

Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis

Cheung, Michelle C M; Walker, Alex J; Hudson, Benjamin E; Verma, Suman; McLauchlan, John; Mutimer, David J; Brown, Ashley; Gelson, William T H; MacDonald, Douglas C; Agarwal, Kosh; Foster, Graham R; Irving, William L; HCV Research UK

DOI:

[10.1016/j.jhep.2016.06.019](https://doi.org/10.1016/j.jhep.2016.06.019)

License:

Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

Document Version

Peer reviewed version

Citation for published version (Harvard):

Cheung, MCM, Walker, AJ, Hudson, BE, Verma, S, McLauchlan, J, Mutimer, DJ, Brown, A, Gelson, WTH, MacDonald, DC, Agarwal, K, Foster, GR, Irving, WL & HCV Research UK 2016, 'Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis', *Journal of Hepatology*, vol. 65, no. 4, pp. 741–747. <https://doi.org/10.1016/j.jhep.2016.06.019>

[Link to publication on Research at Birmingham portal](#)

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

1
2
3
4 **Outcomes a year after successful direct acting antiviral therapy for patients with**
5
6 **chronic hepatitis C and decompensated cirrhosis**
7
8
9

10
11
12
13 Michelle CM Cheung
14

15
16 Alex J Walker
17

18
19
20 Benjamin E Hudson
21

22
23 Suman Verma
24

25
26 John McLauchlan
27

28
29 David J Mutimer
30

31
32 Ashley Brown
33

34
35 William TH Gelson
36

37
38 Douglas C MacDonald
39

40
41 Kosh Agarwal
42

43
44 Graham R Foster
45

46
47 William L Irving
48

49
50 HCV Research UK
51

1
2
3
4 **Author Affiliations**
5

6
7 MCM Cheung - Liver Unit, Blizard Insitute, Queen Mary University of London
8
9

10
11 AJ Walker - Faculty of Medicine & Health Sciences, University of Nottingham
12
13

14
15 BE Hudson - University Hospitals Bristol NHS Trust
16
17

18
19 S Verma - Institute of Liver Studies, King's College London
20
21

22
23 J McLauchlan - MRC-University of Glasgow Centre for Virus Research
24
25

26
27 DJ Mutimer – Centre for Liver Research and NIHR Biomedical Research Unit, Queen
28 Elizabeth Hospital, Birmingham
29

30
31 A Brown – Department of Hepatology, St Mary's Hospital, Imperial College London
32
33

34
35 WTH Gelson – Department of Hepatology, Cambridge University Hospitals NHS
36 Foundation Trust
37
38

39
40 DC MacDonald – UCL Institute for Liver and Digestive Health, University College
41 London
42
43

44
45 K Agarwal - Institute of Liver Studies, King's College London
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4 GR Foster (corresponding author)
5
6

7 Queen Mary University of London
8
9

10 4 Newark Street,
11
12

13
14 London E1 4AT
15
16

17 g.r.foster@qmul.ac.uk
18
19

20
21 Tel – 0207 882 7242 Fax 0207 882 2191
22
23

24
25
26
27 WL Irving
28
29

30
31 NIHR Nottingham Digestive Diseases Biomedical Research Unit
32
33

34 University of Nottingham
35
36

37 Nottingham NG7 2RD
38
39

40 Will.irving@nottingham.ac.uk
41
42

43
44 Tel – 0115 823 0752
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61

1
2
3
4 **Key words**
5

6
7 Hepatitis C virus, sofosbuvir, ledipasvir, daclatasvir, decompensated cirrhosis, MELD
8
9 score
10
11

12
13
14
15
16 **Abbreviations**
17

18
19
20 HCV - Hepatitis C virus
21

22
23 DAA – Direct acting antiviral
24

25
26 MELD – Model of End Stage Liver Disease
27

28
29
30 SVR - Sustained virological response
31

32
33 EAP - Expanded access programme
34

35
36 HCVRUK – Hepatitis C Research UK
37

38
39 Sof - Sofosbuvir
40

41
42 LDV - Ledipasvir
43

44
45 DCV - Daclatasvir
46

47
48 RBV - Ribavirin
49

50
51 OLT - orthotopic liver transplant
52

53
54 HCC - hepatocellular carcinoma
55

56
57 CI – confidence intervals
58

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Word count

Abstract - 250

Main manuscript (including Acknowledgements, Figure legends, References and Tables)

- 4715

Tables - 3

Figures - 3

1
2
3
4 **Conflict of interest**
5

6
7 Dr Cheung is funded by the National Institute for Health Research Doctoral Research
8 Fellowship
9

10
11
12 Dr Agarwal has received speaker and consultancy fees from AbbVie, Achillion, Astellas,
13 Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Merck, Novartis
14
15

16
17
18 Professor Foster has received speaker and consultancy fees from AbbVie, Achillion,
19 Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Idenix, Janssen, Merck, Novartis,
20 Roche, Springbank
21
22

23
24
25 Professor Irving has received speaker and consultancy fees from Roche Products,
26 Janssen Cilag and Novartis, educational grants from Boehringer Ingelheim, MSD and
27 Gilead Sciences, and research grant support from GlaxoSmithKline, Pfizer, Gilead
28 Sciences and Janssen Cilag
29
30
31
32
33
34
35
36
37
38
39
40

41 **Financial support**
42

43
44 NHS England; Medical Research Foundation (Grant reference C0365); Gilead; Bristol-
45 Myers Squibb
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61

1
2
3
4 **Authors' contributions**
5

6
7 The study was designed and led by GRF and WI. MC, BH, SV managed patients in the
8 study, collated the data and assisted in the analysis. MC and AW performed the data
9 and statistical analysis. WI and JM supervised sample collection, data management and
10 assisted with study design and implementation. DJM, AB, WG, DCM and KA led the
11 recruitment and data collection. All authors participated in data analysis and participated
12 in the preparation of the manuscript.
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4 **Abstract**
5

6
7 Direct-acting antivirals have become widely used for patients with chronic hepatitis C
8 virus infection with decompensated cirrhosis. Virological responses are excellent and
9 early improvements in liver function, at least in a proportion of patients, have been
10 observed but the longer term impact of viral clearance on end-stage liver disease
11 complications is unclear.
12
13
14
15
16
17
18

19
20 Methods: Prospective study of patients with decompensated cirrhosis who received 12
21 weeks of all-oral direct-acting antivirals through the English Expanded Access
22 Programme. Endpoints were deaths, liver transplantation, hepatocellular carcinoma,
23 serious decompensation events, sepsis or hospitalisations, and MELD scores between
24 start of therapy to 15 months post treatment start. An untreated cohort of patients was
25 retrospectively studied over 6 months for comparison.
26
27
28
29
30
31
32
33

34
35 Results: Amongst 317/406 patients who achieved sustained virological response at 24
36 weeks post-treatment, there were 9 deaths (3%), 17 new liver cancers (5%), 39
37 transplantations (12%) and 52 with serious decompensations (16%), over 15 months.
38
39
40
41
42
43

44 When compared to the first six months from treatment start and to untreated patients,
45 there was a reduction in incidence of decompensations [30/406 (7%) in months 6-15
46 and 72/406 (18%) in months 0-6 for treated patients vs 73/261 (28%) in untreated
47 patients]. There was no significant difference in liver cancer incidence (10/406 (2.5%) in
48 months 6-15 and 17/406 (4%) in months 0-6 for treated patients vs 11/261 (4%) in
49 untreated patients).
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4 Conclusions: This study suggests that antiviral therapy in patients with decompensated
5
6 cirrhosis led to prolonged improvement in liver function, with no evidence of paradoxical
7
8 adverse impact nor increase in liver malignancy.
9

10
11
12
13
14
15 **Lay summary**
16

17
18
19 This is a report of a large group of patients in England who have hepatitis C virus (HCV)
20
21 infection with advanced liver disease. They have been treated with new anti-HCV drugs,
22
23 which cured the infection in the majority. This study looks at their outcomes a year
24
25 following treatment, in terms of deaths, cancers and other complications of advanced
26
27 liver disease. We conclude that in most patients anti-HCV treatment is beneficial even in
28
29 advanced liver disease.
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4 **Introduction**
5

6
7 All-oral, interferon-free direct-acting antiviral (DAA) therapy for chronic hepatitis C virus
8 (HCV) infection has allowed successful treatment of patients with advanced liver
9
10 disease. Worldwide, large numbers of HCV-infected patients with decompensated
11
12 cirrhosis have received antiviral therapy and although sustained virological response
13
14 (SVR) rates are slightly reduced compared to patients with compensated disease, over
15
16 80% of treated patients still achieve viral clearance. Early analysis of patients who
17
18 responded to therapy showed associated improvements in MELD and Child Pugh
19
20 scores [1] [2-4], although some concerns have been expressed that the rate of
21
22 malignancy may not change or may, paradoxically, increase [5, 6]. Previous studies of
23
24 interferon-based therapies have demonstrated that HCV clearance improves liver
25
26 fibrosis, even in cirrhosis [7]. Moreover, patients who achieved SVR had reduced
27
28 mortality, complications of cirrhosis and hepatocellular carcinoma compared to
29
30 untreated patients or those who failed to achieve SVR [8-10]. However such studies
31
32 involved patients with relatively 'early' cirrhosis and it remains unclear whether these
33
34 long term benefits will be seen in patients treated for more advanced disease. Although
35
36 there is little data on long term outcomes, international guidelines recommend that
37
38 patients with decompensated cirrhosis should be urgently treated with interferon-free
39
40 DAA therapy, regardless of eligibility for liver transplantation [11, 12].
41
42
43
44
45
46
47
48
49
50

51
52 Chronic HCV infection is the main indication for liver transplantation in the Western
53
54 world, and universally recurs causing accelerated disease progression in the liver graft.
55
56 Given the shortage of donor organs and costs of liver transplantation, DAA treatment
57
58 may reduce the need for transplantation in patients with advanced cirrhosis and allow
59
60
61

1
2
3
4 alternative uses for scarce organs. Pooled analysis of over 800 patients with
5
6 decompensated cirrhosis showed that 60% of patients had an improvement in MELD
7
8 score from baseline following therapy, but 23% deteriorated, at post treatment weeks 4
9
10 to 12 [13]. The magnitude of improvement varied with a median of 2 MELD points. It is
11
12 unclear whether this early change is clinically meaningful. Perhaps more importantly,
13
14 minor reductions in MELD may adversely affect access to liver transplantation, if a
15
16 patient no longer meets transplant criteria but is insufficiently improved with a reduced
17
18 quality of life (so called 'MELD purgatory'). In such cases, therapy may not be beneficial.
19
20
21
22
23

24 We recently published data on the virological and clinical outcomes of patients with
25
26 decompensated cirrhosis treated on the English Expanded Access Programme (EAP)
27
28 with 12 weeks of sofosbuvir and a NS5A inhibitor with or without ribavirin [14].
29
30
31

32 Consistent with other studies, the majority of patients successfully achieved viral
33
34 clearance associated with MELD improvements by post treatment week 12. To assess
35
36 the impact of antiviral therapy in patients with decompensated cirrhosis, the study
37
38 compared treated patients to a retrospective cohort of patients with decompensation
39
40 who were untreated for 6 months prior to the availability of DAAs. Treated patients had
41
42 fewer decompensations, reduced deterioration in MELD, and overall adverse events,
43
44 although there were no significant differences in rates of death, liver transplantation or
45
46 hepatocellular carcinoma [14]. To address the longer-term benefits of successful HCV
47
48 clearance, here we report the outcomes in the same patient cohort followed up for one
49
50
51
52
53
54 year after completion of therapy.
55
56
57
58
59
60
61

Patients and Methods

Patients who received DAA therapy through the English EAP were enrolled into the HCV Research UK (HCVRUK) registry for prospective data collection. Patients who started treatment between 1 April and 11 November 2014 were studied. Details of the EAP treatment and patient selection criteria were previously published [14]. In brief, treatment consisted of 12 weeks of sofosbuvir with ledipasvir or daclatasvir, with or without ribavirin. Treatment choice was according to local multidisciplinary meeting decisions by experienced clinicians. Eligible patients included those with past or current decompensated cirrhosis (with ascites, variceal bleed or encephalopathy), Child Pugh score B7 or above, extra-hepatic HCV manifestations or exceptional circumstances which were determined by panel review. Presence of hepatocellular carcinoma was not an indication for treatment in the EAP unless one of the above criteria was also met.

An untreated cohort of patients with decompensated HCV cirrhosis were studied for 6 months to compare early outcomes with patients who underwent treatment on the EAP. They were not studied beyond 6 months of follow-up as data was retrospectively collected. Untreated patients were registered in HCVRUK either at least 6 months prior to the national start date of the EAP (1 April 2014), or 6 months before initiation of treatment for those patients who subsequently received DAAs. Further details on this comparator cohort have been described [14].

The study conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the institution's human research committee. Ethics approval for HCVRUK was given by NRES Committee East Midlands – Derby 1

1
2
3
4 (Research Ethics Committee reference 11/EM/0314) and informed consent was
5
6
7 obtained from each patient included in the study. Patients in the EAP who declined data
8
9 collection (N=13) were treated but were excluded from this analysis.
10

11 12 13 14 15 16 Outcome measures 17

18
19 Data on virological response and clinical outcomes at 12 weeks post treatment on
20
21 consenting patients treated in the EAP was previously published [14]. Here we focus on
22
23 the clinical outcomes in patients with decompensated cirrhosis followed for up to a year
24
25 post completion of therapy (total follow up 15 months since start of therapy). Data was
26
27 collected for the period post treatment week 12 to month 12 (month 6 to 15), via
28
29 standardised electronic forms. Sites were individually re-contacted by the central study
30
31 team with any missing or invalid responses, to ensure completeness and accuracy of
32
33 collected data. This data was combined with earlier data from treatment start to month 6.
34
35
36
37
38

39
40 Viral loads at 24 weeks post treatment end or later were collected. We assessed the
41
42 proportion of patients who achieved SVR24, and those with late relapse after initial
43
44 undetectable viral load at post treatment week 12. All who relapsed were offered
45
46 retreatment with 24 weeks therapy.
47
48

49
50 The following primary clinical endpoints were collected: deaths, liver transplantations
51
52 and hepatocellular carcinoma at 15 months (3 months on treatment, 12 months post-
53
54 treatment). Endpoints were calculated as 15 months from treatment start date, to
55
56 account for premature treatment discontinuations.
57
58
59
60
61

1
2
3
4 For patients who achieved SVR24, the following secondary endpoints were measured:

5
6 serious adverse events (decompensation, sepsis, hospitalisation for any cause)

7
8 between month 6 and 15, MELD scores at 15 months (for non-transplanted patients

9
10 only). For patients who did not attend clinic at month 15, laboratory data from visits

11
12 within 1 month of the timepoint were included. Patients who did not achieve SVR24

13
14 were not included. SVR24 was defined as undetectable HCV RNA (measured at local

15
16 laboratories with a lower limit of quantification of <30iu/mL) at 24 weeks post-treatment.

17
18 Where there was no result available at post-treatment week 24 but subsequent viral

19
20 load was detectable, it was assumed that the patient had not achieved SVR24. MELD

21
22 scores were calculated using results provided by local accredited laboratories. Serious

23
24 adverse event was defined as life-threatening, requiring hospitalisation or prolonged

25
26 existing hospitalisation, resulting in persistent or significant disability, incapacity or death.

27
28
29
30
31
32
33
34 Statistical analysis was performed using Graphpad Prism 5. The following statistical

35
36 tests were performed: chi-squared test (for comparison of proportions), T-test (for

37
38 comparison of means) and log rank test (for comparison of survival).

1
2
3
4 **Results**
5

6
7 Patient population
8
9

10 A total of 480 patients received antiviral therapy through the EAP between the start of
11 the programme on 1 April 2014 to 11 November 2014 – 467 (97.3%) patients consented
12 to provide data to the HCVRUK registry and 406 (87%) patients had decompensated
13 cirrhosis and/or Child Pugh score \geq B7, without previous liver transplantation, at
14 treatment start. Sixty-one (13%) patients were treated for extrahepatic HCV disease or
15 aggressive HCV recurrence in liver grafts.
16
17

18 Table 1 shows the demographics and baseline liver disease of patients with
19 decompensation. The majority (295/406, 72.7%) were Child Pugh B; 41 patients (10.1%)
20 were Child Pugh C. The remaining 70 patients (17.2%) had Child Pugh A disease at
21 baseline but a past history of liver decompensation. Most patients had significant portal
22 hypertension represented by a median platelet count of $75 \times 10^9/L$.
23
24

25
26
27 Virological outcomes
28
29

30 SVR12 was achieved in 329 out of 406 patients (81.0%), including 4 patients originally
31 classified as non-SVR12 because no virology result was available, but who on further
32 follow up, were shown to be HCV RNA negative. Four patients relapsed after having a
33 HCV RNA negative result at post treatment week 12 and a further 8 died in the follow-
34 up period after achieving SVR12. Therefore 317 (78.1%) patients achieved SVR24. Of
35 note there were no late relapses after post treatment week 12 amongst patients without
36 baseline decompensated cirrhosis.
37
38

1
2
3
4 Amongst the 89 patients who did not achieve SVR24, 53 had virological failure (49
5 known before post treatment week 12 and 4 late relapsers), 14 patients died before
6 reaching post treatment week 12, and another 12 between post treatment 12-24 weeks.
7
8 Ten patients had no available viral results at post treatment week 24 although clinical
9 outcomes data was still provided. See supplementary table 1 for SVR24 according to
10 genotype and treatment regimen.
11
12
13
14
15
16
17
18

19
20 Of the 53 patients with virological failure, 21 had viral relapse by post treatment week 4,
21 24 patients by post treatment week 12, and 4 relapsed after post treatment week 12.
22
23 Three patients did not clear virus by the end of therapy and one patient without a known
24 virological result at post treatment week 12 subsequently had documented relapse.
25
26
27
28
29

30 Forty-five of the patients with viral relapse were offered re-treatment with a 24 week
31 course of the same drug regime (switching NS5A inhibitor was not supported by the
32 funders of the EAP), the outcomes of which will be reported separately. Eight patients
33 declined re-treatment.
34
35
36
37
38
39
40
41
42
43

44 Outcomes after 15 months in patients with decompensated cirrhosis

47 Mortality

48
49
50 In the 406 patients with decompensated cirrhosis there were 40 deaths over 15 months
51 (9.9%) – 9 patients died who achieved SVR24 (2.8%), which was not statistically
52 different to patients with known virological failure (3/53, 5.7%, p=0.28) (Table 2).
53
54
55
56
57

58 Although virological failure was predominantly seen in genotype 3 infected patients, the
59
60
61

1
2
3
4 proportion who died did not differ between genotypes – there were 9 deaths amongst 24
5
6 genotype 1 infected patients without SVR24, compared to 21 deaths amongst 60
7
8 genotype 3 infected patients without SVR24 (37.5% vs 35.0%, p=0.83). Figure 1 shows
9
10 the survival rates over the study period.
11
12
13
14
15
16
17

18 Development of Liver Cancer

19
20
21 At treatment baseline, 29 of 406 total patients had a history of HCC (median days
22
23 between diagnosis and DAA start was 287 days). Eighteen of these patients achieved
24
25 SVR24 (Table 1). Two patients with pre-existing liver cancer history developed a new
26
27 HCC (at 20 and 26 weeks from treatment start), both achieved SVR24. There were no
28
29 recurrent HCCs amongst patients with previous cancer who did not achieve SVR24.
30
31
32

33
34 Amongst 317 patients who achieved SVR24, 17 (5.4%) developed a liver cancer (Table
35
36 2) over the follow up period of 15 months (15 de novo and 2 recurrent). Five of the 17
37
38 (29.4%) new liver cancers developed in patients who achieved SVR24 occurred early,
39
40 within 3 months of commencing treatment. There was a reduction (of borderline
41
42 significance) in new cancer rates over 15 months between patients with and without
43
44 SVR24 (17/317, 5.4% vs 10/89, 11.2%, p=0.049) in patients with decompensated
45
46 cirrhosis (hazard ratio 0.33, 95% CI 0.13 - 0.87) (see figure 2). This compares with
47
48 11/261 (4.2%) in untreated patients over 6 months.
49
50
51
52
53
54
55
56
57

58 Other outcomes

1
2
3
4 Table 2 shows the outcomes for patients followed up for 15 months. Amongst the 317
5
6 patients who achieved SVR24, 39 (12.3%) received a liver transplant. Forty-six patients
7
8 experienced serious decompensation between months 0-6 (14.5%) which was markedly
9
10 reduced in months 6-15 (16/317, 5.0%) (p=0.00006). Supplementary table 2 shows the
11
12 details of these events with incidences of decompensations, sepsis and all-cause
13
14 hospitalisations which were graded as serious adverse events.
15
16

17
18
19 For patients who achieved SVR24, 135 (42.6%) experienced at least one serious
20
21 adverse event (death, transplant, liver cancer, decompensation, sepsis or
22
23 hospitalisation), therefore the transplant-free, adverse-event free survival over 15
24
25 months was 57.4%. The group with adverse events contained a significantly higher
26
27 proportion of patients with Child Pugh C disease at baseline – 24/135 (17.8%) for
28
29 patients with adverse events and 5/182 (2.7%) for patients without adverse events
30
31 (p<0.0005) (see Table 1). Figure 3 shows that adverse events were most frequent
32
33 during the treatment period, and decreased over time.
34
35
36
37
38
39

40 Earlier we published on the baseline characteristics of the untreated and treated
41
42 patients, showing that the two cohorts were similar apart from a higher proportion of
43
44 patients using alcohol (of any amount) at baseline amongst untreated patients [14].
45
46 Supplementary table 3 illustrates that after excluding active alcohol users, adverse
47
48 outcomes remained less frequent in treated compared to untreated patients. Amongst
49
50 untreated patients who subsequently received DAAs when they became available, and
51
52 were studied as the treated cohort at least six months later, there were numerically but
53
54 not statistically significantly lower incidences of liver cancers and decompensations
55
56 following treatment.
57
58
59
60
61

1
2
3
4 We previously proposed a model using baseline age and albumin to predict adverse
5
6 outcomes at 6 months. Table 3 shows the proportion of patients without adverse
7
8 outcomes at month 15 based on age and serum albumin at treatment start, however
9
10 these baseline factors did not discriminate the likelihood of developing adverse events
11
12 or not. We did not include MELD score change into the model due to the limited number
13
14 of available comparative scores.
15
16
17
18
19
20
21
22

23 MELD scores for patients with decompensated cirrhosis who achieved SVR24

24
25
26 The mean MELD score change from baseline at month 6 was -0.83 ± 0.14
27
28 (improvement) and $+0.51 \pm 0.4$ at month 15 (deterioration) ($p < 0.0001$) based on 282
29
30 patients with available comparative scores at month 6 and 74 patients at month 15.
31
32 Supplementary figure 1 shows the waterfall plots for MELD score changes between
33
34 baseline and month 6 and month 15 for non-transplanted patients who achieved SVR24.
35
36 MELD improvement was observed in patients with higher baseline score (see
37
38 supplementary table 4) but even in for those with baseline MELD >15 the margin of
39
40 improvement was smaller at 15 months than at 6 months. Supplementary table 5 shows
41
42 that based on the small number of available results, there were no patients with
43
44 baseline MELD <9 who worsened to above 15; for the majority group with baseline
45
46 MELD 10-14 there were similar proportions who improved or deteriorated but 48.8%
47
48 had no significant change in MELD at month 15.
49
50
51
52
53
54
55
56
57
58
59
60
61

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4 **Discussions**
5
6

7 The availability of highly effective all-oral antiviral regimens for patients with chronic
8 HCV infection has transformed the treatment options for infected patients and most
9 patients can now achieve viral clearance. For patients with advanced liver disease it is
10 unclear whether viral eradication is beneficial and there are some reports suggesting
11 that it may be harmful. Indeed the definition of benefit following viral clearance, whether
12 it is patient survival, access to transplantation or avoidance of complications, is
13 debatable.
14
15
16
17
18
19
20
21
22
23
24

25 To evaluate the potential risks and benefits of antiviral therapy in patients with end
26 stage liver disease we examined medium term outcomes in the English Expanded
27 Access Programme. This involved a well-studied, prospectively enrolled cohort of
28 patients managed by experienced clinicians in a limited number of centres. Data
29 collection was to clinical trial standards although external audit was not performed.
30 Although observational studies in non-clinical trial conditions may be confounded by
31 subject or clinician non-compliance, the patient cohort in this study all had advanced
32 liver disease requiring regular medical intervention and the treating centres were all
33 experienced in data handling techniques and were provided with support and resources
34 from the central administration. We therefore believe that our dataset is likely to be
35 accurate and complete with minimal errors from reporting or attendance failure.
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52

53 One limitation of the study is the choice of control subjects – untreated patients with
54 decompensated cirrhosis were selected based on the same criteria as treated patients,
55 from the same registry, but were not otherwise matched. Treated and untreated patients
56
57
58
59
60
61
62
63
64
65

1
2
3
4 had similar demographics and baseline liver disease, apart from the proportion of active
5 alcohol users which was higher in untreated patients. Excluding patients using any
6 amount of alcohol at baseline, who had additional risks for disease progression and
7 potentially poorer engagement with medical input, treated patients remained with fewer
8 decompensations and total adverse events compared to untreated [14]. Although
9 patients during treatment were followed-up more closely, all patients were regularly
10 reviewed due to their advanced liver disease. The study evaluated serious adverse
11 events which were actively monitored for (all patients were offered HCC surveillance) or
12 resulted in hospitalisations. Therefore reporting of such events between treated and
13 untreated patients were not likely to be biased by differences in the frequency of routine
14 follow-up. The majority of the untreated cohort subsequently received DAAs when they
15 became available, and about half were included in the treated cohort. Thus the same
16 patients were studied at least six months later, during their treatment period, and there
17 was no increase in the incidences of decompensations and liver cancers.
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38

39 Recent studies highlighting the possibility of an increased incidence or recurrence of
40 liver malignancy in patients with decompensated cirrhosis who achieve viral clearance
41 with DAA regimens has led some to question the value of treating such patients [5, 6].
42
43 In the English EAP, patients with liver cancer were not indicated for treatment unless
44 they had decompensated cirrhosis. We did not see any evidence of an increase in liver
45 cancer during therapy and the following 12 months. Nearly a third of the newly detected
46 liver cancers occurred in the first 3 months of therapy, suggesting this was growth from
47 cancers which were radiologically undetectable at treatment baseline, rather than de
48 novo development. There is potential bias that in a cohort of patients with
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4 decompensated cirrhosis, development or detection of liver cancer is masked by death
5
6 driven by advanced liver disease. We observed a reduction in cancer rates in patients
7
8 with SVR compared to virological failure, but the relatively short duration of follow up
9
10 and the low incidence of such events prevent a clear conclusion at this stage.
11
12
13

14
15 In the interferon era, antiviral therapy in patients with cirrhosis was associated with
16
17 reduced hepatocellular carcinoma [9]. Large cohorts such as HALT-C have
18
19 demonstrated that reduced cancer development may be an effect of interferon, which
20
21 has anti-tumour properties, rather than viral clearance alone, although this was only
22
23 observed after four years from treatment [15]. The magnitude of the impact of clearing
24
25 HCV with DAAs on liver cancers may require data pooling from studies with longer
26
27 follow-up, and may differ depending on the degree of cirrhosis or whether there is
28
29 previous history of HCC. The reduction in liver cancer rates from 4% in 261 untreated
30
31 patients over 6 months to 1.9% over 9 months after achieving viral clearance in 317
32
33 successfully treated patients reassures us that induction of liver cancer in our patients
34
35 did not occur.
36
37
38
39
40
41

42
43 The long term benefits of viral eradication on liver function and the complications of
44
45 portal hypertension remain unclear. However in our cohort there was a marked
46
47 reduction in liver related serious adverse events in those patients who cleared virus,
48
49 with decreasing adverse events rates over time. We speculate that patients will
50
51 continue to benefit long term although further data will be required to confirm this.
52
53
54

55
56 The value of antiviral therapy in patients with decompensated cirrhosis will remain a
57
58 subject for debate until very large cohorts have been evaluated for extended periods of
59
60
61

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

time. Our data on 12 months follow up after treatment of a large English cohort indicates that there are benefits for many patients, although in patients with Child Pugh C disease viral clearance may have the least impact on liver complications. In our view it is important that liver transplantation remains available for patients with very advanced disease who achieve viral clearance, as such patients may not improve to a level commensurate with a high quality of life.

1
2
3
4 **Acknowledgements**
5

6
7
8 The authors would like to thank the patients, their families and all participating study
9
10 studies for contributing data to this study. We are also grateful to HCV Research UK, in
11
12 particular Elizabeth Holtham and Jennifer Benselin for collecting and collating data.
13

14
15 HCV Research UK was supported by the Medical Research Foundation (grant
16
17 reference C0365). AW was supported by the MRC-funded STOP-HCV consortium. We
18
19 would like to acknowledge NHS England, Gilead Sciences and Bristol-Myers Squibb for
20
21 supplying drugs for the EAP.
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4 **References**
5
6

7 * Author names in bold designate shared co-first authorship
8
9

10
11
12
13
14 [1] **Charlton M, Everson GT, Flamm SL, Kumar P, Landis C, Brown RS, et al.**
15 **Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With**
16 **Advanced Liver Disease. Gastroenterology 2015;149:649-659.**
17
18

19
20
21 [2] **Curry MP, O'Leary JG, Bzowej N, Muir AJ, Korenblat KM, Fenkel JM, et al.**
22 **Sofosbuvir and Velpatasvir for HCV in Patients with Decompensated Cirrhosis. N Engl J**
23 **Med 2015;373:2618-2628.**
24
25

26
27
28 [3] **Leroy V, Hezode C, Metivier S, Tateo M, Conti F, Nguyen-Khac E, et al.**
29 **Daclatasvir Plus Sofosbuvir With or Without Ribavirin in Patients With HCV Infection**
30 **and Decompensated Cirrhosis: Interim Analysis of a French Multicentre Compassionate**
31 **Use Programme European Association for the Study of the Liver, The International Liver**
32 **Congress, Barcelona Spain; 2016.**
33
34
35
36
37
38
39

40
41 [4] **Petersen J, Welzel T, Herzer K, Ferenci P, Gschwantler M, Cornberg M, et al.**
42 **Daclatasvir Plus Sofosbuvir With or Without Ribavirin for the Treatment of Chronic HCV**
43 **Infection in Patients With Decompensated Cirrhosis: Results of a European Multicentre**
44 **Compassionate Use Programme. European Association for the Study of the Liver, The**
45 **International Liver CongressBarcelona, Spain; 2016.**
46
47
48
49
50

51
52 [5] **Reig M, Mariño Z, Perelló C, Iñarrairaegui M, Ribeiro A, Lens S, et al.**
53 **Unexpected early tumor recurrence in patients with hepatitis C virus -related**
54
55
56
57
58
59
60
61

1
2
3
4 hepatocellular carcinoma undergoing interferon-free therapy: a note of caution. J
5
6 Hepatol 2016.

7
8
9 [6] Buonfiglioli F, Conti F, Andreone P, Crespi C, Foschi G, Lenzi M, et al.
10
11 Development of Hepatocellular Carcinoma in HCV Cirrhotic Patients Treated with Direct
12
13 Acting Antivirals. European Association for the Study of the Liver, The International
14
15 Liver Congress Barcelona, Spain; 2016.

16
17
18 [7] Poynard T, McHutchison J, Manns M, Trepo C, Lindsay K, Goodman Z, et al.
19
20 Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with
21
22 chronic hepatitis C. Gastroenterology 2002;122:1303-1313.

23
24
25 [8] van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al.
26
27 Association between sustained virological response and all-cause mortality among
28
29 patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012;308:2584-
30
31 2593.

32
33
34 [9] Shiratori Y, Ito Y, Yokosuka O, Imazeki F, Nakata R, Tanaka N, et al. Antiviral
35
36 therapy for cirrhotic hepatitis C: association with reduced hepatocellular carcinoma
37
38 development and improved survival. Ann Intern Med 2005;142:105-114.

39
40
41 [10] Bruno S, Stroffolini T, Colombo M, Bollani S, Benvegnù L, Mazzella G, et al.
42
43 Sustained virological response to interferon-alpha is associated with improved outcome
44
45 in HCV-related cirrhosis: a retrospective study. Hepatology 2007;45:579-587.

46
47
48 [11] Liver EAfSo. EASL Recommendations on Treatment of Hepatitis C 2015. J
49
50 Hepatol 2015;63:199-236.

1
2
3
4 [12] Panel AIHG. Hepatitis C guidance: AASLD-IDSA recommendations for testing,
5
6 managing, and treating adults infected with hepatitis C virus. Hepatology 2015;62:932-
7
8 954.
9

10
11 [13] Bunchorntavakul C, Reddy KR. Treat chronic hepatitis C virus infection in
12
13 decompensated cirrhosis - pre- or post-liver transplantation? the ironic conundrum in
14
15 the era of effective and well-tolerated therapy. J Viral Hepat 2016;23:408-418.
16
17

18
19 [14] **Foster GR, Irving WL**, Cheung MC, Walker AJ, Hudson BE, Verma S, et al.
20
21 Impact of direct acting antiviral therapy in patients with chronic hepatitis C and
22
23 decompensated cirrhosis. J Hepatol 2016.
24
25

26
27 [15] Lok AS, Everhart JE, Wright EC, Di Bisceglie AM, Kim HY, Sterling RK, et al.
28
29 Maintenance peginterferon therapy and other factors associated with hepatocellular
30
31 carcinoma in patients with advanced hepatitis C. Gastroenterology 2011;140:840-849;
32
33 quiz e812.
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61

Tables 1-3

Table 1. Baseline characteristics of patients according to treatment outcomes.

Virological failure included all patients with a detectable viral load at post treatment week 24 or before, including re-treated patients. Non-SVR24 included in addition patients who died before post treatment week 24 or without available viral load. Serious adverse events included all deaths, transplants, HCCs, decompensations, sepsis and hospitalisation to month 15.

Baseline characteristic	All decompensated	SVR24	Non-SVR24	Virological failure	SVR 24 – serious adverse events	SVR 24 – no serious adverse events
All N (%)	406	317 (78.1%)	89 (21.9)	53 (13.1)	135 (42.6%)	182 (57.4%)
Sof/LDV	18 (4.4)	12 (3.8)	6 (6.7)	4 (7.5)	7 (5.2%)	5 (2.7%)
Sof/LDV/RBV	228 (56.2)	187 (59.0)	41 (46.1)	30 (56.6)	78 (57.8%)	109 (59.9)
Sof/DCV	11 (2.7)	7 (2.2)	4 (4.5)	1 (1.9)	5 (3.7%)	2 (1.1%)
Sof/DCV/RBV	149 (36.7)	111 (35.0)	38 (42.7)	18 (34.0)	45 (33.3%)	66 (36.3%)
Genotype 1	198 (48.8)	174 (54.9)	24 (27.0)	11 (20.8)	75 (55.6%)	99 (54.4%)
Genotype 3	171 (42.1)	111 (35.0)	60 (67.4)	39 (73.6)	45 (33.3%)	66 (36.3%)
Other genotypes	37 (9.1)	32 (10.1)	5 (5.6)	3 (5.7)	15 (11.1%)	17 (9.3%)
Age (years) median, range	54, 28-79	54, 28-79	52, 30-74	52, 33-72	54, 33-76	55, 28-79
Bilirubin (µmol/L) median, range	29, 4-433	28, 4-311	34, 7-433	33, 7-148	30, 4-311	26, 6-90
Albumin (g/L) median, range	31, 17-55	31, 17-49	29, 21-55	30, 21-40	31, 17-45	32, 17-49
Platelets (x10 ⁹ /L) median, range	75, 3-321	75, 3-321	76, 20-277	76, 20-277	74, 20-237	76, 3-321
MELD median, range	12, 7-32	11, 7-32	13, -25	12, 8-23	12, 7-32	11, 7-21
Child Pugh B	295 (72.7)	225 (71.0)	70 (78.7)	42 (79.2)	88 (65.3%)	137 (75.3%)
Child Pugh C	41 (10.1)	29 (9.1)	12 (13.5)	5 (9.4)	24 (17.8%)	5 (2.7%)
Baseline HCC	29 (7.1)	18 (5.7)	11 (12.4)	9 (17.0)	13 (9.6%)	5 (2.7%)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Footnote: Since the earlier publication [4], 3 additional patients were confirmed as transplanted prior to DAA therapy, including one registered for therapy pre-transplant, grafted then initiated treatment. These patients were re-defined as post-transplant at treatment baseline, therefore 406 instead of 409 patients were included in this study.

Table 2. **Deaths, hepatocellular carcinomas (HCC), orthotopic liver transplants (OLT) and decompensations over 15 months for all treated patients according to treatment outcomes, compared to patients untreated for HCV (data for untreated patients derived from [4]). Note all deaths up to post treatment week 24 were defined as non-SVR24. Decompensation events were recorded for patients with SVR24 only.**

Adverse Event	Untreated N=261	All treated N = 406		
		Month 0-6	Month 0 - 6	Month 6 - 15
Died	13 (5.0%)	14 (3.4%)	26 (6.4%)	40 (9.9%)
HCC	11 (4.2%)†	17 (4.2%)	10 (2.5%)	27 (6.7%)
OLT	10 (3.8%)	29 (7.1%)	17 (4.2%)	46 (11.3%)
Decompensation	73 (28.0)	72 (17.7%)	30 (7.4%)	87 (21.4%)

Adverse Event	SVR24 N = 317			Non-SVR24 N=89			Virological failure N = 53		
	Month 0 - 6	Month 6 - 15	Overall	Month 0 - 6	Month 6 - 15	Overall	Month 0 - 6	Month 6 - 15	Overall
Died	0 (0.0%)	9 (2.8%)	9 (2.8%)	14 (15.7%)	17 (19.1%)	31 (34.8%)	0 (0%)	3 (5.7%)*	3 (5.7%)
HCC	11 (3.5%)	6 (1.9%)	17 (5.4%)	6 (6.7%)	4 (4.5%)**	10 (11.2%)	3 (5.7%)	3 (5.7%)	6 (11.3%)
OLT	27 (8.5%)	12 (3.8%)	39 (12.3%)	2 (2.2%***)	5 (5.6%)	7 (7.9%)	1 (1.9%)	5 (9.4%)	6 (11.3%)
Decompensation	46 (14.5%)	16 (5.0%)	52 (16.4%)	26 (29.2%)	-	-	-	-	-

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Footnote:

* denotes two patients who did not have known virological outcomes at 24 weeks post-treatment but had reported deaths, one of the two patients (marked by **) also had a new liver cancer

*** denotes a patient transplanted by month 6 who did not have a known virological outcome at 24 weeks post-treatment

† figure updated from earlier publication

1
2
3
4 **Table 3. Proportion of patients without adverse events (death, transplantation,**
5 **liver cancer, decompensation, sepsis or hospitalisations) according to baseline**
6 **characteristics (total 182 patients out of 317 who achieved SVR24).**
7
8
9

10
11
12
13
14
15

		N	No adverse events (n)	
Age <65	Albumin \geq 35	74	47	63.5%
Age <65	Albumin <35	212	120	56.6%
Age \geq 65	Albumin <35	21	10	47.6%
Age \geq 65	Albumin \geq 35	10	5	50.0%

16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

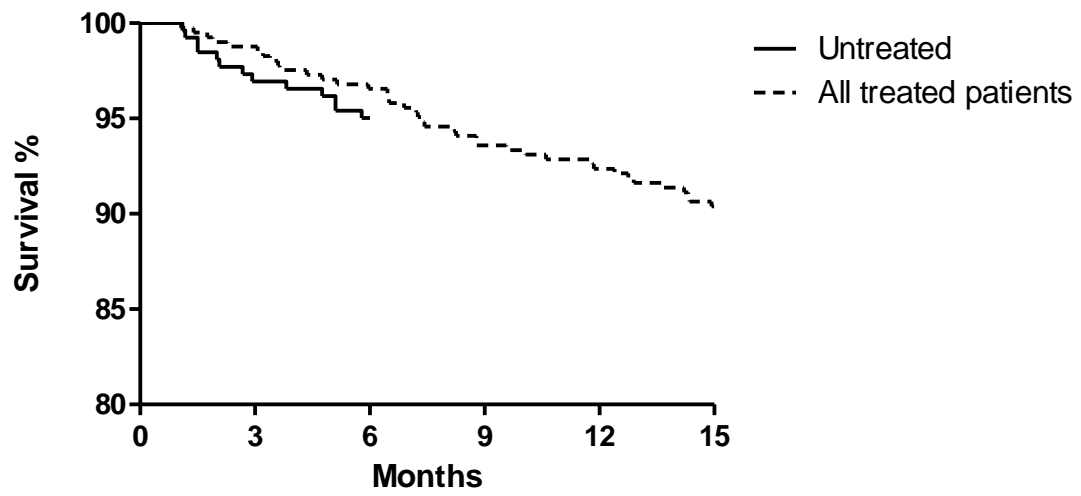
1
2
3
4 **Figure legends**
5
6
7
8
9

10
11 **Fig. 1. Survival of patients over 15 months.** (A) Survival in patients treated and
12 untreated (log rank $p=0.32$). (B) Survival in treated patients with SVR24 and virological
13 failure (log rank $p=0.38$). Note by definition no deaths occurred before month 9 (post-
14 treatment week 24) in both groups.
15
16
17
18

19
20 **Fig. 2. Development of new hepatocellular carcinoma over 15 months.** (A) New
21 hepatocellular carcinoma in untreated and treated patients (log rank $p=0.98$). (B) New
22 hepatocellular carcinoma in patients with and without SVR24 (log rank $p=0.02$)
23
24
25
26

27 **Fig. 3. Combined adverse event rate (death, liver transplant, HCC,**
28 **decompensation, sepsis, all-cause hospitalisation) per person over time, for**
29 **patients with SVR24 (n=307).** Error bars represent 95% confidence intervals.
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

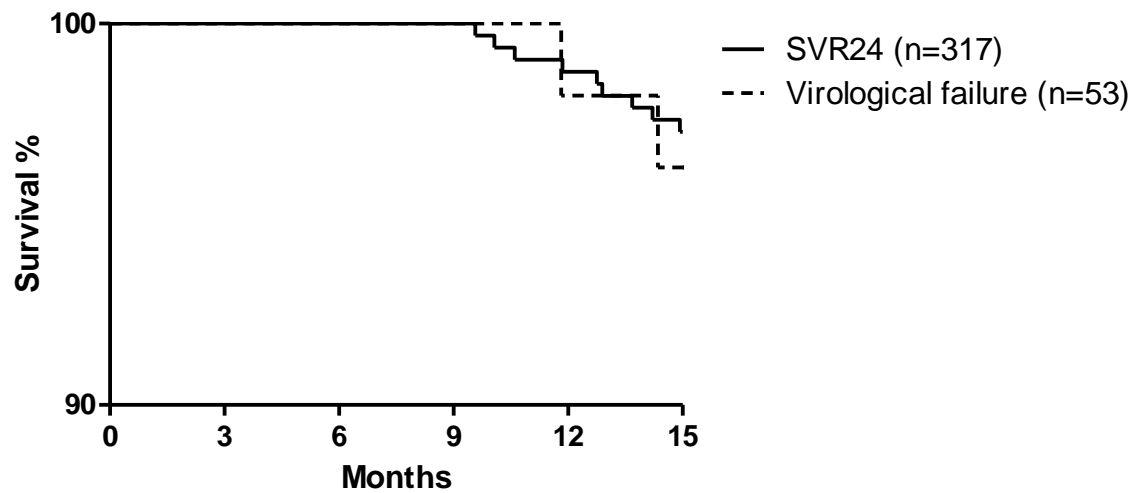
Figure



Number of patients at risk

Month	0	3	6	9	12	15
Untreated	261	254	248	-	-	-
Treated	406	401	392	380	375	366

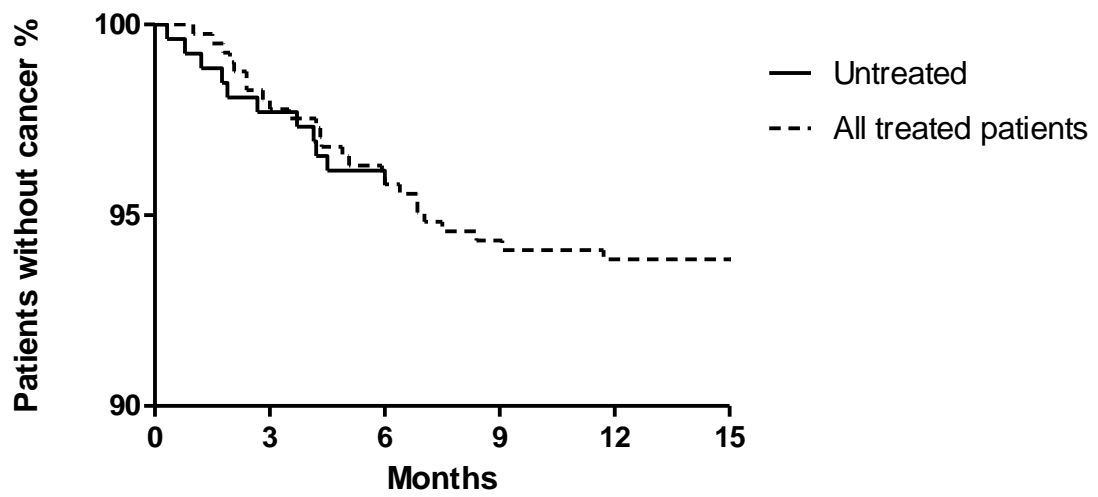
Figure



Number of patients at risk

Month	0	3	6	9	12	15
SVR24	317	317	317	317	313	308
Virological failure	53	53	53	53	53	50

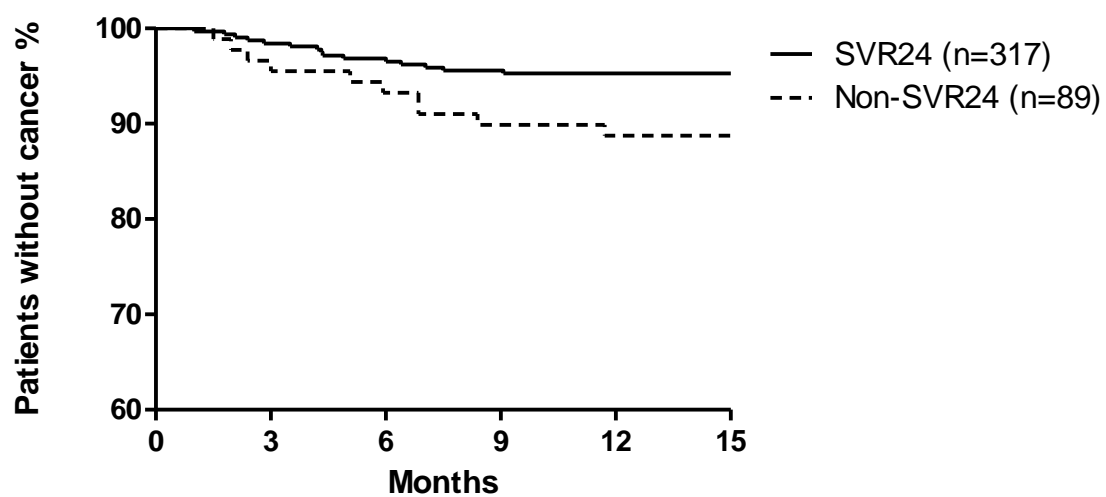
Figure



Number of patients at risk

Month	0	3	6	9	12	15
Untreated	261	255	250	-	-	-
Treated	406	398	389	383	381	379

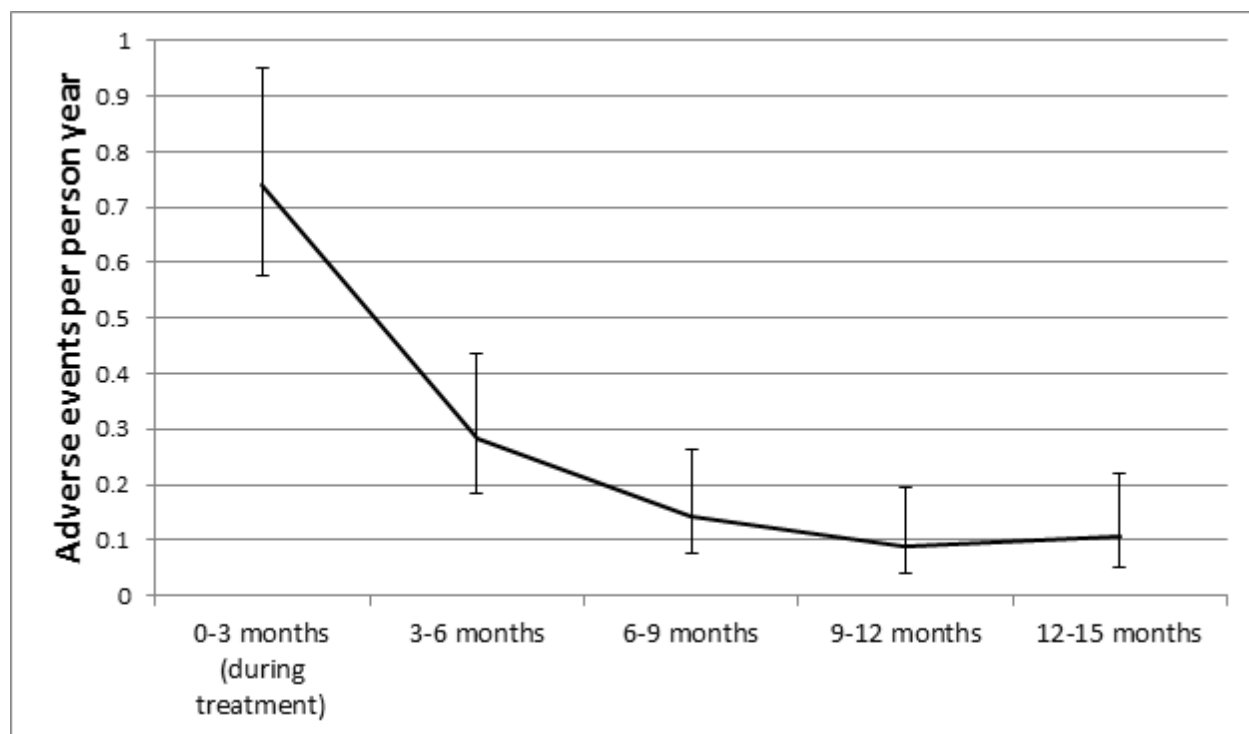
Figure

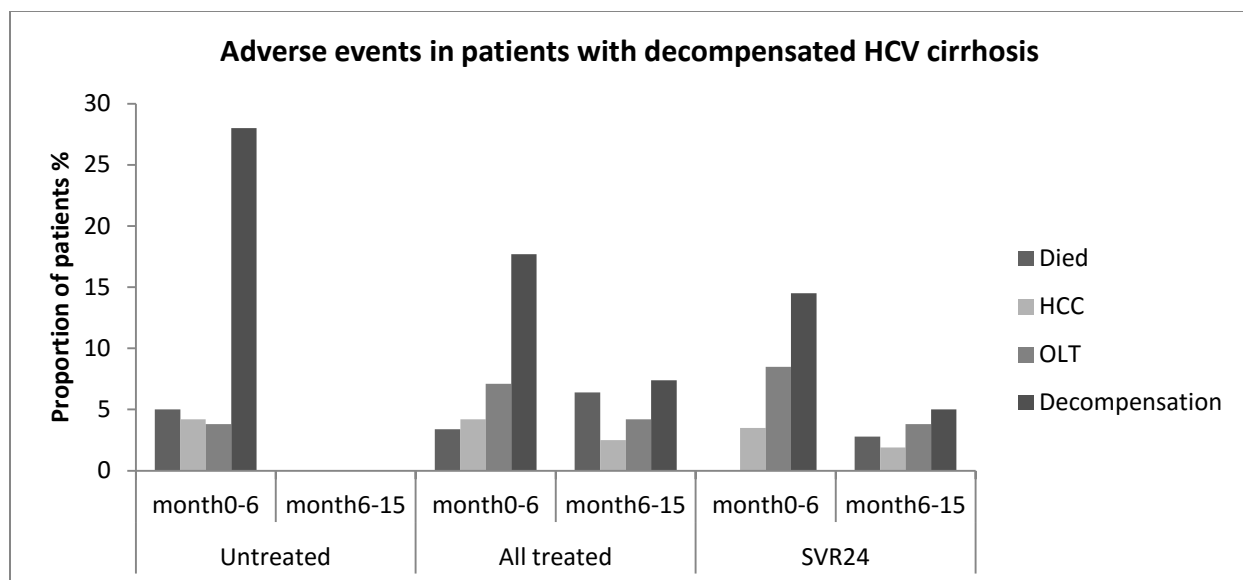


Number of patients at risk

Month	0	3	6	9	12	15
SVR24	317	313	306	303	302	300
Non-SVR24	89	86	83	80	80	79

Figure





Supplementary material

[Click here to download Supplementary material: supplementary material.docx](#)

*ICMJE disclosure form

[Click here to download ICMJE disclosure form: coi_disclosure_cheung.pdf](#)

*ICMJE disclosure form

[Click here to download ICMJE disclosure form: coi_disclosure_walker.pdf](#)

*ICMJE disclosure form

[Click here to download ICMJE disclosure form: coi_disclosure_hudson.pdf](#)

*ICMJE disclosure form

[Click here to download ICMJE disclosure form: coi_disclosure_verma.pdf](#)

*ICMJE disclosure form

[Click here to download ICMJE disclosure form: coi_disclosure_McLauchlan.pdf](#)

*ICMJE disclosure form

[Click here to download ICMJE disclosure form: coi_disclosure_Mutimer.pdf](#)

*ICMJE disclosure form

[Click here to download ICMJE disclosure form: coi_disclosure_Brown.pdf](#)

*ICMJE disclosure form

[Click here to download ICMJE disclosure form: coi_disclosure_Gelson.pdf](#)

*ICMJE disclosure form

[Click here to download ICMJE disclosure form: coi_disclosure_MacDonald.pdf](#)

*ICMJE disclosure form

[Click here to download ICMJE disclosure form: coi_disclosure_agarwal.pdf](#)

*ICMJE disclosure form

[Click here to download ICMJE disclosure form: coi_disclosure_foster.pdf](#)

*ICMJE disclosure form

[Click here to download ICMJE disclosure form: coi_disclosure_irving.pdf](#)