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Factors Associated with Treatment Failure for Hepatitis C in the Era of Direct-Acting Antivirals Therapy in Cameroon

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ABSTRACT

Background: The recent introduction of direct acting antivirals (DAAs) in Cameroon represents an important step in the treatment of chronic hepatitis C which till recently was pegylated interferon based. However, there is still a number of patients who fail DAA-based regimens. The aim of this study was to identify factors associated with these failures in patients treated for chronic HCV in Cameroon.

Methods: We consecutively included patients infected with HCV from six treatment centers in Cameroon. All patients treated with DAAs and having a documented viral load 12 weeks after completion of treatment were included. Factors associated with treatment failure were sought using Pearson's Chi-square test and logistic regression.

Results: We included 272 patients with mean age of 63.4 ±8.8 years. Genotype 1 was the most frequent (43.8%) followed by genotype 4 (31.6%) and genotype 2 (23.5%). In 3 patients (1.2%) there were combined genotypes (G1/G4 in 1 patient and G1/G2 in 2 patients). A high viral load (>800.000 UI/ml) was found in 176 patients (68%) and 148 patients (58%) had severe fibrosis or cirrhosis. Patients with prior exposure to anti-HCV treatment represented 20.2% and treatment failure rate was 25% (68/272). Factors associated with treatment failure were prior exposure to anti-HCV medication and severe fibrosis or cirrhosis.

Conclusion: Oral direct acting antiviral agents have revolutionized the treatment of hepatitis C. However, a number of patients still present failure to this treatment. In Cameroon factors found to be associated to treatment failure were severe fibrosis or cirrhosis and prior exposure to anti-HCV treatment.

Keywords
Hepatitis C, Direct Acting Antivirals, Failure, Cameroon.

Background
According to the World Health Organisation, 71 million individuals worldwide (1% of the population) are chronically infected with the hepatitis C virus (HCV) in 2015 [1]. The burden of HCV infection is due to progression of chronic liver disease, which can lead to cirrhosis, liver failure, hepatocellular carcinoma (HCC), and death. Globally, 27% of all cases of cirrhosis and 25% of all cases of

HCC are attributable to HCV infection [2]. A sustained virological response (SVR) after effective antiviral treatment is associated with decreased risk in liver disease progression and its complications [3].

Recently, treatment options for HCV infection and its efficacy have improved with the development of direct acting antiviral agents (DAA) [4]. Despite high SVR rates following DAA treatment, there is still some patients who fail DAA-based therapies [5]. Host, virus and treatment regimen are factors that could explain DAA failures [6]. In Cameroon, no study has been published on HCV DAA treatment failure. Therefore, this study aims to address this situation.

Methods
Study design and setting
We conducted a retrospectively analysed study in six health facilities including 2 public and 4 private within the cities of Yaoundé and Douala.

Procedure
Patients were selected from the six centres mentioned above. We included all HCV infected patients treated only with DAAs and having the viral load of 12 weeks after the end of treatment available. The viral load of HCV was quantified by real-time PCR (RT-PCR real-time TaqMan Roche®) with a detection threshold of 12-15 IU / ml (1.0 to 1.2 logIU / mL).

The quantification of the viral load was carried out by routing the sample to a laboratory located in France (Cerba® laboratory) with return of results in two weeks. A viral load greater than 800.000 IU/ml (5.9 log UI/ml) was considered as high. The level of fibrosis assessed by Fibrotest® was performed by the Laboratoire Cerba in France. Patients without result of viral load 12 week after the end of treatment, patients still on treatment, patients lost from follow-up and patients with incomplete files were excluded.

Treatment protocols used were: Sofosbuvir/Ledipasvir ± Ribavirin (SOF/LDV ± RBV), Sofosbuvir/Daclatasvir ± Ribavirin (SOF/DLV ± RBV) and Sofosbuvir/Ribavirin (SOF/ RBV). The duration of treatment ranged from 12 to 24 weeks.

The different time points designed to assess efficacy were: At week 4 (rapid virological response), week 12 or 24 (end of treatment virological response) and 12 weeks after completion of treatment (sustained virological response) defined as undetectable HCV RNA by quantitative PCR.

Statistical analysis
Data were entered and analyzed using SPSS 21.0. Means ± standard deviation was used for quantitative variables, frequency and proportions for qualitative variables.

Bivariate analysis was performed, using χ^2 and Fischer's exact test wherever appropriate. A p value of less than 0.05 was considered statistically significant.

Results
Patients characteristics
Baseline demographic data are summarized in Table 1.

Of the 272 patients included in this study they were 111 males (40.8%) and 161 (59.2%) females. The mean age of the study population was 63.46 ± 8.8 years and 247 patients (90.8%) were aged 50 years and above. High blood pressure (77.4%), at risk intake of alcohol (47.2%) and diabetes mellitus (39%) and were the most frequent comorbidities. HBV and HIV coinfection were found respectively in 6 patients (3.4%) and 2 patients (1.4%).

Characteristics		n (%)
Gender	Male	111 (40.8%)
	Female	161 (59.2%)
Age groups (N=263)	≥ 50 ans	247 (93.9%)
	< 50 ans	16 (6.1%)
	Mean age	63.46 ± 8.8 years
BMI	≥ 30	53 (36.8%)
	< 30	91 (63.2%)
Co morbidities	High blood pressure	123/159 (77.4%)
	At risk alcohol intake	68/144 (47.2%)
	Diabetes	46/118 (39.0%)
	HBV co-infection	6/177 (3.4%)
	HIV co-infection	2/141 (1.4%)

Table 1: Baseline demographic data of patients.
BMI: Body Mass Index, HBV: Hepatitis B Virus, HIV: Human Immunodeficiency Virus.

Clinical and biological baseline data are presented in table 2. Genotype 1 was the most frequent (43.8%) followed by genotype 4 (31.6%) and genotype 2 (23.5%). Combined genotypes were present in 3 patients (1.2%) and were one 4/1 and two 1/2. A high viral load (>800.000 UI/ml) was present in 176 patients (68%) and 148 patients (58%) had severe fibrosis or cirrhosis. As reported in table 3, 55 patients (20.2%) included in the study had a past history of anti HCV treatment failure. Among them 12 patients (4.4%) have had prior exposure to direct antiviral agent.

Characteristics		n (%)
Genotypes	1	119 (43.8%)
	2	64 (23.5%)
	4	86 (31.6%)
	Recombinant	3 (1.1%)
Viral load	High (>800.000 UI/ml)	176 (68.0%)
	Low (<800.000 UI/ml)	83 (32.0%)
ALAT level	High (≥ 40 UI/ml)	120 (63.5%)
	Normal	69 (36.5%)
Fibrosis	F3 or F4	148 (58.0%)
	F0, F1 or F2	107 (42.0%)

Table 2: Clinical and biological baseline data.
ALAT: Alanine Aminotransferase.

Characteristics		n (%)
Naïves patients		217 (79.8%)
Past history of treatment failure		55 (20.2%)
Prior exposure to DAA		12 (4.4%)
Prior exposure to interferon		43 (15.8%)
Protocol without ribavirin		120 (44.1%)
Number of DAA	1	61 (22.4%)
	2	211 (77.6%)
Treatment protocol		n= 272
Sofosbuvir/Ledipasvir		109 (40.1%)
Sofosbuvir/Ledipasvir/ Ribavirine		84 (30.9%)
Sofosbuvir/ Daclatasvir		11 (4%)
Sofosbuvir/ Daclatasvir/ Ribavirine		7 (2.6%)
Sofosbuvir/Ribavirine		61 (22.4%)
Treatment duration	12 or 16 weeks	237/272 (87.1%)
	24 weeks	35/272 (12.9%)
Treatment adherence	Poor	20 (7.4%)
	Good	252 (92.6%)

Table 3: Therapeutic profile of the population.
DAA: Direct Acting Antivirals.

Virological response

We had end treatment response of 94.1% and sustained virological response of 75%. The table 4 present the virological response.

Failure to SVR was significantly associated with past history of treatment failure in multivariate analysis. Severe fibrosis or cirrhosis was also associated with treatment failure. In univariate analysis, factors found to be associated with treatment failure were genotype 4, usage of only one DAA.

The table 5 summarize the factors associated with treatment failure.

	Genotype 1	Genotype 2	Genotype 4	Recombinant Genotype	Total
RVR	56/85 (65.9%)	37/48 (77.1%)	53/64 (82.8%)	0/2 (0%)	146/199 (73.3%)
ETR	94/98 (94.9%)	42/48 (87.5%)	72/75 (96.0%)	3/3 (100%)	211/224 (94.1%)
SVR12	92/119 (77.3%)	40/64 (62.5%)	71/86 (82.6%)	1/3 (33.3%)	204/272 (75.0%)

Table 4: Virological response.
RVR: Rapid Virological Response, ETR: End Treatment Response; SVR 12: Sustained Virological Response at 12 weeks.

Discussion

This study was aimed to identify factors associated with DAA regimens failures in Cameroonians with chronic hepatitis C virus infection. It was a multicentric study including 272 patients followed in the different centers of chronic viral hepatitis C treatment. Despite high efficacy of DAA regimens, some of our

	Therapeutic failure n (%)	Therapeutic response n (%)	Total n	OR (95% CI)	p value	Adjusted OR (95% CI)	Adjusted p value
Age ≥ 50 years	63 (25.5%)	184 (74.5%)	247	1.48 (0.40-5.37)	0.76	1.23 (0.31-5.22)	0.73
Male gender	31 (27.9%)	80 (72.1%)	111	1.29 (0.74-2.26)	0.39		
FIbrosis F3F4	39 (26.7%)	107 (73.3%)	146	1.63 (0.87-3.02)	0.12	2.0 (0.88-4.56)	0.09
High viral load	49 (27.8%)	127 (72.2%)	176	1.39 (0.75-2.58)	0.29	1.22 (0.51-2.88)	0.65
Genotype							
1	27 (22.7%)	92 (77.3%)	119/272	0.80 (0.45-1.40)	0.43		
2	24/64 (37.5%)	40/64 (62.5%)	64/272	2.23 (1.22-4.09)	0.08		
4	15/86 (17.4%)	71 (82.6%)	86/272	0.53 (0.27-1.00)	0.05	0.57 (0.22-1.48)	0.25
Recombinant	2 (66.7%)	1 (33.3%)	3/272	6.15 (0.54-68.9)	0.15		
Past history of treatment failure	22/55 (40%)	33/55 (60%)	55/272	2.47 (1.32-4.65)	0.04	2.85 (1.03-7.84)	0.04
Prior exposure to DAA	5/12 (41.7%)	7/12 (58.3%)	12/272	2.23 (0.68-7.28)	0.18	0.29 (0.03-2.21)	0.23
Prior exposure to interferon	17/43 (39.5%)	26/43 (60.5%)	43/272	2.28 (1.14-4.53)	0.01		
Absence of ribavirin	20/120 (16.7%)	100 (83.3%)	120	0.43 (0.24-0.78)	0.05	0.68 (0.25-1.83)	0.45
Number of DAA							
1	25 (41%)	36 (59%)	61	2.7 (1.47-4.99)	0.01	1.96 (0.75-5.13)	0.16
2							
Duration of treatment							
12 or 16 weeks	60 (25.3%)	177 (74.7%)	237/272	1.14 (0.49-2.65)	0.75	0.88 (0.27-2.84)	0.83
24 weeks							
Absence of RVR							
Yes	17	36	53/199	0.85 (0.80-3.24)	0.17	1.14 (0.46-2.81)	0.77
No	33	113					
Poor therapeutic adherence	8/20 (40.0%)	12/20 (60%)	20/272	2.13 (0.83-5.46)	0.10	1.01 (0.27-3.74)	0.98

Table 5: Factors associated with therapeutic failure.
DAA: Direct Acting Antivirals, RVR: Rapid Virological Response.

patients doesn't achieve sustained viral response. Thus, the results of our study should be useful in predicting the patients susceptible to fail DAA based therapies. Many factors have been identified as associated with failure to DAA therapies. They are grouped as host factors (cirrhosis, failure to multiple DAAs, male gender), virus related factors (genotype 1a, 3, baseline NS5A resistance associated variations (RAV)) and treatment regimen related factors (shorten duration of treatment, poor adherence, non-addition of ribavirin) [7].

In the present study, we found an overall failure rate of 25% while earlier studies on fewer populations found lower failure rate as 8.4% [8]. The 25% failure rate reported in this study is high and should for several reasons be analyzed with caution. Firstly, only patients with available sustained virological response were included in the analysis and this could have introduced some selection bias in our study population. Secondly, this failure rate could however reflect the reality as in this study about 58% of the patients had severe fibrosis or cirrhosis and 90.8% were aged 50 years and above which are all known to be associated with low response rate. More so, Sofosbuvir plus ribavirin the available regimen mostly used for treatment of HCV genotype 2 in Cameroon between 2015 and 2018 is also known to provide low sustained virological response rate.

Despite these limits, this study however identifies factors associated with failure to treatment by direct antiviral agents among Cameroonian patients suffering from chronic viral hepatitis C. Past history of treatment failure, severe fibrosis or cirrhosis, use of only one DAA during treatment and genotype 4 were associated with treatment failure. Association observed with genotype 4 and treatment failure in univariate analysis is not common and may be due here to confounding factors. Thus, with multivariate analysis genotype 4 is no more associated with treatment failure. Infection with HCV genotype 3 has been associated with more rapid liver fibrosis progression, liver cancer, and liver-related mortality than other genotypes [12], making these patients more susceptible to treatment failure. This genotype was not found in our patients.

Past history of chronic HCV treatment failure is associated DAA failure [13]. Resistance associated variations (RAV) may contribute to explain this association. The RAVs of hepatitis C have been attributed to a high viral replication rate, high error rate of viral RNA-dependent RNA polymerase, and lack of overlapping reading frames in the hepatitis C nonstructural region [14]. The above-mentioned replicative errors lead to numerous variants known as HCV-quasispecies [15]. During HCV infection, the wildtype of virus predominates but when several isolates in the HCV-quasispecies can undergo mutations and then confer resistance to DAAs by directly or indirectly effects [15]. One main limitation of our study is the absence of screening for RAV in participants. Male gender, shorter duration of treatment, non-addition of ribavirin has not been found associated to treatment failure as described in some studies.

Conclusion
Despite its efficacy in the treatment of HCV infection, DAA based regimens still failed in some patients. In Cameroon, factors found to be associated to this failure are severe fibrosis or cirrhosis and past history of treatment failure. This should alert clinicians regarding this special populations and health authorities to envisage retreatment options.

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