A low risk of post-transplant HCC recurrence, whatever model is used to assess the risk (i.e. Milan criteria, alpha-fetoprotein model or other predictive models of recurrence at listing). b) no signs of HCC progression while on HCC bridging therapy and c) a waiting time >3 months is expected. GRADE III.
- Comment: A decision-making algorithm is proposed in Fig. 1.
18. In patients with HCC not treated with DAAs before LT, the decision and timing of DAA therapy after LT should be deferred until after pathological assessment of the explanted liver. If the risk of HCC recurrence at explant pathology is high, delaying HCV treatment beyond the 2nd year post-LT is advised, unless severe HCV recurrence occurs. GRADE III.
- Comment: In addition, these candidates might benefit from receiving a graft from a suitable anti-HCV positive donor.

Is DAA therapy given across LT (“bridging therapy”) a valuable option?

Background. In patients with stable clinical conditions, the full course of antiviral therapy can be generally completed before LT. Nevertheless, some patients may develop an acute complication that leads to a rapid deterioration of their liver function. Such patients may require an urgent LT and therefore this option should be considered in patients who are still viremic at the time of LT or who have not achieved viral clearance for at least 30 days.

Facts. A single study from Italy²⁷ has recently shown that this strategy is feasible and very effective. Thirty-one patients have been treated with SOF/RBV across transplant for up to 48 weeks and an SVR was achieved in 96% of the patients, without major side effects. No data are yet available with more recent DAA combinations.

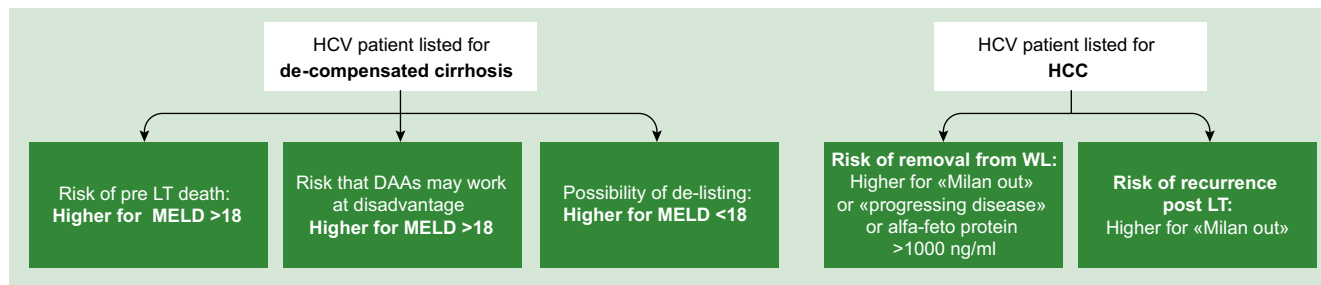


Fig. 1. Patients listed for decompensated cirrhosis or HCC. Factors to be taken into account in the decision-making process before DAA treatment.

Recommendations – pre-transplant phase

- 19. Bridging therapy cannot be recommended on a routine basis. GRADE III.
- 20. In cases of unexpected rapid deterioration of liver function while on DAA therapy, continuation of therapy across transplant can be considered, particularly in patients who are still viremic. Nevertheless, the decision for continuing DAA treatment across transplant should be considered on a case-by-case basis, taking into account liver graft function, postoperative renal function and DDI. GRADE II-3.

Table 4. Drug-drug interactions between HCV DAAs and immunosuppressants.

	SOF	SOF/LDV	SOF/VPV	3D	GZR/EBR	DCV	SIM
Aza							
CsA							
Etanercept							
Everolimus							
Mycophenolate							
Sirolimus							
Tacrolimus							

White: No clinically significant interaction expected.
 Light grey: Potential interaction that may require a dosage adjustment.
 Dark grey: These drugs should not be co-administered.
 SOF, sofosbuvir; LDV, ledipasvir; VEL, velpatasvir; 3D, paritaprevir/r, ombitasvir, dasabuvir; GZR, grazoprevir; EBR, elbasvir; DCV, daclatasvir; SIM, simeprevir; Aza, azathioprine; CsA, cyclosporine A.

How should patients who fail DAA treatment be managed, and when is detection of resistance associated substitutions (RAS) a concern?

Background. Failure to respond to DAA treatment is mainly due to relapse; on treatment virologic breakthrough is rare. Failure to respond to multiple DAA regimens occurs more frequently in genotype 1a patients with cirrhosis, genotype 3 treatment experienced patients with cirrhosis, and in patients receiving shorter duration or RBV-free schedules. Most failures are related to the presence of various proportions of HCV-RAS. A treatment duration that is too short or the absence of RBV are possible relevant cofactors. A cut-off detection rate of RAS of at least 15% seems to correlate with treatment failure. NS3/4A resistance variants tend to disappear after treatment discontinuation. In contrast, NS5A RAS can affect treatment response in certain settings and these variants may persist for many years.²⁸ The development of NS5B RAS is rare and these variants may also disappear over time.

Facts. No standardized test kits for the resistance of HCV to approved drugs are available for purchase. Thus far, resistance testing relies on in-house techniques with variable performances. HCV drug resistance testing is not recommended in naïve patients who are not candidates for LT, as SVR is independent from the presence of NS3/4A or NS5A RAS at baseline. To date, HCV resistance testing at baseline is only recommended in the US SmPC for GZR/EBR when treating patients infected with genotype 1a. In addition, resistance testing may be useful for

choosing the best treatment option in cirrhotic patients infected with genotype 3 who fail multiple DAAs.^{29,14} If resistance testing is not available for such patients, extending treatment and adding RBV is advisable.

Recommendations – pre-transplant phase

- 21. Assessment of RAS can be considered in situations where their presence is likely to influence treatment choice and outcome. This is the case for patients with decompensated cirrhosis and infected with genotype 3, and patients infected with subtype 1a under GZR/EBR treatment; the presence of RAS justifies a longer duration of treatment or the addition of RBV. Patients with RAS that do not tolerate RBV should be treated after LT. GRADE III.
- 22. For patients with decompensated cirrhosis who failed DAA therapy while on the waiting list, it is advisable to retreat these patients after LT. HCV resistance testing is useful for deciding retreatment GRADE III.

Post-transplant phase

Which DAAs should be used after LT? The role of liver function, renal function and DDI

Background. The recipient of a liver transplant should take life-long IS and many other drugs to

Review

treat various co-morbidities such as diabetes mellitus, hypertension, dyslipidemia etc.³⁰ All these drugs must be checked for possible DDI with DAA. Renal dysfunction is another common problem after LT,³¹ which limits the use of SOF.

Facts. DDI with IS: The main DDI between DAA and IS are shown in Table 4 and are also summarized in the EASL Recommendations on Treatment of Hepatitis C 2016.⁶ SOF + DCV, SOF/LDV have no significant DDIs with any IS and antimetabolites. However, potential interactions with everolimus may require additional monitoring. No data are available regarding possible interactions between SOF/VEL and major IS. Regimens containing protease inhibitors such as 2D and 3D combinations strongly interact with all major IS. SIM strongly affects the metabolism of cyclosporine A (CsA) and, to a lesser extent, of tacrolimus (Tac) and mTOR inhibitors through CYP3A4 inhibition but it has no effect on mycophenolate mofetil (MMF) metabolism. A 40%-50% increase in Tac levels is to be expected during co-administration with GZR, while a 15-fold increase in GZR AUC and a 2-fold increase in EBR AUC is expected if co-administered with cyclosporin.⁸ The combination of SOF/LDV has minor interactions with CsA, Tac and mTOR inhibitors.⁶ In addition to DDI, DAA-related HCV clearance can accelerate the metabolism of various IS¹¹ by improving the metabolic functions of the liver.

Possible DDI between DAA and other frequently prescribed drugs^{6,32} should be considered, particularly when antifungal agents, cardiovascular drugs, statins and central nervous system (CNS) drugs are administered simultaneously.

Renal function impairment: Renal dysfunction is frequent after LT either due to early postoperative complications such as acute tubular necrosis or as a result of long-term exposure to calcineurin inhibitors (CNI). HCV-related kidney injury, diabetes and hypertension are other possible factors impairing kidney function. This is why the majority of LT recipients present a 30% GFR decline after one year from LT and a 15%-20% prevalence of severe renal impairment (eGFR <30 ml/min) after 5 years.³³

Recommendations – post-transplant phase

23. SOF + DCV, SOF/VEL can be given safely in combination with any IS. Since SOF/LDV moderately affects CNI/mTOR metabolism, the blood levels of IS should be monitored. SIM, GZR and EBR should not be co-administered with CsA. Monitoring blood levels is required when SIM, GZR and EBR are combined with Tac or mTOR inhibitors. 2D and 3D combinations require monitoring of all major IS. Therefore, SOF + DCV or SOF/LDV should be the preferred regimens after LT due to no or minimal DDI. GRADE II-2.

24. Any other drug co-administered with DAAs after LT should be checked for possible DDI, such as antifungal agents, antibiotics, cardiovascular drugs, CNS drugs, recreational drugs and even hormonal treatments. Given the frequent occurrence of arrhythmia after LT, close attention should be paid to patients treated with DAAs. Amiodarone should be avoided as per recent recommendations.⁶ GRADE II-2.
25. SOF requires dose adjustment when the eGFR is below 30 ml/min. Although no firm recommendation can be made on the extent of the dose adjustment,⁶ SOF administration every other day is currently used with an acceptable risk/benefit ratio. Although tolerability and efficacy of GZR/EBR are satisfactory in patients with renal insufficiency, their use is not recommended after LT due to major DDI with many IS. This is also true for the 3D combination. GRADE II-3.
26. The issue of an increased risk of rejection following HCV clearance is of concern but needs to be evaluated in properly designed studies. In the meantime, close monitoring of CNI/mTOR is recommended, particularly at the end of DAA therapy when the cessation of DDIs and the improved metabolic capacity of the liver may alter the exposure to various IS.¹¹ GRADE III.

What rate of sustained virological response is expected after treating patients for HCV disease recurrence?

Background. The natural course of HCV infection is significantly accelerated in LT recipients when compared to immunocompetent individuals, with 15% to 30% of the patients progressing to cirrhosis within 5 years after LT, and approximately 50% developing liver failure shortly thereafter. A subset of patients (2-9%) may develop fibrosing cholestatic hepatitis (FCH), which is defined by progressive cholestasis, very high HCV RNA levels, hepatocyte ballooning and rapid progression to graft failure.¹⁻³ The management of HCV recurrence has been a challenge in the era of IFN-based therapies due to the combined effect of limited efficacy, risk of rejection³⁴ and high toxicity of IFN. This sequence of events explains why HCV positive recipients had a 10% reduced graft and patient survival when compared to other indications for LT. However, IFN-induced SVR significantly improved outcomes after LT, resulting in 5-year survival rates similar to those for HCV-negative patients.³⁵ As the new DAAs are much more effective and far better tolerated than IFN-based regimens, the outcome of LT for HCV recipients is expected to improve and become similar to that of patients with non-HCV indications.

Facts. HCV recurrence: Considering patients with HCV recurrence after LT, the virological response to DAA has been assessed in 14 studies^{11,12,14,36-46}

dealing mainly with experienced genotype 1 patients. Results from the main studies are summarized in Table 5 and 6, which separate patients according to severity of liver disease, type of DAA regimen and HCV genotypes.

Compensated cirrhosis: In patients with mild fibrosis stages and compensated cirrhosis (Child-Pugh A) (Table 5), SVR was achieved in more than 90% of patients, with a good safety profile. In the SOLAR 1 study,¹¹ the combination of SOF/LDV + RBV (1,000–1,200 mg) given to patients with genotype 1 or 4 infection, resulted in SVR12 rates higher than 90%, irrespective of treatment duration (12 or 24 weeks). Similar excellent SVRs of about 90% have been reported with SOF + SIM³⁹ in patients infected with genotype 1, 2 or 4 but not in those infected with genotype 3, where the SVR was only 60%. The 3D combination³⁷ was equally effective only when administered to patients without cirrhosis. Finally, SOF + DCV was very effective in all patients except those with decompensated cirrhosis.¹⁴ In patients not eligible for RBV, the optimal duration of treatment is unknown but SOF/LDV for 24 weeks in genotype 1 and 4 patients seems to be a reasonable option post-LT.⁸ Although RBV has been associated in most DAA regimens after LT, its use may be problematic because of renal impairment. Indeed, in a recent study focusing on treatment of HCV infection after kidney transplantation, SOF/LDV for 12 or 24 weeks in genotype 1/4 without RBV resulted in SVR rates of 96 to 100% indicating that excellent results can also be achieved in immunosuppressed patients without RBV.⁴⁷

Decompensated cirrhosis: In patients with decompensated cirrhosis after LT, the SVR rates were 10% to 30% lower than what is generally observed in patients without decompensation^{11,12,43} (Table 6). Interestingly, although an SVR rate of around 85% in Child-Pugh B has been reported in the SOLAR 1 study,¹¹ this result was not confirmed in the SOLAR 2 study where post-LT SVR was 95% and 100% in patients treated for 12 and 24 weeks respectively.¹² An improvement in MELD and Child-Pugh scores has been reported in 50%–60% of patients after treatment with different DAA combinations, such as SOF + DCV, DCV + SIM⁴⁶ or SOF/LDV + RBV (600 mg increased as tolerated).^{11,12} On average, the improvement was of two points for Child-Pugh score and three points for MELD score.

Fibrosing cholestatic hepatitis: In the French multicentre cohort CUPILT,⁴⁵ SVR12 rates of 88% and 100% were obtained in patients with strictly defined severe forms of FCH treated with SOF + RBV or SOF + DCV ± RBV (600 mg increased as tolerated) for 24 weeks. There was no graft loss at the end of follow-up and a significant improvement in liver graft function was constantly observed. Studies based on smaller numbers of patients with FCH confirmed these excellent results in patients with FCH treated with SOF/LDV + RBV for 12 or

24 weeks^{11,12} (Table 2, post-LT). An improvement in MELD and Child-Pugh scores has also been reported in patients with FCH after treatment with SOF + DCV or DCV + SIM.⁴¹

SVR according to genotypes

Genotype 1a: When SOF + SIM is given to patients with advanced fibrosis (F3–F4) the expected SVR rate is about 80% (Table 5), which is at least 10% lower than that observed in patients infected with genotype 1b with or without advanced fibrosis.^{39,41,42}

Genotype 3: For patients without cirrhosis, the combination SOF + DCV ± RBV (1,000–1,200 mg/die) resulted in excellent results, with SVR of about 90%.¹⁵ For patients with cirrhosis, the optimal DAA combination and duration are still to be defined. The promising SVR rate of 85% obtained with SOF/VEL + RBV¹⁴ given to immunocompetent patients with decompensated cirrhosis needs to be verified in the transplant setting.

Recommendations – post-transplant phase

27. Early treatment of FCH with SOF + DCV + RBV RBV (600 mg, increased as tolerated) for 24 weeks or SOF/LDV + RBV RBV (600 mg, increased as tolerated) for 12 weeks is recommended. GRADE II-1.
SOF + VEL might be an alternative option, but no published data are available to date. GRADE III.
28. LT recipients with genotype 1/4, infection can be treated in the same way as non-transplant patients in terms of combinations of DAA and duration of treatment. SOF/LDV ± RBV or SOF + DCV for 12 weeks are recommended. The same combinations should be used for 24 weeks in patients not eligible to RBV. If the 3D combination is considered, careful monitoring of CNI trough levels is advised, as strong DDI are expected. GRADE II-1.
29. LT recipients with genotype 1a HCV and advanced fibrosis (F3–F4) should not be treated with SOF + SIM because of lower SVR rates (~10%) compared to other DAA combinations. GRADE II-2.
30. LT recipients with genotype 3 HCV infection without cirrhosis or with compensated cirrhosis, should be treated with SOF + DCV + RBV for 12 weeks or with SOF + DCV without RBV for 24 weeks in case of ineligibility to RBV. GRADE II-1.
The combination of SOF/VEL ± RBV for 12 weeks should be tested urgently in the LT setting. GRADE III.
IFN is not recommended post-LT to limit the risk of IFN-induced rejection. GRADE III.
31. Renal function impairment and frequent use of drugs at risk of DDI (www.hepcdruginterac-

Table 5. DAA treatment for HCV recurrence after liver transplantation in patients with mild fibrosis and compensated cirrhosis.

	Charlton ³⁸	Gutierrez ³⁹	Faisal ⁴⁰	Brown ⁴¹	Pungpagong ⁴²	Kwo CORAL-1 ³⁷	Poordad Ally-1 ¹⁵	Charlton Solar 1 ¹¹	Manns Solar 2 ¹²
Patients (n)	40	61	120	151	123	34	53	162	168
Therapy	SOF + RBV: 24 wk	SOF/SIM ± RBV: 12 wk	SOF + SIM ± RBV: 12 wk or SOF/RBV 24 wk or SOF/LED: 12 to 24 wk	SOF + SIM ± RBV (21% starting dose 800 mg): 12 wk	SOF + SIM ± RBV: 12 wk	3D combination + RBV: 24 wk	SOF + DCV + RBV: 12 wk	SOF/LED + RBV: 12 vs. 24 wk	SOF/LED + RBV: 12 vs. 24 wk
GT1-4/2-3	83% (GT1a: 55%-GT1b: 28%)-3%/15%	All GT1 1a:57% 1b: 43%	GT1: 83%	All patients GT1 GT1a: 56.3% GT1b: 26.9%	All GT1 GT1a: 60% G1b: 35%	GT1a 85% GT1b	GT1: 77% GT1a: 58% GT1b: 19% GT3: 21% GT6: 2%	GT1: 99% G1a: 70% G1b: 29%	GT1: 87% 1a: 49% 1b: 38% GT4: 13%
Treatment-experienced	88%	69%	82%	56.3%	82%	71%	58%	82%	81.5%
F3/F4	62%	38%	48%	64.2% (F4)	30%	0	55%	29.6% (F4)	40% (F4)
SVR 12	70%	93.4%	85%	88%	90%	97%	94%	97%	97%
Overall								Similar between 12 vs. 24 wk	
GT1	GT1a: 73% GT1b: 55%	GT1a: 89% GT1b: 100%	GT1a: 83% GT1b: 100%	GT1a 85% GT1b: 94%	GT1a: 86% GT1b: 95% (n.s.)	GT1a: 97% GT1b: 100% (n.s.)	GT1: 95% GT1a: 97% GT1b 90% (n.s.)	n.a.	GT1: 97%
GT3/4	100%/-	n.a.	100%	n.a.		n.a.	91%/-	n.a.	-/95%
F0-F2/F3-F4	n.a.		91%/81%	93%/86%	93% vs. 81%; <i>p</i> = 0.05	n.a.	n.a.	Similar SVR	97%/97%
GT1aF3-4	n.a.	67%		82%	71% (vs. 93%)	n.a.	n.a.	n.a.	n.a.
Relapse/breakthrough	30%/-	Higher among GT1a F3/4	6%/0.8%	7%/0.6%	6.5%/2.4%	3%/-	n.a.	1.2%/0	
SAE	5%; anemia 20%	Low	Severe anemia 13%	11.9%	1.6%	6%	0%	15%	

DCV, daclatasvir; GT, genotype; LED, ledispavir; n.a., not applicable; n.s., not significant; RBV, ribavirin; SAE, serious adverse event; SOF, sofosbuvir; SIM, simeprevir.

Table 6. DAA treatments for severe HCV recurrence after liver transplantation in patients with decompensated cirrhosis and fibrosing cholestatic hepatitis.

	Fibrosing cholestatic hepatitis			Decompensated cirrhosis		
	Forns ^{§43}	Charlton and Manns SOLAR 1 and 2 ^{11,12}	Leroy (CUPILT) ⁴⁵	Fontana ^{*46}	Charlton SOLAR 1 ¹¹	Manns SOLAR 2 ¹²
Patients (n)	52	11	22	97	61	53
Therapy	SOF + RBV or SOF + RBV + PegIFN 24 wk	SOF + LEDI + RBV 12 vs. 24 wk	SOF + RBV ± PegIFN or SOF/DAC 24 wk	DCV + SOF ± RBV (n = 77); DCV/SIM ± RBV (n = 18) 24 wk	SOF/LED + RBV 12 vs. 24 wk	SOF/LED + RBV 12 vs. 24 wk
GT1-4/2-3	GT1: 86% GT1a: 42% GT1b: 44% GT2/3: 4% GT4: 10%	All GT1 GT1a: 82% GT1b: 18%		GT 1: 93% GT1a: 39% G1b: 47% GT3: 2% GT4: 4%	GT1 98.6% G1a 74% G1b 24.6% G4: 1.4%	GT1: 85.6% 1a: 49% 1b: 39.6% GT4: 11.4%
Treatment-experienced	n.a.	82%		55% before LT 37% after LT	85%	83%
Child-Pugh B/C	n.a.	n.a.	n.a.	31%/12% Cholestatic pattern: 37%	85%/15%	85%/15%
SVR 12	73%	100%	88% vs. 100% SOF/RBV vs. SOF + DCV + RBV	87% DCV + SOF vs. DCV + SIM 91% vs. 72% (p = 0.047) RBV + vs. RBV- n.s.	83.6% 12 vs. 24 wk 80% vs. 86.6%	92.4% 12 vs. 24 wk 88% vs. 93.1%
Overall		Similar SVR in wk 12 and wk 24				
GT1	n.a.	GT1a: 100% GT1b: 100%		n.a.	n.a.	GT1: 93.6%
GT3/4	n.a.	n.a.			n.a.	-/83.3%**
Child-Pugh B/C	n.a.	n.a.	n.a.	n.a. Cholestatic vs. non cholestatic 86% vs. 87%; p >0.99	86.5% vs. 66.6%*	97.7% vs. 62.5% [‡]
GT1a F3-4	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Relapse/breakthrough	8%/-	0/0		2%/5% (All with DCV + SIM)	6.5%/0	1.8%/-
SAE	2% drug discontinuation due to SAE. Death 13%.	27% No study drug discontinuation.		20% Two SAE possibly related to DAA. No drug interruption.	No SAE leading to study drug discontinuation.	26%
Improvement of liver function	Decrease in bilirubin from 4.7 to 0.7 mg/dl. Median of 8 MELD points improvement.	Normalization of INR, bilirubin and albumin on post-treatment wk 4.	100% Normalization of LFT in the CUPILT study.	Average Child-Pugh/MELD improvement: 1/2.3 patients. % of Child-Pugh/MELD deterioration: 13%/17%.	% of Child-Pugh/MELD improvement: 59%/45%. Average Child-Pugh/MELD improvement: 2.2/3.3pt. % of Child-Pugh/MELD deterioration: 7%/18% (only in Child-Pugh B). Decrease in bilirubin by 0.5 & 1.5 mg/dl, in Child-Pugh B and Child-Pugh C, respectively, increase in albumin by 0.5 g/dl.	% of Child-Pugh/MELD improvement: 77%/60%. Average Child-Pugh/MELD improvement: 1.8/3.5pt. % of Child-Pugh/MELD deterioration: 2.5%/23%.

DCV, daclatasvir; GT, genotype; LED, ledispavir; n.a., not applicable; n.s., not significant; pt, points; PegIFN, pegylated interferon; RBV, ribavirin; SAE, serious adverse event; SOF, sofosbuvir; SIM, simeprevir; SVR, sustained virological response.

[§] Early severe recurrent hepatitis.

* 43% CP B/C, 37% cholestatic pattern on cirrhosis.

** Only six genotype 4 patients.

[‡] Only eight Child-Pugh C patients.

tions.com) may limit the use of some DAAs in the post-LT phase. DAA regimens should therefore be used for LT patients, as described in recommendations 23 to 25. GRADE II-2.

What is the best timing for DAA treatment after LT?

Background. In patients with active HCV replication before LT, post-transplant HCV recurrence is rapid and virtually universal. HCV RNA can be detected as early as a few hours post-transplant⁴⁸ and HCV graft re-infection subsequently leads to symptomatic HCV hepatitis between 1 and 4 months post-LT, with variable clinical patterns. Two different approaches can be considered to overcome the deleterious consequences of HCV recurrence post-LT:

- Very early or early DAA treatment, before biochemical manifestations of HCV recurrence develop *i.e.* pre-emptive therapy.
- Later treatment initiated in response to biochemical and histopathological evidence of HCV recurrence, *i.e.* clinically oriented treatment.

In the IFN/RBV era, pre-emptive therapy was found to be ineffective and difficult to manage,⁴⁹ because of severe hematological side effects and risk of rejection in the early post-LT period. Pre-emptive treatment has therefore never been adopted as the standard of care. Treatment of patients with histologically-proven HCV recurrence and minimal fibrosis (stage F1-F2 in the METAVIR scoring system) was the norm.^{50,51} Given the far better risk-benefit ratio of DAA therapy, those principles of management can be reconsidered.

Facts. Results from phase III studies show that excellent SVR rates >93% can be achieved with DAA therapy in patients with HCV-related chronic active hepatitis and Child-Pugh A cirrhosis or FCH post-transplant. SVR rates are lower in patients with decompensated cirrhosis (see above). Although very early DAA-based pre-emptive therapy may be an attractive option to manage HCV recurrence, no large data are currently available on the efficacy and safety of this approach. Of note, in the very early post-transplant phase, optimal use of DAAs may be hampered by reduced postoperative liver function, impaired renal function and DDI.

Recommendations – post-transplant phase

32. At present, pre-emptive DAA therapy cannot be recommended on a routine basis. Prospective studies generating data on the efficacy, safety, optimal dose, timing and duration of pre-emptive treatment should be encouraged to assess the benefit of DAA regimens in this setting. GRADE III.

33. DAA treatment of HCV recurrence should be considered in any LT recipient as early as clinically feasible, irrespective of fibrosis stage. The aim is to prevent progression to cirrhosis and to maximize SVR. Initiation of DAA therapy between 3 and 6 months post-LT is encouraged. GRADE III.

Can HCV therapy be expected to have a beneficial impact on extra hepatic manifestations of HCV?

Background. Active HCV replication after LT is involved in several extra hepatic manifestations. HCV is a well-established independent risk factor for post-LT renal function impairment,³³ insulin resistance and diabetes mellitus.⁵² HCV is also a major etiological factor for type 2 cryoglobulinemia post-LT⁵³ and a co-factor facilitating poly- or monoclonal B-cell proliferation.^{54,55} Diabetes mellitus and renal impairment are independent negative predictors of survival post-LT.^{33,56} Improved renal function after achieving SVR post-LT was observed in the IFN/RBV era.⁵⁷ In immunocompetent subjects, SVR has also been shown to reduce the risk of renal impairment and cardiovascular-related morbidity.⁵⁸

Facts. The impact of DAA on renal function and glucose metabolism post-LT has not yet been evaluated in phase III prospective clinical trials or in retrospective investigator-driven studies. So far, studies have focused on SVR, liver function and safety as the primary and secondary endpoints.

Recommendations – post-transplant phase

34. A beneficial effect of DAAs on extra hepatic manifestations of HCV post-LT is an attractive hypothesis that may contribute to improved long-term outcomes. The impact of DAA treatment on renal function and insulin resistance post-LT should be considered as secondary endpoints in forthcoming prospective clinical trials or observational studies. GRADE III.
35. DAA treatment should be considered on an individual basis in the event of post-LT renal dysfunction or insulin resistance, irrespective of liver disease. GRADE III.
36. In the case of post-LT symptomatic mixed cryoglobulinemia or HCV-associated malignant B-cell proliferation, DAA treatment should be used as in the non-transplant setting.⁶ GRADE III.

Is re-transplantation for HCV infected recipients a reliable option under DAA therapy?

Background. The use of re-transplantation for severe HCV recurrence with decompensated cirrhosis has been controversial due to poor results in patients with pronounced hyperbilirubinemia (>5 mg/dl), renal dysfunction or MELD score >28.^{59,60} The significant burden of re-transplantation is also a

consideration in LT programmes with a high prevalence of HCV-related primary liver transplants, such as in southern European countries or in the USA.

Facts. It is unknown how DAA therapies may impact the outcome of re-transplantation for severe HCV recurrence. The issue has not been addressed in any published clinical trials. Treatment of severe recurrence after primary LT has been reported to improve liver function,^{43–46} and may therefore reduce the need for re-transplantation. DAA therapies are likely to improve outcome because viral clearance can be achieved either before or after re-transplantation.

Recommendations – post-transplant phase

- 37. Outcome of re-transplantation due to HCV-related primary graft loss should be re-assessed in the DAA era by prospective, observational studies which specifically target this population. GRADE III.
- 38. Re-transplantation can be considered on a case-by-case basis, considering the intrinsic risks of re-transplantation and organ availability. GRADE III.

Can HCV positive donors be used more extensively?

Background. Depending on the geographical area, the prevalence of HCV among organ donors ranges from 1.4% to 5.5%^{61–63} and is two to threefold higher than in the general population. Due to variations in HCV replication in highly selected donors, transmission of HCV is not universal. It occurs in roughly 50% of recipients of a graft from a HCV positive donor. The use of HCV positive liver or kidney grafts in HCV positive recipients has been encouraged by health authorities on the grounds that 5-year liver^{63–65} or kidney graft function is similar to that observed with organs from HCV-negative donors. Yet HCV positive organs have remained under-used⁶⁶ because of a reluctance on the part of health care professionals. Caution was heightened in the IFN era because of poorer outcomes associated with HCV positive donors older than 50 years.⁶⁷ The possibility of recipients acquiring the donor HCV genotype was also of concern in the case of genotype 1/genotype 3 donor-recipient mismatching. The high pan genotypic efficacy of DAA regimens may render HCV positive liver grafts safer and may extend the use of such grafts even in HCV-negative recipients, enabling a substantial expansion of the donor pool. This debate has been recently opened in the kidney transplant community. The chair of the Ethics Committee of UNOS and the co-chair of the American Society of Transplant Surgeons have both recently argued in favour

of the use of HCV positive kidneys in HCV-negative recipients.⁶⁸

Facts. To date, DAAs have not been tested after LT in patients who have received a graft from an HCV positive donor. The risk/benefit ratio of engrafting HCV positive organs deserves re-assessment in both HCV positive and HCV-negative recipients. This may be particularly important in genotype 1 recipients receiving genotype 3 liver grafts, because of inferior SVR rates observed in genotype 3 before VEL becomes available. Using such grafts in candidates with previous SVR to anti-HCV therapy is also illogical and unethical, although the risk/benefit ratio of such a policy may again merit assessment in urgent situations.

Recommendations – post-transplant phase

- 39. Given the current under-use of HCV positive organs, clinical studies under the control of ethical authorities should be designed for both HCV positive and HCV-negative recipients. The aim would be to evaluate the impact of an anti-HCV positive donor on virological outcome, graft and patient survival. The impact on the donor pool should also be studied. (GRADE III).
- 40. In general, liver grafts from HCV positive donors should not be transplanted to HCV positive candidates in whom HCV has been previously eradicated before LT, for both ethical and cost-effectiveness reasons. GRADE III.
However, in case of rare urgent situations, when the risk of death outweighs the risk of using an HCV positive graft in a previously treated patient, a HCV positive organ may be considered, again after obtaining candidate's or relatives' informed consent. GRADE III.
- 41. In candidates with decompensated cirrhosis and medium MELD scores and in candidates with HCC in whom a long waiting time can be expected, treatment of HCV infection before LT should be balanced against the benefit of accelerated access to LT using an HCV positive liver graft. GRADE III.

Conclusions

Data accumulated over the last 3 years on the use of DAAs pre- and post-LT opened the door to considerable changes in the treatment of HCV infection in the liver transplantation field. ELITA therefore decided to compile this series of consensus statements, which focus primarily on very specific LT issues that had not been extensively addressed previously. These consensus statements are a starting point and will be updated regularly, because of the rapid changes in knowledge availability of new compounds. We are aware that some questions are

still waiting for an answer. For example: Will delisting due to clinical improvement be a safe and sustainable option? What is the risk of HCC in patients delisted after DAA treatment? What is the impact of DAA on extra hepatic manifestations of HCV? What will the impact of DAAs on re-transplantation be? Will DAAs allow a wider use of HCV positive grafts? How these guidelines apply to programs with a high proportion of living donor liver transplants?

ELITA is open to support multinational European initiatives to specifically address all these open questions.

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Conflict of interest

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Authors' contributions

LSB organized the ELITA monothematic conferences, manuscript writing, critical review for intellectual content and approval of the manu-

script. CD organized the ELITA monothematic conferences, manuscript writing, critical review for intellectual content and approval of the manuscript. TB expert at the 2 ELITA monothematic conferences, critical review for intellectual content and approval of the manuscript. MS expert at the 2 ELITA monothematic conferences, critical review for intellectual content and approval of the manuscript. SF expert at the 2 ELITA monothematic conferences, critical review for intellectual content and approval of the manuscript. SK expert at the 2 ELITA monothematic conferences, critical review for intellectual content and approval of the manuscript. GPP expert at the 2 ELITA monothematic conferences, critical review for intellectual content and approval of the manuscript. IC expert at the 2 ELITA monothematic conferences, critical review for intellectual content and approval of the manuscript. MP expert at the 2 ELITA monothematic conferences, critical review for intellectual content and approval of the manuscript. AC expert at the 2 ELITA monothematic conferences, critical review for intellectual content and approval of the manuscript. DS expert at the 2 ELITA monothematic conferences, critical review for intellectual content and approval of the manuscript. MB expert at the 2 ELITA monothematic conferences, critical review for intellectual content and approval of the manuscript. ELITA BOARD MEMBERS approval of the manuscript.

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Supplementary data

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