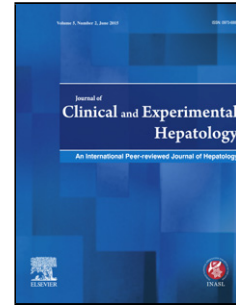


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TITLE PAGE

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Abbreviations : DAA: Direct Acting Antivirals, HCV: Hepatitis C Virus (HCV), SOF: Sofosbuvir, LDV: Ledipasvir, DCV : Daclatasvir, RBV: Ribavirin, SVR12: Sustained

Virological Response at post-treatment week 12 (SVR12), HBV : Hepatitis B, HIV : Human Immunodeficiency Virus (HIV), EASL : European Association of Study of the Liver (EASL), RVR : Rapid Virological Response, ETR: End of Treatment Response, SVR: Sustained Virological Response, mITT : modified Intention to treat, ITT : Intention to treat, HCC : Hepatocellular carcinoma

Impact of Direct Acting Antiviral therapy for treatment of Hepatitis C genotypes 1,3 and 4: A Real life experience from India

ABSTRACT:

Objective: To assess impact of direct acting antiviral (DAA) therapies for treatment of hepatitis C virus (HCV) genotypes 1,3 and 4 in a real-world cohort from India.

Methods: Adults with chronic HCV infection treated with sofosbuvir (SOF) and ledipasvir (LDV) (genotypes 1 and 4) or SOF and daclatasvir (DCV) (genotype 3), with or without ribavirin (RBV) between December 2015 and December 2016 were included. The primary endpoint was sustained virological response at post-treatment week 12 (SVR12).

Results: Of the 648 patients, 181 received SOF/LDV (65 with RBV) and 467 received SOF/DCV (135 with RBV). Most patients were males (65.4%), aged 41-60 years (49.4%) and treatment-naïve (92.6%). Genotype 3 (72.1%) was most common, followed by genotypes 1 (22.4%) and 4 (5.6%). Forty two percent patients (n=271) had cirrhosis (112 patients were decompensated). SVR12 (modified

intention-to-treat) was achieved by 98.1% of patients (512/522); (100% in genotypes 1 and 4, 97.3% (362/372) in genotype 3). On intention to treat analysis, SVR-12 was 88.1% (512/581) [genotype 1- 96.8%(121/125), genotype 3- 85.2%, genotype 4- 93.5% (29/31)]. Seventy patients had treatment failure (non response in 6, virological breakthrough in 2, 10 patients relapsed, 2 died and 50 were lost to follow up). High SVR was observed regardless of HCV genotype, presence of cirrhosis or past history of treatment. No major adverse events warranting discontinuation of treatment were noted.

Conclusions: DAA therapy for HCV genotypes 1, 3 and 4 achieves high SVR rates in all patients, including those with cirrhosis and previous non-responders.

Key words: Hepatitis C, Direct acting antivirals, Real life experience

KEY POINTS

- Oral combinations of direct acting antivirals (DAA) have become standard of care in treatment of chronic hepatitis C virus (HCV) infection.
- Phase-3 Trials have shown SVR rates exceeding 90% in HCV patients treated with DAAs, irrespective of the severity of liver disease and previously failed interferon based therapy.
- Present study shows higher SVR-12 rates for HCV patients treated with DAAs in a real world cohort from India when compared to Phase III trials and data from Western countries.
- Treatment with DAAs was well tolerated and none of the patients had serious adverse events requiring treatment discontinuation.

INTRODUCTION

The introduction of oral combinations of direct acting antivirals (DAAs) has quickly changed the landscape of hepatitis C virus (HCV) treatment in last few years. Due to higher efficacy, safety and fewer side effects than interferon-based regimes, these DAAs have now become the standard of care for treatment of chronic HCV infection.¹⁻³

Various clinical trials have shown high rates of sustained virological response (SVR) after treatment with direct acting antivirals. In a phase 3 open label study (ION-1) involving treatment naïve genotype 1 patients with or without cirrhosis, combination therapy with sofosbuvir (SOF) and ledipasvir (LDV) with or without ribavirin (RBV) achieved SVR rates between 97-99%. ION-2 trial included genotype 1 patients who were treatment experienced and those with cirrhosis (20%) and SVR rates were 94% and 96% with SOF/LDV without and with ribavirin respectively. The SVR rates increased to 99% in both groups when treatment duration was increased to 24

weeks. ⁴ In patients with genotype 4, the SYNERGY trial showed SVR rates of 95% with SOF/LDV and RBV. ⁵

Genotype 3 patients have been reported to have a relatively lower response rate with the DAAs. In a phase 3 trial ALLY-3, sofosbuvir (SOF) and daclatasvir (DCV) given without RBV in treatment naïve patients achieved SVR rates of 97% and 58% in non cirrhotic and cirrhotic patients respectively. In patients who were treatment experienced, SVR rates were 94% and 69% in non-cirrhotic and cirrhotic patients, respectively. ⁶ In the ALLY 3+ trial, treatment naïve and experienced patients with advanced fibrosis (METAVIR F3) and cirrhosis were treated with SOF, DCV and ribavirin (RBV) for 12 and 16 weeks. SVR rates in patients with advanced fibrosis were 100% both after 12 and 16 weeks of therapy, while in cirrhotics SVR rates were 83% and 88% with 12 and 16 week therapy respectively. ⁷

As the clinical trials are conducted in controlled settings, the results derived from these may not be generalizable to the real world settings. The efficacy of the drugs in a real world setting is influenced by several factors like drug compliance, adverse events leading to discontinuation and other factors like cost and availability of the drugs. The present study was done to assess the efficacy and safety of DAAs and assess the impact of therapy in a real world setting in the northern state of Punjab, India.

METHODS

Setting

This was a single center, prospective, observational study evaluating the treatment outcomes in a real-world cohort of patients with chronic HCV genotypes 1, 3 and 4 who were treated with DAAs between December 2015 to December 2016.

Patients and treatment

All patients diagnosed as chronic hepatitis C with or without cirrhosis, including those who were treatment naïve or previously exposed to interferon based regimens and were considered for all oral direct acting antiviral therapy were included in the present study. Patients who had co-infections with hepatitis B (HBV) or human immune deficiency viruses (HIV) were also included. Patients with chronic kidney disease were not offered therapy as there was a lack of data on safety of DAAs in this group during the study period. Other exclusion criteria were advanced liver disease (CTP>13 or MELD > 20), portal vein thrombosis and patients with hepatocellular carcinoma unfit for liver transplantation or locoregional therapies.

A detailed history and clinical examination was undertaken for all the patients. Anti-HCV antibody was tested for all patients by ELISA (ELISCAN HCV; RFCL Limited, Dehradun, India), quantification of HCV RNA was done by RT-PCR (COBAS TaqMan HCV Test 2.0; Roche Diagnostics Corporation, Indianapolis, IN, USA) and determination of genotype by real time PCR sequencing. High viral load was defined as HCV RNA > 600,000 IU/ml. Complete blood counts, liver and renal biochemical tests, thyroid function tests, prothrombin time index, fasting blood sugar, α -fetoprotein, and ultrasound abdomen and fibroscan were also done. Cirrhosis was diagnosed on the basis of clinical, laboratory, radiological, endoscopic, and/or histological criteria (where available). Liver stiffness values of >14.6 kPa (FibroScan®; Echosens, France) were considered to represent cirrhosis. Child-

Turcotte-Pugh (CTP) and Model for End-stage Liver Disease (MELD) scores were calculated for patients with cirrhosis. Decompensated cirrhosis was defined as patients with CTP B/C or patients presenting with jaundice, ascites, encephalopathy and / or variceal bleeding.

The European Association of Study of the Liver (EASL) guidelines (2015) were followed for treatment and the regimes followed are summarised in Table 1.⁸ The patients were considered compliant if the antiviral drugs were not missed for 2 or more consecutive days. Drug list of all the patients was reviewed by two dedicated counsellors who explained about the possible interactions of DAA based therapy with other drugs before the start of treatment. Patients were advised to discontinue proton pump inhibitors (or take them with sofosbuvir) and consult the counsellor before starting any other treatment.

This study was approved by the Institutional Review Board at Dayanand Medical College and Hospital, Ludhiana (India).

Efficacy assessment

The treatment efficacy was monitored at 4 weeks, at the end of therapy (12 or 24 weeks) and 12 weeks after the end of treatment for rapid virological response (RVR), end of treatment response (ETR) and sustained virological response (SVR) respectively. Non response was defined as failure to achieve ETR, breakthrough as reappearance of HCV RNA at any time during treatment after a negative result or increase of 1 log₁₀ IU/ml from nadir and virological relapse as undetectable HCV RNA at the end of treatment, but failure to achieve SVR.

Safety Assessment

Patients were followed up on regular intervals for any adverse events or abnormal findings on physical examination and clinical laboratory tests. For patients who were treated with ribavirin based regimes, haemoglobin was monitored according to the CTCAE (common terminology criteria for adverse events) and dose reduced by 200 mg each week if Hb was <10g/dl, till the value rose to 10g/dl or greater. RBV was withheld in patients with HB <8.5 g/dl. The dose of DAAs remained unchanged.

Statistical analysis

Patients were enrolled based on the clinical need for treatment and not the statistical considerations. The primary population for efficacy analysis [modified intention to treat (mITT)] included patients who started treatment and received at least one dose of the medicine and had no virological failure, those who were lost to follow up or had missing SVR data were excluded. In addition, efficacy was analysed based on intention to treat (ITT) population which included all patients who received atleast one dose of the planned regimen and had HCV RNA at 12 weeks post treatment (SVR 12), patients who were still on treatment at the time of analysis were excluded. The data was analyzed using descriptive and inferential statistics. The measures of descriptive statistics used in this study were frequency and percentage distribution tables. Chi-square test was used as inferential statistics in the present study.

RESULTS

Baseline characteristics and demographics

A total of 842 patients were diagnosed with HCV infection during the study period, of which 648 (77%) opted for treatment with DAAs (Figure 1). The mean age was 43.7 ± 14.1 years and a majority of patients were males ($n=424$, 65.4%), in the age group of 41-60 years ($n=320$, 49.4%). Forty eight patients (7.4%) were treatment experienced. Patients were most commonly infected with genotype 3 ($n=467$, 72.1%) and genotype 1 ($n=145$, 22.4%) and 49.7% ($n=320$) had high viral load. Several concurrent medical conditions were noted (Table 2), and 25.6% of the patients had history of concurrent significant alcohol intake. History of intravenous drug abuse was noted in 51 (7.9%) of the patients. Cirrhosis was present in 271 patients (41.8%), and among them a majority ($n=159$, 58.7%) were compensated. Hepatocellular carcinoma (HCC) was noted in 11 patients, all of whom were eligible for locoregional therapies and thus offered DAAs with intent of reducing liver related morbidity and mortality and preventing recurrence of HCC after treatment. Coinfection with HBV was noted in 5 patients and three patients were post renal transplant recipients.

Efficacy assessment

Of the 648 patients who started therapy, RVR was achieved in 612/648 (94.4%) patients and ETR in 597/605 (98.7%) patients (Figure 1). SVR (mITT) in genotypes 1 and 4 (treated with SOF/LDV with or without RBV) was 100% while in genotype 3 (treated with SOF/DCV with or without RBV) 97.3% of the patients achieved SVR. On ITT analysis overall SVR 12 was achieved in 512/581 (88.1%) patients. SVR 12 in genotypes 1, 3 and 4 on ITT analysis were 96.8% (121/125), 85.2% (362/425) and 93.5% (29/31), respectively. In patients with genotype 3, SVR rates were significantly higher in younger patients (age<40), those who achieved RVR and among the non

cirrhotic patients when compared to those with cirrhosis (Table 3, Figure 2). As compared to the patients who were previously treated with interferon based regimes, treatment naïve patients had a higher SVR, though the difference was not statistically significant (Table 3, Figure 2). SVR rates were 100% in patients with genotypes 1 and 4, irrespective of the liver status and history of previous treatment (Table 3, Figure 2). SVR rates were similar among patients with low and high viral load, irrespective of the genotype.

Treatment Failure

Virological failure was noted in 70 patients (2.8%). A majority of these (n=50) were the patients who were lost to follow up during or after treatment. Six patients had non response, 2 had breakthrough and 10 relapsed. Treatment failures were more commonly seen in genotype 3 (non response in 5, both patients with breakthrough and all 10 patients with relapse). Two patients died due to massive variceal bleed and intracranial bleed respectively. Among these, one patient had achieved ETR and the other died while on treatment, after achieving RVR.

Adverse Events

Though a few patients experienced minor side effects, none of them had to stop therapy due to drug intolerance or adverse events. The side effects like fatigue and anemia [seen in 53 patients (8.3%)] were more common in patients where ribavirin was added to the DAAs and improved with dose reduction.

DISCUSSION

The introduction of DAAs has revolutionized the treatment of HCV infection over the last few years. Though various Phase-3 trials have reported high efficacy and safety of these all oral therapies for chronic hepatitis C, these outcomes need to be assessed in the real world where patient compliance, comorbidities and other factors can affect the SVR rates. We report here a real life experience from India with DAA based regimes for treatment genotypes 1, 3 and 4 chronic hepatitis C.

A large number of patients diagnosed with hepatitis C (77%) opted for treatment. Overall, SVR 12 was achieved in 98.1% on modified ITT analysis (88.1% on ITT analysis). SVR rate in genotypes 1 and 4 was 100% (mITT) and that in genotype 3 was 97.3% (mITT). These SVR rates were higher than those in the Phase-3 trials and other real life studies. The response rates were consistently high in all patients, irrespective of their liver status or the regimen used. There were no major adverse effects warranting discontinuation of therapy though addition of RBV in patients with advanced liver disease caused anemia in 53 patients (8.3%) requiring dose reduction.

Real world experiences have shown high SVR 12 rates (91-98%) in patients treated with SOF/LDV with or without RBV in patients with genotype 1, including patients with cirrhosis and those who were treatment experienced.⁹⁻¹⁸ However, most of these studies are from the developed countries like United States, United Kingdom, Italy, Spain and Germany.⁹⁻¹⁸ There are no real world studies from the Asian subcontinent and developing countries like India. Real world data for efficacy of SOF/DCV in patients with genotypes 3 and 4 are limited. In a recent French open-label, multicenter trial, SVR 12 rate in patients with genotype 3 treated with SOF/DCV with or without RBV was noted to be 89%.¹² In the European compassionate use programme conducted in a real world setting before approval of daclatasvir, 485

patients were included from 100 centres in Germany, Austria, the Netherlands, Sweden and Norway between April 2014 to April 2015¹⁹. One hundred and two patients had genotype 3, 85% of whom had cirrhosis (52% with decompensation) and after treatment with SOF and DCV with or without RBV, SVR 12 was achieved in 88% of the patients. Another multicenter trial from Spain showed SVR rate of 94% with SOF/DCV with or without RBV in patients with genotype 3 who had cirrhosis.²⁰ In a recent study from Spain, treatment of patients with genotype 4 with SOF/LDV±RBV (n=130) yielded high SVR rate (95.4%).²¹ Preliminary results from a study being conducted in Egypt on 170 patients with genotype 4 have shown high SVR 4 rates, however SVR 12 data were not available.²²

Our study showed higher rates of SVR in genotypes 1, 3 and 4 when compared to the Phase-3 trials and the real world experiences from the West. The possible reasons for higher SVR could be related to both viral and host related factors. There were a fewer number of patients with HBV coinfection and none with HIV coinfection in our study. A larger number of patients with genotype 1b, which is considered to have a better therapeutic response with DAA therapy could also have contributed to higher rates of response. We also observed a higher prevalence of sub-genotype 3a, as noted from the neighbouring areas in Pakistan and these patients had an excellent response to treatment.^{23 24} High SVR could also be attributed to host factors like a larger number of treatment naïve and non-cirrhotic patients.

The lower cost of sofosbuvir based protocols (as compared to Western world) and fewer side effects have increased the acceptability of therapy in developing nations like India. Our previous real life experience with pegylated interferon and ribavirin

showed a much lower (one-third) acceptance for initiation of treatment and low SVR rates due to poor tolerability (6%) and non response (1%).²⁵ In the present cohort of patients treated with DAAs, 77% of the patients diagnosed with hepatitis C infection opted for treatment and the therapy was well tolerated even in difficult to treat groups of patients like those with cirrhosis and past history of treatment failure. There were no major adverse events requiring discontinuation of therapy. Six patients (0.9%) had non response to therapy. None of these had achieved RVR and the duration of therapy in all these patients was 12 weeks (Figure 1). Extension of therapy to 24 weeks after a failed RVR in these patients may have increased the SVR rate.

Our study also presents the first real world experience of treatment of genotype 4 with SOF/LDV with or without RBV from Asia. SVR 12 rate in this group of patients (including cirrhotics and treatment experienced patients) was 100%. Though the number of patients with genotype 4 was small, these results support the efficacy of these regimens in patients with genotype 4 infection as shown in clinical trials.

The study had a few limitations. It was a single center study. Subtyping into genotype 1a and 1b was not done in 43% of the patients. The number of patients with genotype 4 was small (though expected due to low prevalence of genotype 4 in Asia).

In conclusion, our data show that DAA-based regimens are safe and have a high success rate in the treatment of patients with genotypes 1,3 and 4 HCV infection in real-life setting. This is independent of the liver status and past history of treatment. The availability of the dual-DAA regimens at low cost or free of cost at some areas

under health care schemes, lower rates of major adverse events, ease of oral dosing has lead to increasing acceptability of treatment. Development of comprehensive strategies to improve awareness of hepatitis C, provision of universal screening with confidential testing for all, provision of drugs at low cost and counselling to reduce spread and reinfection in populations at high risk can help us achieve a world free of hepatitis C virus.

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Table 3 : Factors determining SVR (Total- 512)

Factors			Genotype 1&4 SOF+LDV+/- RBV (n=150)	P value	Genotype 3 SOF+Dac+/- RBV (n=362)	p-value
Viral factors	Viral load	Low	74	0.359	180	0.515
		High	76		182	
Host factors	Age	<40 yrs	56	0.846	215	0.016
		>40 yrs	94		147	
	Gender	Male	103	0.310	235	0.880
		Female	47		127	
	BMI	<23	57	0.555	136	0.648
		23-25	19		80	
		>25	74		146	
	Alcohol use	Present	47	0.089	86	0.541
		Absent	103		276	
	IVDU	Present	13	0.327	29	0.259
		Absent	137		333	
	Comorbidities	Present	30	0.746	59	0.508
Absent		120	303			
Status of liver	Chronic hepatitis	90	0.841	217	0.016	
	Cirrhosis	60		145		
Treatment	Naïve		132	0.370	341	0.742
Details	Experienced		18		21	
RVR4weeks	Present		145	0.727	347	0.013
	Absent		05		15	
Coinfection	HIV		00	0.648	00	0.279
	HBV		01		04	

CTP: Child Turcotte Pugh Score, IVDU : Intravenous drug abuse, SOF: Sofosbuvir, LDV: Ledipasvir, DCV: Daclatasvir, RBV: Ribavirin, RVR: Rapid Virological Response, HIV: Human immunodeficiency virus, HBV: Hepatitis B Virus

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Table 2. Demographic profile of patients who opted for treatment (n=648)

Total Patients	648
Age in years, mean (SD)	43.7±14.1
<20	15 (2.31%)
21-40	228 (35.19%)
41-60	320 (49.38%)
>60	85 (13.12%)
Gender (Males:Females)	424:224
BMI	
<23	245 (37.8%)
23-25	190 (29.3%)
>25	213 (32.9%)
Comorbidities/Addictions	
Diabetes Mellitus	56 (8.6%)
Hypertension	28 (4.3%)
Hypothyroidism	7 (1.1%)
Bronchial Asthma	4 (0.6%)
Alcohol use	166 (25.8%)
Smoker	28 (4.3%)
IVDU	51 (7.9%)
Coinfections	
HIV/HCV	00 (0%)
HBV/HCV	05 (0.8%)
Family History of CHC	143 (22.1%)
Genotype	
Genotype 1	145 (22.4%)

- 1a	- 18
- 1b	- 64
- Subtype not specified	- 63
Genotype 3	467 (72.1%)
- 3a	- 286
- 3b	- 04
- Subtype not specified	- 177
4	36 (5.6%)
Viral load	
<600,000 IU/l	328 (50.6%)
>600,000 IU/l	320 (49.4%)
Liver status	
Chronic hepatitis	377 (58.2%)
Cirrhosis	271 (41.8%)
- HCC	11 (1.7%)
CTP	
A	159 (24.8%)
B	92 (14.2%)
C	20 (3.1%)
Treatment status	
Naïve	600 (92.6%)
Experienced	48 (7.4%)
- Interferon based	40 (6.2%)
- SOF+RBV	08 (1.2%)

BMI: Body Mass Index, IVDU : Intravenous drug abuse, CHC:Chronic Hepatitis C, HIV: Human immunodeficiency virus, HBV: Hepatitis B Virus, HCC: Hepatocellular carcinoma, CTP: Child Turcotte Pugh Score, SOF: Sofosbuvir, RBV: Ribavirin

Table 1- Regimens of Direct Acting Antivirals for treatment of HCV infection

Patients		Genotypes 1 and 4	Genotype 3
Chronic Hepatitis	Treatment naïve	SOF ^a /LDV ^b for 12 weeks	SOF ^a +DCV ^c for 12 weeks
	Treatment experienced	SOF ^a /LDV ^b for 12 weeks	SOF ^a +DCV ^c +RBV ^d for 12 weeks SOF ^a +DCV ^c for 24 weeks if contraindications for use of RBV
Compensated Cirrhosis (CTP A)	Treatment naïve	SOF ^a /LDV ^b for 12 weeks	SOF ^a +DCV ^c +RBV ^d for 24 weeks
	Treatment experienced	SOF ^a /LDV ^b +RBV ^d for 24 weeks if negative predictors of response	
Decompensated Cirrhosis (CTP B, C upto 12 points)		SOF ^a /LDV ^b +RBV ^d 12 weeks SOF ^a /LDV ^b for 24 weeks (if contraindications to use of RBV)	SOF ^a +DCV ^c +RBV ^d for 24 weeks

SOF-Sofosbuvir 400mg, LDV-Ledipasvir 90mg, DCV-Daclatasvir 60mg, RBV-Ribavirin 200mg

a+b:fixed dose combination once a day, a+c one tablet each daily, d- RBV 1000 mg/day if <75 kg,

1200mg/day if >75 kg, in divided doses.

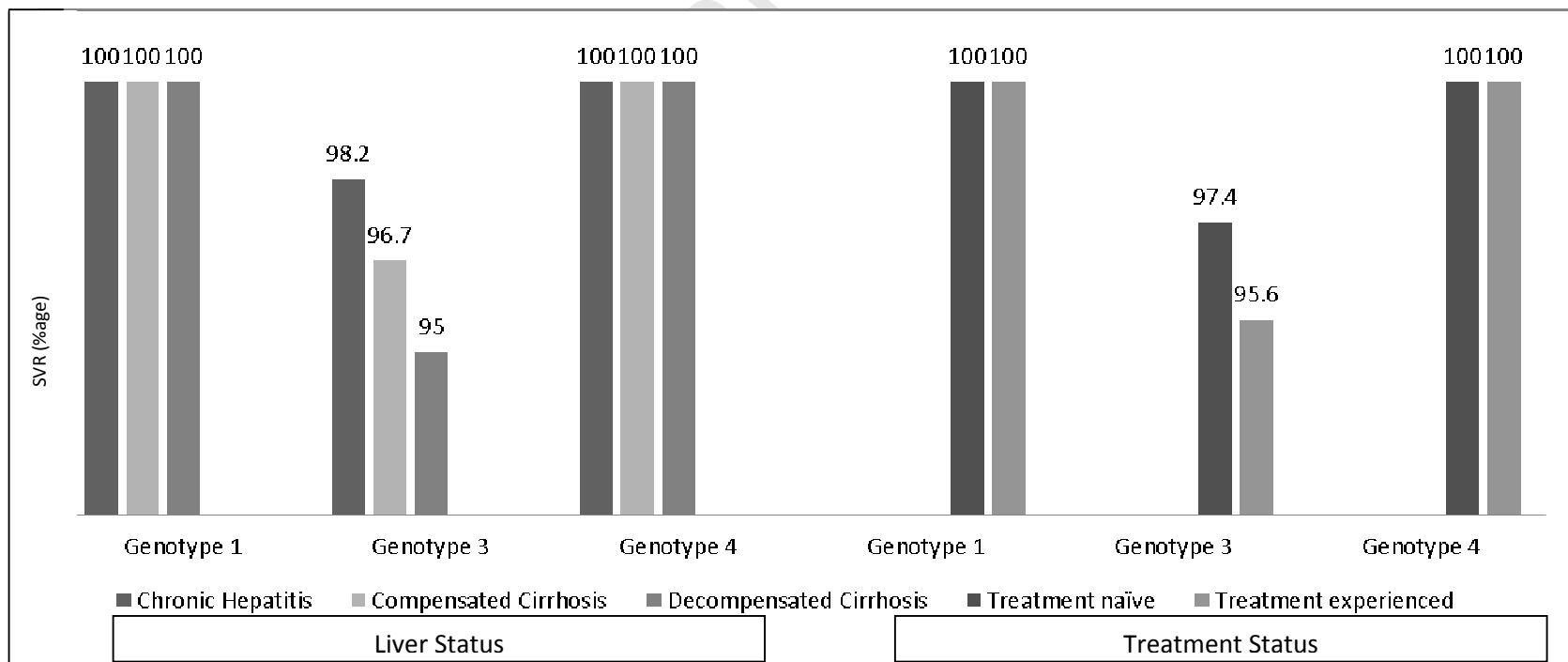


Figure 2 : Rates of sustained virological response (SVR 12) according to genotypes and liver status

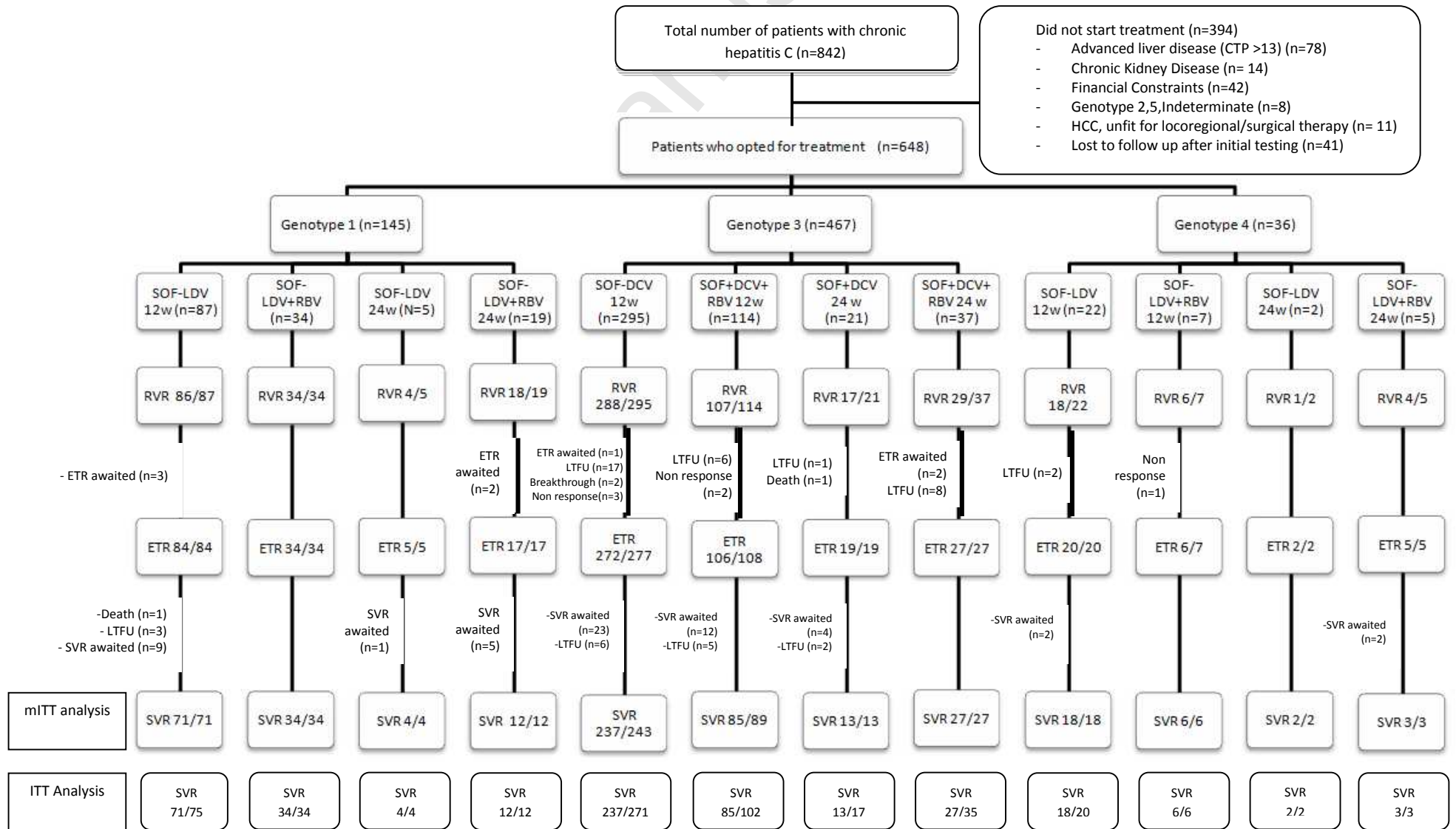


Figure 1 : Flow of patients with Chronic Hepatitis C treated with Direct Acting Antivirals

mITT: all treated patients, except for those who were lost to follow-up, withdrew informed consent or withdrew for undocumented reasons

ITT : all patients who received ≥ 1 dose of the programme regimen, excluding those where ETR/SVR was awaited due to ongoing treatment

CTP, Child Turcotte Pugh; DCV, daclatasvir; ETR, End of treatment response; HCC: Hepatocellular carcinoma; ITT, intention-to-treat; LDV , Ledipasvir;

LTFU, Lost to follow up; mITT, modified intention-to-treat; RBV, ribavirin; RVR, Rapid Virological Response, SOF; sofosbuvir; SVR12, sustained virological response at post-treatment week 12