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FACTORS ASSOCIATED WITH UNSUPPRESSED VIRAL LOAD AMONG PEOPLE WITH CHRONIC HEPATITIS C ON TREATMENT IN KIGEME DISTRICT HOSPITAL, RWANDA.

Authors **:** Gildas ndibanje[1]*, Charles Nsanzabera[1,2,]

[1] *Department of Public health, Mount Kenya University Rwanda*
[2] *Department of Public Health, Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya.*

**Correspondence: Gildas Ndibanje[1]*
Email: ndibanjegildas@gmail.com

Abstract

Background: Globally, an estimated 58 million have chronic hepatitis C virus infection. Cirrhosis, end-stage liver disease, and hepatocellular cancer affect 10% to 20% of those who have been chronically infected with HCV for 20 to 30 years. The current use of direct-acting anti-viral (sofosbuvir and daclatasvir) has generated remarkable treatment success. However, many factors were found to reduce the treatment's success. This study aimed at investigating factors associated with treatment failure using sofosbuvir and daclatasvir in the Kigeme DH catchment area from April 2019 to December 2021.

Methods: Thy study has involved 310 study participants with chronic hepatitis C (CHC) on sofosbuvir/ daclatasvir with SVR 12 using the Yamane sample size formula. The data collection was performed by info and SPSS version 21 was used for data analysis. This study was conducted in Kigeme DH, Rwanda. The significance of a P-value less than 0.05 was considered.

Results: The overall results showed that the experienced treatment patients, the high viral load at the starting point of the DAA, being cirrhotic were significantly associated with treatment failure with AOR: 57.67, 95%CI:(7.60-437.01), p <0.001; AOR: 26.9, 95%CI:(3.01-240.13), p=0.003; 29.81, 95%CI:(1.80-491.54), p=0.018, respectively. The comorbidities were also associated with the treatment failure, mostly hepatitis B, HIV, hypertension, and diabetes with AOR:79.85, 95%CI:(2.53-173.5),p=0.013; AOR:27.54,95%CI:3.78-200.33), p=0.001; AOR of 20.68,95%CI:2.20-193.8), p=0.008; AOR:17.38,95%CI:3.74-80.66, p<0.001.

Conclusion: Clinical and comorbidity management is advisable for ensuring the treatment's success. Hence the policymakers and MoH have created a new strategic and successful hepatitis C management.

Keywords: Hepatitis C, SRV12, prevalence,

Introduction

Globally, an estimated 58 million people have chronic hepatitis C virus infection, with about 1.5 million new infections occurring per year (WHO, 2022). Around 30% (15–45%) of infected persons spontaneously clear the virus within 6 months of infection without any treatment (Global hepatitis report, 2017). The remaining 70% (55–85%) of persons will develop chronic HCV infection.

Serological signs of past or present HCV infection can be found in 2.3 million HIV-positive patients. The most common HCV genotypes are 1 (44 percent of cases), 3 (25 percent of cases), and 4 (25 percent of cases) worldwide (15 percent of cases). Cirrhosis, end-stage liver disease, and hepatocellular cancer affect 10% to 20% of those who have been chronically infected with HCV for 20 to 30 years (Global prevalence and genotype distribution of hepatitis C virus infection, 2015).

The current standard of care for most patients with persistent HCV infection is a PegIFN and RBV combination (Ribavirin). In two pivotal clinical trials in treatment-naive patients receiving PegIFN-2b or PegIFN-2a combined with ribavirin, treatment failure, defined as persistent HCV replication up to 24 weeks after the end of treatment (EOT), occurred in 18 percent and 24 percent of patients infected by genotype 2 or 3 and 58 percent and 54 percent of patients infected by genotype 1, respectively (Wei L et al., 2016).

Treatment failure is more common groups, such as African Americans and those infected with HIV (Manns M P et al., 2012). Furthermore, previous medicines (Pegylated IFN based) were challenging to use and had substantial side effects, resulting in high rates of noncompliance and reluctance to begin therapy. In addition, some studies showed that around 5% of patients faced treatment failure while on DAA (Compagnoni S et al., 2021).

Direct-acting antivirals (DAA) are curative, dramatically reducing HCV-related mortality and the need for livable to meet the WHO 2030 eradication target, increased diagnosis and linkage to care through universal access to affordable point-of-care diagnostics and pan-genotypic direct-acting antiviral medicine are required (Froudot Roudot, 2021).

Sub-Saharan Africa has the highest HCV prevalence rate (5.3%). They discovered consistent evidence of significant HCV prevalence in numerous African nations after reviewing the published literature (Applegate, T. L et al., 2018). In Sub-Saharan Africa, Central Africa has the greatest estimated prevalence of 6%, followed by West Africa with 2.4 percent, and Southern and East Africa with 1.6 %. Cameroon exhibited the highest prevalence with 13.8%, 11.3% in Burundi, and 4-5% in Rwanda where, adults over 55 years presented 16.5%, 6.5% for prisoners, and 4.7% in HIV-infected individuals. (Pan African Medical Journal, 2013; Riou J et al., 2016). The introduction of DAA regimens in Rwanda's system (sofosbuvir/ribavirin, sofosbuvir/ledipasvir, and sofosbuvir/daclatasvir) has produced successful results (Gupta N & Nsanzimana S, 2018). However, many factors are still an issue to the treatment success and VHC elimination.

This study aimed to This study aimed at investigating factors associated with treatment failure using sofosbuvir and daclatasvir in the Kigeme DH catchment area from April 2019 to December 2021.

Methods

This is a cross-sectional study design with quantitative method. The study has involved 310 study participants with chronic hepatitis C (CHC) on sofosbuvir/ daclatasvir with SVR 12 using Yamane sample size formula. The data collection was performed by info and SPSS version 21 was used for data analysis. This study was conducted in Kigeme DH, Rwanda. The significance of P-value less than 0.05 was considered.

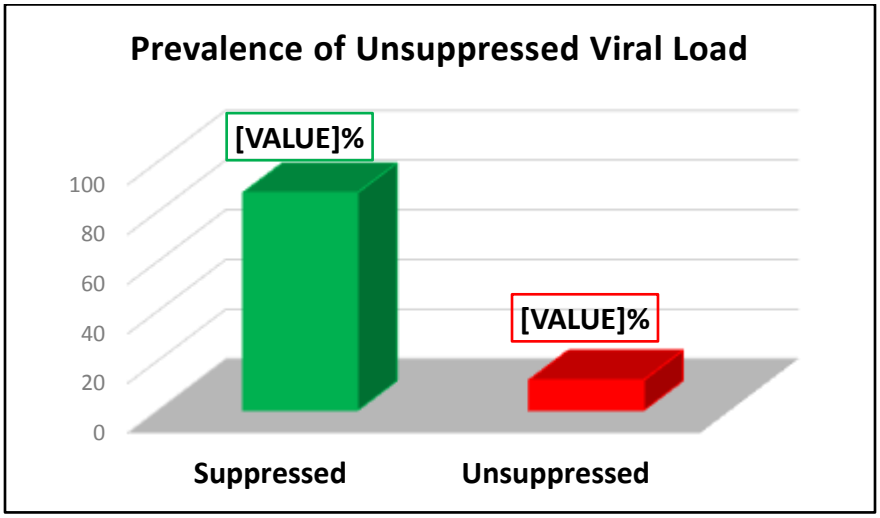
Results

As shown in table 1, the age structure from 50 years and above represented 77.5% of all the study participants, Nyamagabe district was the most represented district with 96.8% while 23.9% of the study participants were from Gasaka sector. Female study participants were the majority with 68.1% and 68.1% were all married. The study participants were dominated by 50.6% of illiteracy.

Table 1: Social demographic characteristics of the study participants

Variable	Frequency	Proportion (%)
Age structure		
<= 20	2	.6
21-30	10	3.2
31-40	24	7.7
41-50	34	11.0
51-60	78	25.2
61+	162	52.3
Gender		
Male	99	31.9
Female	211	68.1
Economic level		
Low level	43	13.9
Middle level	84	27.1
High level	183	59.0
Marital status		
Single	7	2.3
Married	211	68.1
Widow	85	27.4
Divorced	7	2.3
Education level		
Illiteracy	157	50.6
Primary level	107	34.5
Secondary level	39	12.6
University	7	2.3
Occupation		
Unemployed	1	.3
Student	7	2.3
Farmer	254	81.9
Business	46	14.8
Formal employee	2	.6
Residence District		
Nyamagabe	300	96.8
Nyaruguru	9	2.9

The suppressed viral load was based on the indetectable results of the viral load test. Figure 1 showed that 12.3% were the respondents with unsuppressed viral load among hepatitis C patients 12 weeks after the end of treatment at the catchment area of Kigeme district hospital.



The bivariate analysis findings shown in Table 2 ,3,4 demonstrated the relationship of demographic factors, clinical factors, and comorbid factors toward the unsuppressed viral load among hepatitis C patients.

Table 2: Bivariate analysis of demographic factors associated with unsuppressed hepatitis C viral load after SVR12

Variables	Viral Load at the end of treatment (after SVR 12)		Total(%)	$X^2(df)$	*p-value*
	Suppressed VL(%)	Unsuppressed VL(%)			
Age structure					
>=60					
Yes	143(46.1)	33(10.6)	176(56.8)	15.955(1)	**<0.001**
No	129(41.6)	5(1.6)	134(43.2)		
Gender					
Male	85(27.4)	14(4.5)	99(31.9)	0.480(1)	0.3
Female	187(60.3)	24(7.7)	211(68.1)		
Economic level					
Low level (Cat I)	31(10.0)	12(3.9)	43(13.9)	11.367	**0.001**
High level(Cat II-III)	241(77.7)	26(8.4)	267(86.1)		
Marital status					
Married					
Yes	191(61.6)	20(6.5)	211(68.1)	4.74(1)	**0.030**
No	81(26.1)	18(5.8)	99(31.9)		
Education level					
Low level	229(73.9)	35(11.3)	264(85.2)	1.653	0.199
High level	43(13.9)	3(1.0)	46(14.8)		
Occupation					
Unemployed	8(2.6)	0(0.0)	8(2.6)	1.1470	0.285
Employed	264(85.2)	38(12.3)	302(97.4)		
District of residence					
Nyamagabe district					

No	9(2.9)	1(0.3)	10(3.2)	0.049	0.825
Yes	263(84.8)	37(11.9)	300(96.8)		

Source: Secondary data, 2022

The four socio-demographic factors were significantly associated with unsuppressed hepatitis viral load among patients at the end of treatment. The age structure showed that aging was significantly associated with the unsuppressions of viral load with X^2=15.9, p<0.001. Economic level, and marital status were also linked with the unsuppressions of viral load.

Table 3: Bivariate analysis of clinical factors associated with unsuppressed hepatitis C viral load patients after SVR12

Variables	Viral Load at the end of treatment		Total(%)	$X^2(df)$	*p-value*
	Suppressed VL(%)	Unsuppressed VL(%)			
Status of the liver					
Cirrhotic	36(11.6)	23(7.4)	59(19.0)	48.389(1)	**<0.001**
Non- Cirrhotic	236(76.1)	15(4.8)	251(81.0)		
Treatment history					
HT-Experienced	8(2.6)	17(5.5)	285(91.9)	78.558(1)	**<0.001**
HT-Naïve	264(85.2)	21(6.8)			
APRI Score Levels					
Low level (<=1.49)	225(72.6)	16(5.2)	241(77.7)	31.785(2)	**<0.001**
High level (>=1.5)	47(15.2)	22(7.1)	69(22.3)		
Treatment period					
12 Weeks	232(74.8)	9(2.9)	241(77.7)	73.192(1)	**<0.001**
24 Weeks	40(12.9)	29(9.4)	69(22.3)		
Hemoglobin value					
Normal level Hb(>=12g/dl)	249(80.3)	33(10.6)	282(91.0)	0.897	0.344
Abnormal level Hb(<12mg/dl)	23(7.4)	5(1.6)	28(9.0)		
WBC Levels					
Abnormal Wbc(<4k/mm³)	68(21.9)	10(3.2)	78(25.2)	0.031	0.861
Normal Wbc(>4k/mm³)	204(65.8)	28(9.0)	232(74.8)		
Platelets levels/value					
Normal value platelets (>=150k/µL	198(63.9)	17(5.5)	215(69.4)	12.34(2)	**0.001**
Abnormal value platelet(<150k/µL)	74(23.9)	21(6.8)	95(30.6)		
ALAT(GPT) levels					
Low level (<42 UI/L)	182(58.7)	19(6.1)	201(64.8)	4.183(1)	**0.04**
High level (>42 UI/L)	90(29.0)	19(6.1)	109(35.2)		
ASAT(GOT) Levels					
Normal level (:<37 UI/L)	139(44.8)	8(2.6)	147(47.4)	12.076(1)	**<0.001**
High level (>37 UI/L)	133(42.9)	30(9.7)	163(52.6)		

Source: Secondary data, 2022

The above results showed that the relationship of 7 clinical factors were significant toward the unsuppression of viral load with p<0.05. However, hemoglobin value levels and white blood cells levels were not linked with the non-suppression of viral load (Table 3).

Table 4: Bivariate analysis of comorbid diseases with unsuppressed hepatitis C viral load

Variables	Viral Load at the end of treatment (after SVR12)		Total (%)	$X^2(df)$	*p-value*
	Suppressed VL(%)	Unsuppressed VL(%)			
Hypertension					
Yes	97(31.3)	24(7.7)	121(39.0)	10.593(1)	**<0.001**
No	175(56.5)	14(4.5)	189(61.0)		

Diabetes					
Yes	25(8.1%)	27(8.7)	52(16.8)	91.397(1)	**<0.001**
No	247(79.7)	11(3.5)	258(83.2)		
Alcohol use					
Yes	150(48.4)	29(9.4)	179(57.7)	6.123(1)	**0.01**
No	122(39.4)	9(2.9)	131(42.3)		
Gastritis					
Yes	65(21.0)	9(2.9)	74(23.9)	0.001(1)	0.9
No	207(66.8)	29(9.4)	236(76.1)		
Hepatitis B					
Yes	9(2.9)	9(2.9)	18(5.8)	25.309(1)	**<0.001**
No	263(84.8)	29(9.4)	292(94.2)		
HIV					
Yes	18(5.8)	17(5.5)	35(11.3)	48.373(1)	**<0.001**
No	254(81.9)	21(6.8)	275(88.7)		

Source: Secondary data, 2022

The findings shown in table 4 demonstrated that the relationship of hypertension, diabetes, hepatitis B and HIV was highly significant with p=0.001 toward the unsuppressed viral load at the end of treatment (after SVR 12). Gastritis was not significant.

Table 5: Multivariate analysis of factors associated with unsuppressed hepatitis C viral load patients after SVR12

	Unsuppressed Hepatitis C VL		P-value
	AoR	95%CI	
Treatment history			
HT-Naïve	**Ref.**		
HT- Experienced	57.63	7.60-437.01	**<0.001**
Status of the liver			
Non-Cirrhotic	**Ref.**		
Cirrhotic	29.81	1.80-491.54	**0.018**
Hypertension			
Yes	20.68	2.207-193.84	**0.008**
No	**Ref.**		
Diabetes			
Yes	17.38	3.74-80.66	**<0.001**
No	**Ref.**		
Hepatitis B			
Yes	79.85	2.53-173.5	**0.013**
No	**Ref.**		
HIV			
Yes	27.54	3.78-200.33	**0.001**
No	**Ref.**		

Source: Secondary data, 2022

After the elimination of non-significant factors and Odd Ratio adjustment, the findings in table 5 showed that hepatitis B and HT-experienced were highly associated with the unsuppression of viral load after 12 weeks of treatment with AOR=79.85,95%CI (2.20-193.84) p=0.013 and AOR:57.63,95% (7.60-437.01, p<0.001, respectively. Hypertension, diabetes, and HIV were also significant with the unsuppression of viral load after 12 weeks of treatment.

Discussion

This study findings were dominated by female with 68.1% and 77.5% of age structure from 50 years and above. Mean age for the study participants was 59.75 years (Table 1). Although old age was associated with the non-suppression of hepatitis C viral load in bivariate analysis (Table 2), it was not the case in multivariate analysis (Table 3). This is similar to the study which demonstrated that old age was not strongly associated with anti-viral treatment success (Alexandre, 2019).

The findings showed that the relationship of economic level and illiteracy toward the unsuppressed viral load was significant whereas the residence, gender and occupation were not significantly linked with the unsuppressed viral load (Table 2).

Figure 1 displayed the prevalence of unsuppressed viral load among hepatitis C patients which was 12.3% which marked a sustained virological response (SVR12) of 87.7% of patients on SOF/DCV after SVR12. This treatment success is moderately high in comparison with 87% treatment success rate found in Rwanda military hospital (Gupta and associates, 2018).

However, it is also a low treatment success compared to other study which presented 91.0% of SVR12 in old age population (Alexandre, 2019). The reduction of treatment success was at some extent justified by the treatment experienced patients who presented a failure rate of 17(68%) of all 25 experienced patients (Table 3), the cirrhotic status and the illiteracy level of more than 50% which may also indicate the low drug compliance (Alexandre, 2019; Chen, 2021). Another study showed the rise of treatment success to 96% and 94.4% by two drugs anti-viral combination after the failure of SOF/DCV in the period of 12-week sustained virological response (SVR12) (Said, 2022).

Almost clinical factors relationship toward the unsuppressed viral load was significant. However, hemoglobin value levels and white blood cells levels were not significantly linked with the unsuppressed viral load (Table 3). While Baseline low hemoglobin was found to be strong predictor of treatment failure at 12 weeks after EoT(Phuong, 2022).

The relationship of Low platelets with the unsuppressed viral load was significant in bivariate analysis results. However, it was not significant in multivariate analysis. Another study showed that from two weeks on the (Direct acting antiviral) DAA treatment, platelets levels increase slowly but remain lower until 12 weeks (Hsu, 2019).

This study findings showed that the low level of platelets relationship with unsuppressed viral load was significant for bivariate analysis, and it was the same in the study of Salomon and colleagues in 2018 who said that low platelet was linked to treatment failure. Which is also justified by a study that demonstrated that the hepatitis C virus create the autoimmune reaction which creates the platelets sequestration and bone marrow suppression. Hence, the study goes on showing a compromise of sustained virologic response (SRV12) due to thrombocytopenia before the initiation of DAA (Sumit, 2017).

Hypertension was the highly associated variable with AoR(95%CI): 20.68(2.207-193.842), while Diabetes had AoR(95%CI) of 17.38(3.75-80.66), $p<0.001$. This is like another study which

highlighted insulin resistance as a predictor of compromised Sustained viral response (SVR). In other words, Insulin resistance creates the non-suppression of hepatitis C viral load (Khattab, 2010) and causes the response impairment of anti-viral treatment (Abdel-Rahman, 2012). However, another study demonstrated that insulin resistance was not strongly associated with SRV12 (Danielle, 2012). Although Insulin resistance was shown to impair the Hepatitis C treatment, Insulin resistance, hypertension and atherosclerosis were also demonstrated to be induced by Viral Hepatitis C (Dominik, 2016).

HIV and Hepatitis B followed with AoR: 27.54, (95%CI): (3.79-200.33), 79.85(2.53-173.5), p=0.001 and p=0.013, respectively (Table 5) and this may be due to drug interaction. The lack of association of APRI score was justified by a sustainable decline of it due to treatment course (Hsu, 2019). Low platelet is often linked to high APRI score and cirrhotic status, and some studies supported that the low platelet was associated with the treatment failure (Salomon, 2018).

The AoR of 57.63 (95%CI) :(7.60-437.01) with p value of < 0.001 were the findings of experienced treatment patients (prior exposure to anti HCV drugs). This showed that the fact of prior experiencing anti HCV drugs could be strongly associated with the treatment failure after SVR12, this is supported by Kowo and colleagues in their study conducted in 2020 in Cameroon.

Cirrhosis state was also strongly linked to treatment failure with an OR of 29.81 (1.80-491.54) after adjustment. These findings are supported with other authors (Chen, 2021; Kowo, 2022).

Conclusion

This study revealed that most important significant factors for hepatitis C treatment failure were experienced treatment patients, cirrhotic status. Comorbidities such as hypertension, diabetes, hepatitis B, and HIV were also strongly associated with the Hepatitis C treatment failure.

Those DAAs have revolutionized the treatment of chronic hepatitis C which recently was pegylated interferon based. However, there's still patients who failed on DAAs treatment regime. Relying on those strongly associated factors, the early treatment, low initial platelets correction and counselling of experienced patients can significantly reduce the treatment failure. In addition, the correct management of comorbidities is a crucial predictive intervention for successful treatment outcome.

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