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# Hepatitis C Treatment Failure with Direct Acting Antiviral Therapy: Demographics and Clinical Management

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## Abstract

**Background:** DAA failure was seen in a small percentage of Hepatitis C (HCV) infected patients in clinical trials. The incidence of this DAA failure against HCV infection may vary in clinical practice. Those patients who had initial DAA failure are generally managed with an alternate regimen of DAA or by addition of ribavirin for a longer duration.

**Aims:** To find out the incidence of DAA failure in clinical practice and also to define the associated clinical characteristics and DAA regimen used in those patients.

**Methods:** Retrospective, single center study conducted at a tertiary care center utilizing an Electronic Medical Record (EMR) of all patients treated with DAAs for HCV infection at our institution. We analyzed the database for patients who did not achieve Sustained Virological Response at 24 weeks (SVR24) between October 2014 and July 2017. The DAA failure rate, viral genotypes and related host factors were evaluated in this group. Patients were excluded if full treatment course of DAA was not completed.

**Results:** Total 1686 patients received treatment of HCV infection with DAA during the study period, 53 patients (3.14%) of them did not achieve SVR24. 9 of the 53 patients (16.9%) were excluded due to an incomplete course, leaving 44 cases for review. 56.8% of patients were treatment naïve, and 43.2% were treatment-experienced to prior antiviral therapy. DAA failure was most commonly seen in the Ribavirin (RBV)/Sofosbuvir (SOF) group (40.9%), males (81.8%), cirrhotics (63.6%), and in patients who received proton pump inhibitor therapy (27.3%).

**Conclusion:** DAA failure rate in the treatment of hepatitis C was low (3.14%) in our study. The DAA failure group had varying clinical and viral characteristics. PPI therapy should be avoided with certain DAA therapy. In case of DAA failure, different DAA regimen should be used or ribavirin should be added to the existing one for a longer duration. A better understanding of patients' clinical characteristics and viral resistance may guide future treatment algorithms.

**Keywords: Direct acting anti-virals (DAA) for hepatitis C; DAA failure; Treatment of hepatitis C; HCV infection**

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## Introduction

The evolution of treatment of HCV infection has been long since its discovery in 1989 [1]. The standard of care for chronic HCV infection was pegylated interferon and ribavirin (PEG/RIBA) between 2001 to 2011. Direct Acting Antivirals (DAAs) were first approved in the United States in May, 2011 and replaced the PEG/RIBA as the standard of care for the treatment of chronic hepatitis C. DAAs are agents which work on the non-structural proteins of HCV genome [2] and disrupts viral replication (Figure 1).

Initially, two first generation NS3/4A protease inhibitors telaprevir and boceprevir were introduced into the market to be used with PEG/RIBA. But due to multiple side effects, drug-drug interactions, complex regimen, high price and long duration of therapy, their production was discontinued and they were taken out of the market in 2014 and 2015 respectively. Then second generation NS3/4A protease inhibitor simeprevir and NS5B nucleotide polymerase inhibitor sofosbuvir came to the market to be used with PEG/RIBA. Subsequently, complete interferon-free regimen sofosbuvir plus simeprevir, sofosbuvir plus Ledipasvir and sofosbuvir plus daclatasvir and 4 fixed drug combinations dasabuvir, ombitasvir, paritaprevir and ritonavir with or without interferon got approved for the treatment of hepatitis C [2]. Over the years multiple classes of DAAs have been developed. These include 3/4A Protease Inhibitors (PIs), NS5B nucleoside polymerase

**Table 1:** Demographics of HCV patients who failed DAA therapy.

| | | |
|---|---|---|
| Gender | Male | 81.8% (36/44) |
| | Female | 18.2% (8/44) |
| Genotype | 1 | 72.7% (32/44) |
| | 2 | 13.6% (6/44) |
| | 3 | 11.4% (5/44) |
| | 4 | 2.2% (1/44) |
| Cirrhosis | Yes | 63.6% (28/44) |
| | No | 36.4% (16/44) |
| Treatment Exposure | Naive | 56.8% (25/44) |
| | Experienced | 43.2% (19/44) |
| Proton Pump Inhibitor Exposure | High Dose | 15.9% (7/44) |
| | Low Dose | 11.4% (5/44) |
| | None | 70.5% (31/44) |
| | Unlisted | 2.2% (1/44) |

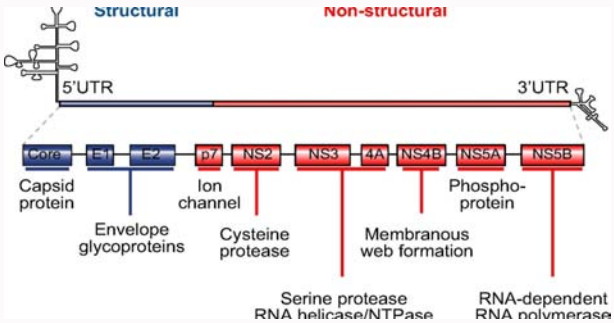


**Figure 1:** HCV genome.

inhibitors, NS5B non-nucleoside polymerase inhibitors and NS5A inhibitors [3]. In the era of DAAs, eradication of HCV infection has been extremely successful with most of the studies showing the achievement of Sustained Virologic Response (SVR) greater than 90%. In clinical practice, we see a small percentage of patients not achieving SVR when we treat HCV infection with DAAs. The reason for this is not yet clearly elucidated, but several viral and host factors can exist which include viral resistance (NS5A resistance associated substitutions, Q80K polymorphism) patterns [4,5], certain HCV genotypes (GT-1 and GT-3) more resistant to DAAs than others, presence of cirrhosis and usage of a proton pump inhibitor at the time of sofosbuvir/Ledipasvir and sofosbuvir/velpatasvir-based treatment [6]. Considering all these factors for DAA failure, we conducted a retrospective study of patients at our institution who failed DAA therapy with the aim of better understanding if an association exists between failed therapy and patients' clinical and demographic factors.

## Methods

### Study design

This was a single center retrospective study including 1686 patients treated with DAAs between October 2014 and July 2017. Our institution kept a detailed database of all patients who received DAA treatment. The database consisted of patient's age, gender, presence or absence of cirrhosis prior to treatment, prior anti-HCV treatment exposure, time of initiation, and termination of DAA, initial viral load, SVR12 and SVR24 and cure status. We searched for all patients who were listed as "not cured" and did a retrospective chart review on particular DAA regimen used, patients' gender, HCV genotype, presence or absence of cirrhosis, prior anti-HCV treatment experience and use of PPI during DAA therapy. The data was analyzed in Microsoft excel.

**Table 2:** Treatment regimens in HCV patients who failed DAA therapy.

| DAA Regimen | % Treated |
|---|---|
| Ribavirin/Sofosbuvir | 40.90% |
| Ledipasvir/Sofosbuvir | 29.50% |
| Simeprevir/Sofosbuvir | 13.60% |
| Daclatasvir/Sofosbuvir | 6.80% |
| Sofosbuvir/Velpatasvir | 2.20% |
| Ribavirin/Elbasvir/Grazoprevir | 2.20% |
| Ribavirin/Simeprevir/Sofosbuvir | 2.20% |
| Ombitasvir/Paritaprevir/Ritonavir/Ribavirin | 2.20% |

The two most common treatment regimens that patients received after failed therapy were sofosbuvir/Ledipasvir (34.1%) and sofosbuvir/Ledipasvir/ribavirin (9.1%). No patients were retreated with the same medication they were initially exposed to. 24% did not have clearly established further treatment plans.

## Results

Of the 1686 patients treated with DAAs during the study period, 53 (3.14%) did not achieve SVR24. Of the 53 patients who were not cured, 9 (16.9%) were excluded due to an incomplete course of treatment, leaving 44 cases for review. Of these 44 patients, 25 (56.8%) were treatment naïve and 19 (43.2%) had prior exposure to treatment.

### Clinical characteristics and demographics

The results of patients' gender, HCV genotypes, presence or absence of cirrhosis and PPI exposure at any point during DAA treatment are summarized in Table 1. Of the 44 patients reviewed, 36 (81.8%) were male and 8 (18.2%) were female. 32 (72.7%) had genotype 1; 6 (13.6%) genotype 2; 5 (11.4%) genotype 3; 1 (2.2%) genotype 4. 28 (63.6%) patients were cirrhotic at the time of treatment.

PPI usage was classified according to dose, with high dose considered anything greater than or equal to 40 milligrams (mg) per day and low dose considered 20 mg per day. 27.3% of patients were on a Proton Pump Inhibitor (PPI) at the time of treatment initiation.

### Failed regimens

Of all the 44 DAA failure cases, the treatment failed most often was ribavirin/sofosbuvir (40.9%). Ledipsavir/sofosbuvir was the second most commonly failed treatment (29.5%); simprevir/sofosbuvir was the third most commonly failed treatment (13.6%). A breakdown of the remaining regimens that were failed is displayed in Table 2.

## Discussion

DAA has revolutionized the treatment of HCV infection. Patients receive oral medications for a shorter period of time without many side effects. Drug-drug interactions are also less. The findings of our study indicate that DAA for the treatment of HCV infection is highly successful and DAA failure rate is low in clinical practice. But DAAs are expensive medications. Patients get insurance approval of DAA for their hepatitis C treatment after going through various laboratory and imaging studies. So DAA failure for HCV eradication becomes not only less cost-effective but also frustrating to the patients and the treating physicians. On the other hand, successful eradication of HCV infection gives multitude of health benefits which include reduction or decrease in progression of hepatic fibrosis, decreased

risk of developing hepatic failure and hepatocellular carcinoma, control of some extra-hepatic complications of HCV infection and overall, improvement of survival [7-10]. Kondili et al. [11] did a study on the incidence of DAA failure in patients with advanced liver disease due to HCV infection. The DAA failure rate was 7.6% for patients who received sofosbuvir plus ribavirin or simeprevir plus sofosbuvir plus ribavirin, whereas it was 1.4% for other regimens containing sofosbuvir plus daclatasvir or sofosbuvir plus Ledipasvir or other DAAs [11]. In our study, among the DAA failure cases, the most commonly failed treatment was ribavirin/sofosbuvir followed by Ledipasvir/sofosbuvir followed by simeprevir/sofosbuvir. 27.3% of those DAA failure cases were receiving PPI therapy. Solubility of Ledipasvir and velpatasvir decreases as the gastric pH increases i.e. they require an acid environment for their absorption [12,13]. Tapper et al. [14] found that patients receiving sofosbuvir/Ledipasvir regimen and twice daily PPI had lower SVR12. HCV genotype 1 infection, male patients and cirrhotic patients had higher DAA failure rate than non-genotype 1, female patients and non-cirrhotic patients in our study. Jacobson et al. [15] in FUSION study found that sofosbuvir/ribavirin therapy was more effective for HCV genotype 2 patients than HCV genotype 3 patients. In our study, DAA failure rate was slightly higher in HCV genotype 2 patients than HCV genotype 3 patients for uncertain reason. Our study also found that DAA failure rate was more in treatment-naïve patients than treatment-experienced patients. This could be explained as most of the treatment experienced patients were PEG/RIBA experienced and they responded nicely with the DAA therapy. We did not investigate whether or not genotype 2 patients and treatment-naïve patients received more PPI therapy. DAA failure cases were further treated with different DAA regimen.

## Conclusion

DAAs are now the standard of care for the treatment of HCV infection and fortunately DAA failure rate is low in real life clinical practice. Host factors, viral factors and certain DAA regimen play into account for the DAA failure. Host factors include male gender, presence of cirrhosis and PPI intake in Ledipasvir and velpatasvir based therapy. Viral factors include genotype of HCV as genotype 1 HCV is more resistant than non-genotype 1 HCV. Certain DAA regimens like ribavirin/sofosbuvir, Ledipasvir/sofosbuvir and simeprevir/sofosbuvir have more failure rate than other DAAs. In case of a particular DAA failure, different DAA regimen should be used.

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