Liver Function Following Hepatitis C Virus Eradication by Direct Acting Antivirals in Patients With Liver Cirrhosis: Data from The PITER Cohort

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Research Article

Keywords: Hepatitis C virus, Human Immunodeficiency virus, real-life cohort, direct-acting antivirals, advanced liver disease, decompensated cirrhosis

Posted Date: January 4th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-133427/v1

Abstract

Background: The development of direct-acting antivirals (DAA) for HCV has revolutionized the treatment of HCV, including its treatment in patients with HIV coinfection. The aim of this study was to compare the changes in liver function between coinfected and monoinfected patients with cirrhosis who achieved HCV eradication by DAA in the multicenter PITER cohort.

Methods: Patients with pre-treatment diagnosis of HCV liver cirrhosis, consecutively enrolled in PITER, who achieved a sustained virological response (SVR12) and with an available follow-up after DAA treatment, were analysed. Liver function was prospectively evaluated as changes in Child-Pugh (C-P) class during patient's follow-up after the end of DAA treatment. Cox regression analysis was used to evaluate factors independently associated with changes in liver function following viral eradication.

Results: We evaluated 1350 successfully DAA treated patients with cirrhosis, of whom 1242 HCV monoinfected (median follow-up of 24.7, range 6.8-47.5 months after viral eradication) and 108 (8%) HCV/HIV coinfected (median follow-up of 27.1, range 6-44.6 months after viral eradication). Despite the significant younger age ($p<0.001$), coinfected patients had higher liver disease severity in terms of C-P class score ($p<0.001$). Following HCV eradication, C-P class improved in 17/20 coinfected (85%) and in 53/82 (64.6%) monoinfected patients with a pre-treatment C-P class B or C ($p>0.05$). C-P class worsened in 3/56 coinfected (5.3%) and in 84/1024 (8.2%) monoinfected patients with pre-treatment C-P class A or B ($p>0.05$).

Factors independently associated with C-P class deterioration were male sex (HR=2.01; 95% CI=1.19-3.40), platelet count <100,000/μl (HR=1.88; 95% CI 1.17-3.03) and higher pretreatment INR value (HR=2.34; 95% CI 1.47-3.71).

Following viral eradication, in 7 of 15 coinfected (47%) and in 61 of 133 (45.6%) monoinfected patients with previous history of decompensation a new decompensating event occurred. An incident decompensating event was recorded in 4 of 93 (4.3%) coinfected and in 53 of 1109 (4.8%) monoinfected patients.

Conclusions: Improvement of liver function is observed following HCV eradication in the majority of patients with cirrhosis; however viral eradication does not always mean cure of liver disease in both monoinfected and coinfected patients with advanced liver disease.

Background

Hepatitis C Virus (HCV) eradication by direct-acting antiviral agents (DAA) is linked to an improved outcome at all stages of liver disease. Available data suggest that the maximum benefit is obtained by treating patients before they reach the stage of advanced fibrosis or cirrhosis. Sustained virologic response (SVR) reduces the risk of liver decompensation and of hepatocellular carcinoma (HCC) and improves survival. However, a "point of non- return" in terms of deterioration of liver function has been

observed in part of patients regardless of viral eradication, potentially due to the pre-treatment severe liver fibrosis and presence of other cofactors of liver disease progression. As cofactor, HIV coinfection negatively affect the natural course of chronic HCV infection. Patients have a faster progression of liver fibrosis, an earlier transition to cirrhosis, a higher risk of hepatic decompensation and occurrence of HCC compared with HCV-monoinfected patients as well as a potential toxicity of antiretroviral therapy in the liver (1–6).

The development of DAA against HCV has revolutionized the treatment of hepatitis C, including its treatment in patients with HIV coinfection, which have resulted with similar SVR rates as those of HCV monoinfected patients, shorter and simpler regimens with minimal treatment-related side effects compared to previous Interferon (IFN)-based therapies (7–14). However, for HIV/HCV-coinfected patients with cirrhosis, the potential benefits of viral eradication could be counterbalanced by a poorer recovery of liver function. Indeed, given that HIV coinfection enhances fibrosis progression, it might also impair the regression of fibrosis after SVR and, hence, the recovery of liver function.

In the present study, we assess changes in Child-Pugh (C-P) class as a measure of improvement or worsening of liver function and the occurrence of a decompensating event, in a real-life cohort of patients with advanced liver disease due to HCV infection with or without HIV coinfection.

Methods

Patients

Patients were recruited from the Italian platform for the study of viral hepatitis therapy (PITER) cohort between April 2014 and June 2019. PITER is a prospective multicentric study, consecutively enrolling chronic HCV infected patients, who were not receiving HCV treatment at the time of inclusion (15). In this study, we analysed HCV/HIV coinfected patients and HCV monoinfected patients with known HIV negative status, with pre-treatment diagnosis of liver cirrhosis who had achieved SVR12 to IFN-free DAA regimens, excluding patients with a history of liver transplantation prior to treatment. Patient's data were recorded prior to the treatment start and during the follow-up after the end of treatment.

Fibrosis stage was defined based on liver transient elastography data, which were considered as validated if each patient had at least 10 valid stiffness measurements, with a success rate of at least 80%, an interquartile range of less than 30% of the median stiffness score, and a body mass index (BMI) of < 30 kg/m^2 (16). Liver cirrhosis was defined when the stiffness score was equal to or higher than 12.5 kPa or according to biochemical and instrumental data of portal hypertension (16).

Outcome variables

Clinical outcomes evaluated included the occurrence of a decompensating event (ascites and/or gastrointestinal bleeding due to portal hypertension and/or hepatic encephalopathy) and changes in the

severity of liver disease in terms of C-P class deterioration or improvement whatever occurred first during the follow-up after the end of treatment.

Statistical analysis

Patient's main baseline characteristics were reported as median and interquartile range (IQR) or as proportions (N and %) for continuous and categorical variables, respectively. The Mann-Whitney U test was used for continuous variables to assess differences between distribution, and the Chi-squared test was used for comparisons of proportions. A p-value of < 0.05 was considered statistically significant.

Variables independently associated with improvements or worsening in liver function, as determined by changes in C-P class after the end of treatment, were evaluated by Cox proportional hazard models. All analyses were performed using the STATA/SE 15.1 statistical package (StataCorp LP, College Station, TX, USA).

Results

Baseline characteristics of patients

A total of 108 HIV/HCV coinfected (81.5% males) and 1242 HCV monoinfected patients (58.1% males) were considered in the present analyses. Baseline characteristics of these patients are summarised in Table 1.

		HCV/HIV co-infected (N=108*)		HCV mono-infected (N=1242*)		
Quantitative variables		Median	IQR	Median	IQR	p**
Age (years)		52.5	50 - 55	64.0	54 - 72	**< 0.001**
ALT (IU/L)		63.0	40.0 - 91.0	74.0	47.0 - 115.0	**< 0.05**
AST (IU/L)		60.0	44.0 - 95.0	70.0	47.0 - 105.0	> 0.05
Platelets/µL		105000	74000 - 154000	119000	86350 - 159000	> 0.05
Albumin (g/dL)		3.9	3.5 - 4.2	3.9	3.6 - 4.2	> 0.05
Bilirubin (mg/dL)		0.8	0.6 - 1.3	0.9	0.6 - 1.1	> 0.05
INR		1.1	1.0 - 1.2	1.1	1.0 - 1.2	> 0.05
Categorical variables		N.	%	N.	%	p***
Sex	Male	88	81.5	722	58.1	**< 0.001**
	Female	20	18.5	520	41.9	
BMI	Underweight	5	4.6	14	1.1	**< 0.001**
	Normal	70	64.8	514	41.4	
	Overweight	25	23.2	550	44.3	
	Obese	8	7.4	163	13.1	
Alcohol use	Never	50	52.1	803	66.0	**< 0.001**
	Current	26	27.1	116	9.5	
	Past	20	20.8	297	24.4	
HCV-	1 (Non subtyped)	5	4.6	36	2.9	**< 0.001**
genotype	1a	33	30.6	170	13.7	
	1b	15	13.9	665	53.5	
	2	4	3.7	168	13.5	

	3	31	28.7	120	9.7	
	4	20	18.5	83	6.7	
	5	0	0.0	0	0.0	
Diabetes	Yes	16	14.8	259	20.9	> 0.05
	No	92	85.2	983	79.2	
Anti-HBc+	Yes	48	44.4	274	22.1	**< 0.001**
	No	60	55.6	968	77.9	
HBsAg+	Yes	4	3.7	15	1.2	**< 0.05**
-	No	104	96.3	1227	98.8	
Previous	Yes	30	27.8	415	33.4	> 0.05
Interferon	No	78	72.2	827	66.6	
HCC	Yes	1	0.9	78	6.3	**< 0.05**
	No	107	99.1	1164	93.7	
Previous	Yes	15	13.9	133	10.7	> 0.05
decompensations	No	93	86.1	1109	89.3	
Child-Pugh	A-5	39	52.7	762	69.5	**< 0.001**
Score	A-6	14	18.9	242	22.1	
	B-7	12	16.2	58	5.3	
	B-8	8	10.8	28	2.6	
	B-9	0	0.0	6	0.6	
	C-10	1	1.4	0	0.0	

***** For some variables inconsistencies are due to missing values

** p value Mann–Whitney rank-sum test

*** p value Chi-square test

Coinfected patients were significantly younger (median age of 52.5 vs 64 years, $p < 0.001$) and compared to monoinfected patients, had a significant lower BMI ($p < 0.001$).

A significantly different distribution in HCV genotypes in monoinfected compared to coinfected patients was observed. About half of the monoinfected patients (n = 665, 53.5%) were infected by HCV genotype 1b, whereas genotype 1a and 3 were dominant in coinfected patients (n = 33, 30.6% and n = 31, 28.7%, respectively) ($p < 0.001$).

Higher prevalence of anti-HBc (44.4% vs 22.1%, $p < 0.001$) and HBsAg (3.7% vs 1.2%, $p < 0.05$) positivity was detected in coinfected compared to monoinfected patients.

A significant difference in the prevalence of HCC between coinfected and monoinfected patients was observed (0.9% vs 6.3%, respectively; $p < 0.05$). Before starting therapy, 15 (13.9%) co-infected and 133 (10.7%) monoinfected patients had reported a previous liver decompensating event.

Coinfected patients had an increased liver disease severity in terms of C-P class distribution (A5: 52.7% vs 69.5%; A6: 18.9% vs 22.1%; B7: 16.2% vs 5.3%; B8: 10.8% vs 2.6%), compared to HCV monoinfected patients ($p < 0.001$).

Changes in liver function following SVR12

Similar rates of SVR12 were observed in coinfected (93.9%) and monoinfected (94.1%) patients.

Coinfected and monoinfected patients were evaluated during a median follow-up of 27.1 (range 6-44.6) and 24.7 (range 6.8–47.5) months after viral eradication, respectively. Changes in the severity of liver disease in terms of C-P class increase or decrease are shown in Fig. 1. During the follow-up C-P class worsened in 3/56 (5.3%) coinfected patients (from C-P class A to B) and in 84/1024 (8.2%) HCV-monoinfected patients (of whom 79 from C-P class A to B, 4 from C-P class B to C and 1 from C-P class A to C) ($p > 0.05$).

No difference in the occurrence of a decompensating event following viral eradication was observed between coinfected (n = 11, 10.2%) and monoinfected (n = 114, 9.2%) ($p > 0.05$) patients. Of patients with decompensated cirrhosis prior to therapy in 7 of 15 (47%) coinfected and in 61 of 133 (45.6%) monoinfected patients a new decompensating event occurred following viral eradication. A total of 4 of 93 (4.3%) coinfected and 53 of 1109 (4.8%) ($p > 0.05$) monoinfected patients had their first decompensating event. Decompensating events recorded after viral eradication in both patients with or without a previous history of decompensation were mainly represented by the presence of ascites, however encephalopathy and variceal bleeding were also present (Table 2).

Table 2
Occurrence of decompensating event following viral eradication

	HCV/HIV co-infected (N = 11)		HCV mono-infected (N = 114)	
Patients with a pre-treatment history of decompensated cirrhosis	N.	%	N.	%
Ascites	6	85.7	32	52.5
Ascites + hepatic encephalopathy	0	0.0	8	13.1
Ascites + gastrointestinal bleeding	0	0.0	2	3.3
Ascites + gastrointestinal bleeding + hepatic encephalopathy	0	0.0	2	3.3
Hepatic encephalopathy	0	0.0	9	14.8
Gastrointestinal bleeding	1	14.3	8	13.1
TOTAL	**7**	**100.0**	**61**	**100.0**
Patients with incident decompensating event	N.	%	N.	%
Ascites	3	75.0	32	67.9
Ascites + hepatic encephalopathy	0	0.0	6	3.8
Hepatic encephalopathy	1	25.0	6	11.3
Gastrointestinal bleeding	0	0.0	9	17.0
TOTAL	**4**	**100.0**	**53**	**100.0**

Predictors of Child-Pugh class worsening following SVR12

Variables significantly associated with C-P class increase included male sex [Hazard ratio (HR) = 2.01; 95% Confidence Interval (CI) = 1.19–3.40], platelet count lower than 100,000/μL (HR = 1.88; 95% CI 1.17–3.03) and higher baseline international normalized ratio (INR) value (HR = 2.34; 95% CI 1.47–3.71) (Table 3). HIV coinfection was not associated with the C-P class deterioration.

Table 3
Baseline factors associated with a Child-Pugh class increase following viral eradication. Univariate and multivariate analysis.

Baseline factors	Crude HR	95% CI	Adjusted HR	95% CI
HIV infection	0.68	0.21–2.15	0.50	0.15–1.68
Age (increasing years)	1.00	0.98–1.02	1.00	0.98–1.02
Sex (ref. female)	**1.77**	**1.12–2.81**	**2.01**	**1.19–3.40**
BMI: overweight/obese (ref. under-normalweight)	0.88	0.58–1.34	0.77	0.50–1.20
Current/past alcohol use (ref. never)	0.99	0.63–1.55	0.77	0.47–1.25
ALT (increasing IU/L)	1.00	0.99–1.00	1.00	0.99–1.01
AST (increasing IU/L)	1.00	0.99–1.00	0.99	0.98–1.00
Platelets (ref. >100,000/μL)	**2.01**	**1.31–3.08**	**1.88**	**1.17–3.03**
Albumin (decreasing g/dL)	1.57	0.99–2.43	1.39	0.85–2.29
Bilirubin (increasing mg/dL)	0.98	0.87–1.12	0.86	0.62–1.20
INR (increasing unit)	**2.15**	**1.45–3.19**	**2.34**	**1.47–3.71**
HCV-genotype (3 vs others)	1.51	0.80–2.84	1.55	0.75–3.17
Diabetes	1.14	0.69–1.89	0.95	0.56–1.61
Anti-HBc+	1.02	0.63–1.65	1.05	0.63–1.75
Previous Interferon treatment	0.82	0.52–1.29	0.75	0.47–1.21
HCC	**2.32**	**1.20–4.49**	1.87	0.86–4.05
Previous decompensating event	**1.97**	**1.17–3.31**	1.28	0.70–2.35

Discussion

This is one of a few multicentric cohort studies, representative of patients with chronic HCV infection in care in Italy that prospectively evaluated the medium-term outcomes following HCV eradication by DAA in consecutively enrolled patients with severe liver disease, based on HIV status. Regarding the HIV coinfection our study population consisted of HIV coinfected patients at least 10 years younger than HCV monoinfected patients. This age difference potentially reflect the epidemiology of HIV infection mainly related with a later epidemic wave compared to the post transfusion and nosocomial epidemic wave of HCV monoinfection in Italy (17). The longer duration of chirrosis due to the longer time of infection in monoinfected patients could explain the higher HCC prevalence in monoinfected compared to coinfected patients before therapy (2–6). However, despite the younger age, coinfected patients had more advanced liver cirrhosis which confirm a faster liver disease progression compared to monoinfected patients (C-P class B and C: 28.4% vs 8.4% in coinfected and monoinfected patients, respectively, $p < 0.001$).

We found that the overall SVR12 rate (93.9% and 94.1% in coinfected and monoinfected patients, respectively) is similar to those reported in clinical trials and in our previous study (18), confirming the high efficacy of DAA therapy in the real-world setting also in patients with advanced liver disease, regardless of HIV coinfection (18–21). The results of this medium-term study confirm that HCV clearance obtained by DAA is feasibly linked to an improved outcome in patients with advanced liver disease, independently by HIV-coinfection.

In our previous study, it has been shown a similar cumulative incidence of HCC in coinfected and monoinfected patients after viral eradication, suggesting that HIV coinfection is not associated with a higher probability of developing liver complications in successfully DAA treated patients with compensated cirrhosis (20). Here, we expand our previous findings, including patients with advanced/decompensated cirrhosis. Data in this group of patients are limited because patients with significant advanced liver disease were not included in clinical trials on DAA efficacy and were either excluded or, if included, their numbers were extremely low in real-life studies. Moreover, there are no long-term studies that prove the extent of clinical benefit for these patients.

Improvements in C-P scores have been noted and predictors of improvement have been described in patients with chronic HCV infection after viral eradication (22–25). We found that a successful DAA therapy for both HCV monoinfected and HIV/HCV coinfected patients with compensated/decompensated cirrhosis was also associated with a decrease of the liver disease severity. Specifically, after successful DAA treatment, an improvement in C-P class was observed in 85% of coinfected and in 64.6% of monoinfected patients, suggesting that viral eradication helps liver function recovery in the majority of patients with liver cirrhosis. Several studies reported liver stiffness regression after successful HCV treatment with the better improvement in patients with higher baseline fibrosis stage, with no significant difference between monoinfected and coinfected patients (13, 14, 26, 27).

As it has been previously reported, in almost 50% of patients with cirrhosis at baseline, who achieved the SVR following an IFN based treatment, a METAVIR score lower than F4 were observed in their post-

treatment liver biopsy (28). Other studies which evaluated a longer duration have confirmed these findings, reporting even higher percentages of patients in whom significant decrease of high fibrosis score were observed (29, 30, 31).

However, when IFN-based therapy was used, only patients with low C-P scores were treated with Peg-IFN and Ribavirin for 6 months showing a beneficial clinical outcome during the median follow-up of 30 months after the SVR (32). Different results in terms of clinical outcomes could be observed in patients treated with DAA, because following their use in real-life, more compromised patients in terms of severity of liver damage have been treated (10, 33–35).

In this study, we observed that although most HCV-coinfected patients with baseline cirrhosis that achieve SVR12 experienced improvement of liver function tests, part of those kept the risk of liver disease progression regardless of viral eradication. We found that C-P class worsened in 8.2% HCV-monoinfected patients and in 5.4% HIV/HCV-coinfected patients. Male sex, higher baseline INR and platelets counts lower than 100.000, surrogate markers of severe liver damage and portal hypertension, were independently associated to C-P class deterioration, while HIV coinfection was not an independent factor of liver disease worsening. In previous studies, additional analyses have suggested that patients above the age of 65 with reduced hepatic synthetic function (serum albumin 635 g/L) were less likely to benefit from DAA therapy as well, although these factors were not sufficiently discriminative to identify a subgroup in which antiviral therapy should be deferred in favour of liver transplant (28).

A critical issue for patients with cirrhosis is the prediction of the risk of decompensations. In the present study we found that a new decompensating event occurred in part of patients with a history of previous decompensation: 47% of coinfected and 45.6% of monoinfected patients with a history of hepatic decompensation before treatment start, kept the risk of a decompensating event following viral eradication. In addition, liver disease progression with the appearance of an incident decompensating event was observed after viral eradication, emphasising the finding that the virological efficacy is not always translate in clinical efficacy in patients with advanced liver disease.

Our findings confirm the existence of a point of no return, after which antiviral treatment may be too late to influence the natural history of HCV related liver disease, however more data are needed to better define this patient’s population.

Conclusion

Viral eradication after DAA therapy represents a positive prognostic factor of liver function improvement, in particular in terms of C-P class. However, during a medium time of a clinical follow-up, following the SVR (more than 2 years) achieved after the DAA treatment, this benefit was not extended in almost 10% of patients in whom liver disease progression continues regardless of viral eradication in both HCV monoinfected and HCV/HIV coinfected patients.

Abbreviations

BMI: Body Mass Index

CI: Confidence Interval

C-P class: Child-Pugh class

DAA: Direct-Acting Antivirals

HCC: Hepatocellular Carcinoma

HCV: Hepatitis C Virus

HIV: Human Immunodeficiency Virus

HR: Hazard ratio

IFN: Interferon

INR: International Normalized Ratio

IQR: Interquartile Range

PITER: *Italian Platform for the Study of Viral Hepatitis Therapy*

SVR: Sustained Virologic Response

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice. The study protocol was approved by the Ethics Committee of the Istituto Superiore di Sanità (Italian National Institute of Public Health) and by the local Ethics committees of each clinical center. The patients' data were evaluated through an anonymous analysis, adopting codes generated by the electronic case report forms. All patients gave their written informed consent to participate in the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare no conflicts of interest regarding the present study.

Funding

This study was funded by Italian Ministry of Health, Grant number RF-2016-02364053.

Authors' contributions

Conceptualization: L.A.K. Formal analysis and investigation: L.A.K, M.G.Q. Writing - original draft preparation: L.A.K., M.G.Q. Data curation: M.G.Q., L.F., F.D. Resources: X.T., C.C., A.C., S.R.B., M.L., A.G., M.Mar., V.C., G.B., M.D., M.D., M.C., L.C., M.Mas., M.Maz., P.D., D.L., L.B. Supervision: L.A.K. All the authors have read and approved the final manuscript.

Acknowledgements

Authors wish to thank PITER collaborating group and all clinical centres (available in www progettopiter.it) which are involved in the study on a voluntary basis and Giampaolo La Terza (Medisoft Informatic Services) for Database maintenance and implementation.

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Figures

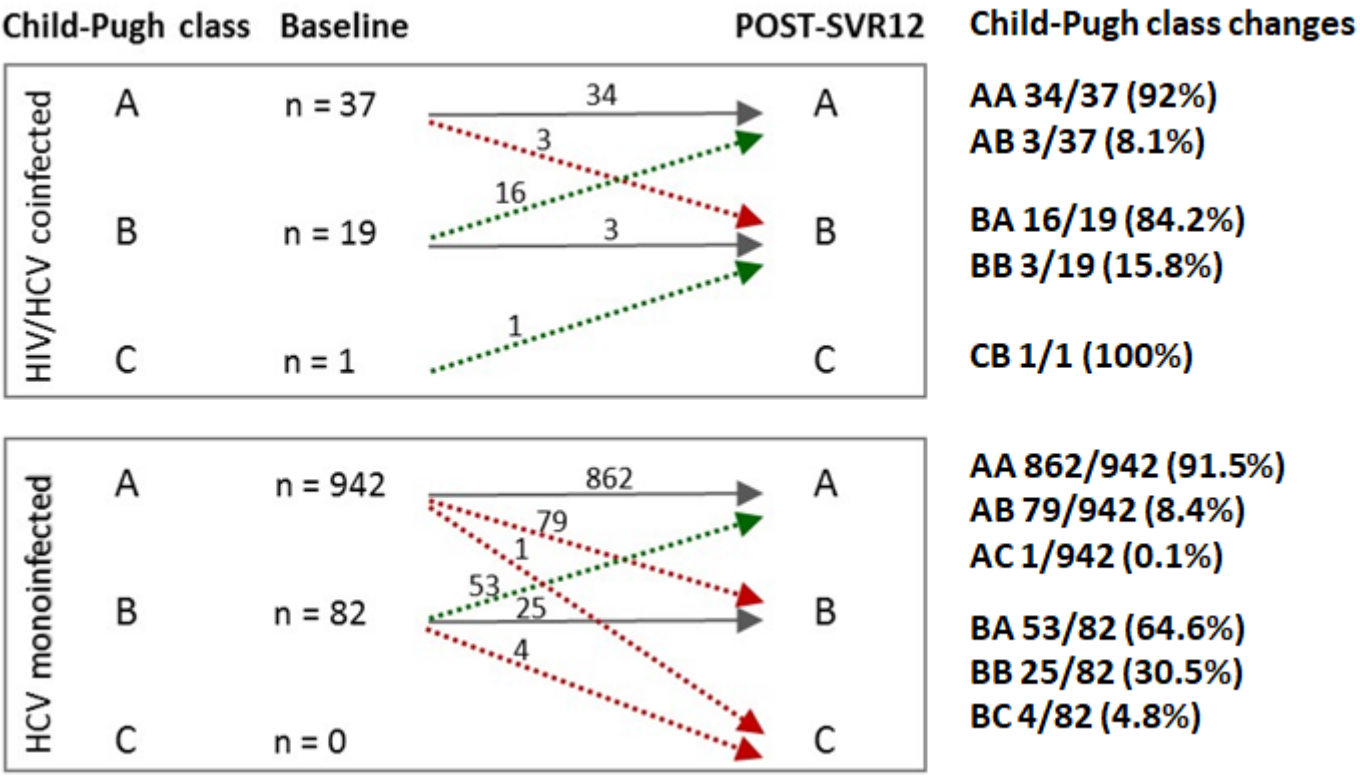

Figure 1

Changes in the severity of liver disease in terms of C-P class increase or decrease in monoinfected and coinfected patients.