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Pangenotypic Hepatitis C Therapy with Direct Acting Antivirals: A Southern Nigeria Pilot Experience

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Viral hepatitis C (HCV) is a global health challenge affecting at least 3.3% of the world population. Sub-Saharan Africa still battles with under diagnosis, and poor access to diagnostic facilities occasioned by a lack of manpower/facilities to treat infected persons bringing about an increase in HCV-associated morbidity and mortality. The goal of this prospective observational study is to assess the efficacy of sofosbuvir/daclatasvir (SOF/DAC) combination as a pangenotypic treatment for hepatitis C without HCV genotype determination in patients with hepatitis C attending the hepatology clinic at the Rivers State University Teaching Hospital (RSUTH).

Method: One hundred and fifty (150) HCV RNA positive patients were enrolled into the study. Their sociodermographic factors, clinical and laboratory parameters including pre and post treatment HCV RNA were assessed. Treatment eligible patients received sofosbuvir 400mg and daclatasvir 60/90mg for 12 weeks which was extended to 24 weeks in patients with decompensated liver disease. Treatment success was defined as undetectable HCV RNA 12 weeks after completion of therapy (SVR-12).

Results: One hundred and nine **(**109) of the 150 recruited patients were eligible for treatment. The male to female ratio of the study population was 1.1:1(79, 52.7%):71,49.3%) with a mean age of 47.78±13.39 years. Eighty-six (86,78.9%) of the 109 treated patients had undetectable HCV RNA at SVR-12 and this was most likely to occur in patients with low viremia (OR=2.52, 95%CI=0.985-6.436, p=0.050). Extension of treatment duration played no apparent role in the achievement of SVR-12 (SVR-12=33.3%), however, previously treated HCV patients had a better outcome.

Conclusion: Sofosbuvir/ daclatasvir pangenotypic therapy is effective for treatment of HCV patients without genotyping.

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1. INTRODUCTION

Viral hepatitis C is a global health challenge affecting at least 3.3% of the world population. Globally, approximately 180million people are chronically infected with the viral hepatitis C (HCV) [1]. The HCV, a single-stranded RNA virus of the Flaviviridae is implicated as a direct cause of viral hepatitis, an inflammatory disease of the liver which produces a prodrome of liver disorders ranging from viral hepatitis, cirrhosis, liver failure and hepatocellular carcinoma.

Despite the advancement in clinical care for HCV infected patients obtainable in advanced societies, sub-Saharan Africa still battles with under diagnosis, and poor access to diagnostic facilities occasioned by a lack of manpower/ facilities to treat infected persons. As stated in a 2016 first ever guideline for Viral Hepatitis treatment in Nigeria [2], Nigeria accounts for 4.5% of the global burden of HCV with a prevalence of 2.2% affecting approximately 4million Nigerians.

Hepatitis B and C are responsible for an increasing rate of liver related morbidity and mortality including liver cancer in a large population of Nigerians [3,4]. Bojuwoye et al. [5] reported that liver disease is the third most common cause of medical-related deaths with a prevalence of 12.1% in his study conducted at the University college hospital, Ibadan-southwestern Nigeria. He further stated that Primary Liver Cell Carcinoma (PLCC) was observed to be the most common malignancy in the medical wards at the hospital accounting for 491/100,000 admissions [5]. Nwokediuko et al. [6] in his retrospective study on pattern of liver admissions in south eastern Nigeria reported that liver diseases accounted for 7.9% of medical admissions with PLCC as the most common liver related reason for hospital admission.

The direct acting antivirals (DAA) were introduced in the year 2011 with a higher sustained virological response (SVR) and better adverse effect profile compared to the Interferon based and ribavirin older regimen [7]. Prior to 2014, HCV therapy was based on the use of pegylated Interferon- a once weekly injectable anti-viral and ribavirin a nucleoside analogue. This therapy was compounded with a lot of adverse effects chiefly anemia, neutropenia, thrombocytopenia, flu-like symptoms, metabolic disorders (hypothyroidism, hyperthyroidism) fatigue and depression [8]. Additional challenges of pegylated interferon therapy include its high cost, poor availability, poor compliance of patients on the therapy occasioned by the multiple adverse effects and prolonged duration of therapy are also noteworthy. Manns et al. [8] noted that HCV treatment with pegylated interferon and Ribavirin was dismally unsatisfactory as it was ineffective in some HCV genotypes especially genotype 1 with SVR of about 40-50%.

These aforementioned challenges led to the development of newer drugs- the DAAs which has changed the paradigm of the treatment of Hepatitis C. The DAAs can achieve SVR of up to 90% in persons with HCV infection [7] and this occurs within a definite treatment duration thus reducing the risk of hepatic decompensation, liver cirrhosis, hepatocellular carcinoma, and improving survival. The potential of achieving an SVR is regarded as ‘cure’ in HCV patients on treatment [9]. Thus, the primary goal of treatment is to achieve SVR defined as undetectable serum HCV RNA 12 weeks after the end of treatment [10]. Studies have shown that HCV infected patients with compensated or decompensated Cirrhosis who achieve a “cure” have significant improvement in their clinical symptoms such as fatigue [11], notable change in hepatic portal pressure [12], and an overall better outcome and survival [13].

The first DAAs introduced in 2011 were Boceprevir and Telaprevir while Sofosbuvir and Daclatasvir were introduced in 2013 and 2014 respectively. However, these were inaccessible in resource poor countries like Nigeria due to their high cost, lack of a viral hepatitis care consensus and poor universal health coverage. The average cost of HCV treatment and care in Nigeria despite the availability of the DAA generic is 650-750 USD for a 12 week therapy and an average of 4 months and 18 months wages are needed for HCV RNA test and treatment respectively [14,15].

The WHO Global Health Sector Strategy [16] on viral hepatitis drafted in 2016 as an initial roadmap to the elimination of viral hepatitis as a public health problem by 2030 by achieving a >90% reduction in incidence, >90% programme intervention coverage and 65% reduction in mortality by 2030. This guidance was intended to

"motivate countries to take rapid and appropriate action toward viral hepatitis elimination by providing a framework to measure their efforts at reducing new viral hepatitis B and C infection, and reduction of death from liver cirrhosis and hepatocellular carcinoma" [16].

To overcome the barriers to achieving viral hepatitis elimination, we must improve people's access to treatment and care. The affordable generic DAAs were only available on a large scale in Nigeria in 2017 through the Clinton Health Access Initiative (CHAI) program for subsidized HCV care. Two centers were chosen in Nigeria for this pilot study including the Rivers State University Teaching Hospital (RSUTH). Two of the second generation DAAs were introduced- Sofosbuvir, an NS5B polymerase inhibitor that suppreses HCV replication and life cycle in genotypes 1 to 4 and Daclatasvir, an inhibitor of the NS5A phosphoprotein of the hepatitis C virus.

Sofosbuvir, a uridine nucleotide analog is a prodrug which after ingestion passes through the first pass metabolism in the liver to produce its active moiety 5'triphosphate nucleotide PSI-749. This then mimics the physiological nucleotide and blocks the non-structural protein NS5B polymerase thus inhibiting the HCV-RNA synthesis by RNA chain termination [17,18]. The pan-genotypic effect of Sofosbuvir being effective in the treatment of genotype 1,2,3,4 and 6 is because this catalytic site is well preserved in all HCV genotypes [18].

Furthermore, Daclatasvir- a hepatitis C phosphoprotein 5A and 4A (NS5A & NS4A) inhibitor is used in combination with other antivirals such as Sofosbuvir and is effective against genotypes 1,2, and 3 with a resultant SVR-12 of 89%-98% [19].

The World Health Organization (WHO) recommends the use of pangenotypic regimen in the treatment of chronic HCV infected individuals older than 18 years [20,21]. Pangenotypic regimens according to Zoratti et al. [22] "provides new opportunities for the public health response to HCV infection, with simplified procurement, an omission of resource-intensive genotyping, and no need for frequent laboratory monitoring".

The goal of this prospective observational study is to assess the efficacy of sofosbuvir/daclatasvir combination as a pangenotypic treatment for hepatitis C without HCV genotype determination in patients with hepatitis C attending the hepatology clinic at RSUTH.

2. METHODOLOGY

2.1 Study Design

This was an observational prospective cohort study of HCV positive patients seen at the medical outpatient clinic (MOPC) of the Rivers State University Teaching Hospital (RSUTH), Port Harcourt, a tertiary hospital and a specialist referral center in southern Nigeria for a 3-year period between April 2017-April 2020.

Collaborative Memorandum of Understandings (MoU) was signed between CHAI/ISN and our institution that allowed access pricing of HCV RNA tests and the direct acting antivirals-sofosbuvir 400mg and Daclatasvir 60mg to be domiciled in our facility.

2.2 Study Participants

Consenting adults (≥18 years) who had a positive preliminary HCV antibody screening test for hepatitis C virus using a third generation Enzyme linked immunosorbent assay (ELISA) that detects HCV antibody in both patients with active and inactive infection diagnosed in this facility or referred from neighboring centers by a Physician who were willing to accept treatment were recruited into the study. Included patients were HCV treatment naïve or Pegylated interferon/Ribavirin experienced with a serum creatinine levels of ≤ 150mmol/l. Children (≤ 18years), Pregnant women, direct acting Antiviral experienced Patients, patients with Renal impairment with serum creatinine ≥150mmol or who do not give consent were excluded from the study.

The sociodemographic data of the participants were taken. All standard laboratory and radiological measurements including Liver function tests, total protein, serum albumin, full blood count, Kidney function tests, and abdominal ultrasound scan were recorded during the period of treatment. Pre/ post treatment HCV RNA (SVR-12) quantification was performed using a COBAS AmpliPrep TaqMan kit (Roche Diagnostics, Branchburg, NJ, USA), the lower limit of quantification (LLOQ) is 15IU/mL. Patients were screened for hepatitis B and human immunodeficiency virus to identify co-infected cases.

2.3 Evaluation of Effectiveness, Safety and Outcomes

Treatment eligible patients received Sofosbuvir 400mg daily and Daclatasvir 60mg daily for 12-24 weeks according to treatment guidelines with HCV RNA values (pre-treatment and post-treatment SVR-12) documented. The primary end-point of this study was Treatment success defined as undetectable HCV RNA 12 weeks after completion of therapy (SVR-12) [23]. Treatment failure was defined as lack of SVR-12 in any patient who was initiated on the Sofosbuvir/Daclatasvir therapy for the stipulated treatment duration. Virologic failure was considered as a cause of treatment failure and was defined as HCV RNA > 15 IU/mL at 12 weeks after end of treatment. The safety of the administered treatment was evaluated using self-reported patients' self-assessment.

2.4 Statistical Analysis

The results were analyzed using the SPSS version 22(Statistical Package for Social Science version 22). The results have been expressed using mean ± standard deviations, percentages, tables and pie charts. Continuous variables were compared with the Students t-test and categorical parameters were compared with the chi-square ($\chi 2$) test. The confidence interval was set at 95% and all tests were considered to be statistically significant at the p-value < 0.05.

3. RESULTS

From April 2017-2020, a total of 167 HCV positive patients were seen at the Hepatology clinic, eight of which were excluded from treatment (3 pregnant, 5 abnormal renal parameters - eGFR<60 mL/min/1.73m^2). So total number enrolled in the study was 159, however, four (4) of these participants died during the study period without completion of their treatment duration and 5 participants were lost to follow-up. 150 participants were thus included in the study Fig. 1.

Seventy-nine (79, 52.7%) of the 150 participants were males while 71 (47.3%) were females. The mean age of the participants was 47.78±13.39years with an age range of 18 – 74 years, with the majority of participants being in the young and middle-aged brackets as shown in Fig. 2.

Forty-one (27.3%) of the 150 patients had undetectable pre-treatment HCV RNA and thus were not eligible for treatment while 109 patients with detectable HCV RNA were eligible for treatment. Further evaluation of the Forty-one (27.3%) patients who spontaneously cleared the virus revealed that males were more likely to spontaneously clear the virus (OR=2.14, 95%CI=1.002-4.462, p=0.047) (Table 1). Furthermore, thirty-one (75.6%) of the 41 persons that spontaneously cleared the virus were young adults and this was statistically significant (x2 =16.416, p<0.001) see Table 2.

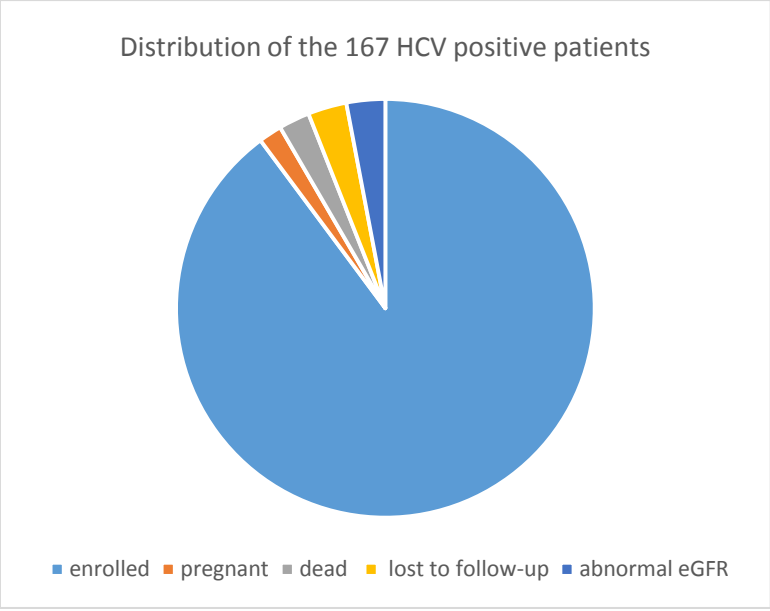

Fig. 1. Distribution of recruited patients

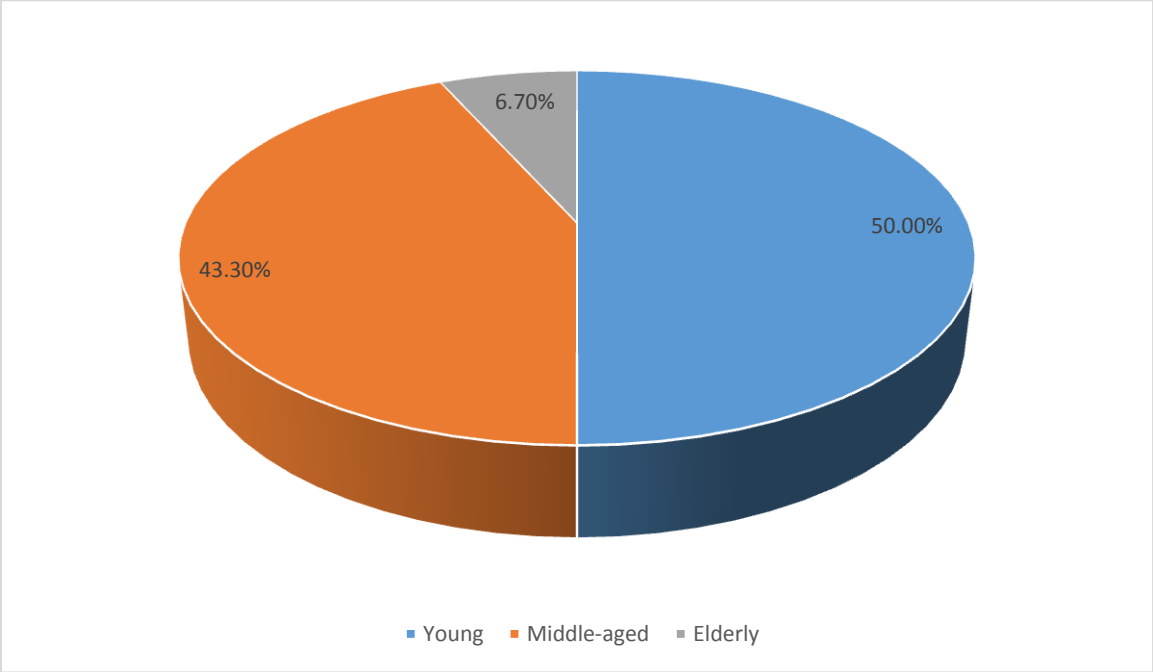

Fig. 2. Age distribution of the study population (n=150)

The median HCV RNA was 275600 ± 43.36 with a minimum to maximum value of 1,452 to 42,800000. The 109 treatment eligible patients were then commenced on tablets sofosbuvir and Daclatasvir. The dose of Daclatasvir was adjusted from 60mg to 90mg in four (2.7%) patients who had HCV/HIV co-infection (and were on Efavirenz-combined therapy) while the remainder of the patients received Sofosbuvir 400mg daily and Daclatasvir 60mg daily. Also, the treatment duration of 9 patients (6.0%) who were diagnosed with decompensated Cirrhosis was extended to 6 months in accordance with the guidelines [23,24].

Table 1. Spontaneous HCV clearance according to gender

		Gender	
		Male n (%)	**Female n (%)**
Spontaneous viral Clearance	Yes	27 (34.2)	14 (19.7)
	No	52 (65.8)	57 (80.3)
Total		79 (100)	71 (100)

3.1 Radiological Findings of the Study Population

The Abdominal ultrasound findings were normal in over half of the study population. However, common abnormalities noted were fatty liver (10.7%), liver cirrhosis (8.0%) and hepatitis (6.0%). Abdominal ultrasound findings are summarized in Table 1.

Comparing abdominal scan findings with the age of the study population we observed that abnormal abdominal USS findings were common in the middle-aged group as 71.9% of the abnormal findings were in this category while 7% of abnormal findings were found in the elderly patients and this was statistically significant (χ^2=32.774, p<0.001).

Notably, Female participants were more likely to have abnormal abdominal scan findings as 37(64.9%) of abnormal USS findings were documented in women and this was statistically significant (χ^2=11.369, OR=3.21, 95%CI=1.613-6.391, p=0.001).

Contrasting spontaneous viral clearance to the abdominal ultrasound scan finding in this study, we noticed that patients who did not clear the HCV virus spontaneously were more likely to have abnormal abdominal USS findings. (OR=3.37, 95%CI=1.426 to 7.958, p=0.004).

3.2 Virological Response

Following treatment, 86(78.9%) of the 109 treated persons had SVR at 12 weeks post treatment (SVR-12) and all 6 persons

who had been previously treated for HCV with Pegylated Interferon/Ribavirin were able to achieve SVR at 12 weeks post treatment. In the 9 (6.0%) patients with decompensated Cirrhosis, treatment duration was extended from 3 to 6 months out of which 3(33.3%) persons achieved SVR-12, while 6 persons did not.

Table 2. Age stratification of patients who spontaneously cleared the virus

		Age category		
		Young n (%)	**Middle aged n (%)**	**Elderly n (%)**
Spontaneous viral	Yes	31 (41.3)	7 (10.8)	3 (30.0)
Clearance	No	44 (58.7)	58 (89.2)	7 (70.0)
Total		75 (100)	65 (100)	10 (100)

Table 3. Abdominal ultrasound findings of the study population

	Number (%)
Normal scan report	93(62.0)
Cirrhosis	12(8.0)
Ascites	2(1.3)
Hepatomegaly	8(5.3)
Gas	1(0.7)
Fatty liver	16(10.7)
Hepatitis	9(6.0)
Cholelithiasis	2(1.3)
Gastritis	2(1.3)
Hydatid cyst	2(1.3)
PLCC	1(0.7)
Liver abscess	1(0.7)
PUD	1(0.7)

Table 4. Abdominal ultrasound (USS) findings versus age categories

		Abdominal USS	
		Normal USS n (%)	**Abnormal USS n (%)**
Age category:	Young	63 (67.7)	12 (21.0)
	Middle aged	24 (25.8)	41 (71.9)
	Elderly	6 (6.5)	4 (7.0)
Total		93	57 (100)

Table 5. Abdominal ultrasound findings versus gender

		Abdominal USS	
		Normal USS n (%)	**Abnormal USS n (%)**
Gender	Male	59 (63.4)	20 (35.1)
	Female	34 (36.6)	37 (64.9)
Total		93 (100)	57 (100)

Table 6. Abdominal USS findings versus spontaneous clearance

		Abdominal USS	
		Normal USS n (%)	**Abnormal USS n (%)**
Spontaneous viral	Yes	33 (35.5)	8 (14.0)
Clearance	No	60 (64.5)	49 (86.0)
Total		93 (100)	57 (100)

Table 7. The SVR-12 of patients with high VL compared with low VL

		Sustained virological response at 12 weeks post treatment	
		Yes n (%)	No n (%)
High viral load	Yes	26 (30.2)	12 (52.2)
	No	60 (69.8)	11 (47.8)
Total		86 (100)	23 (100)

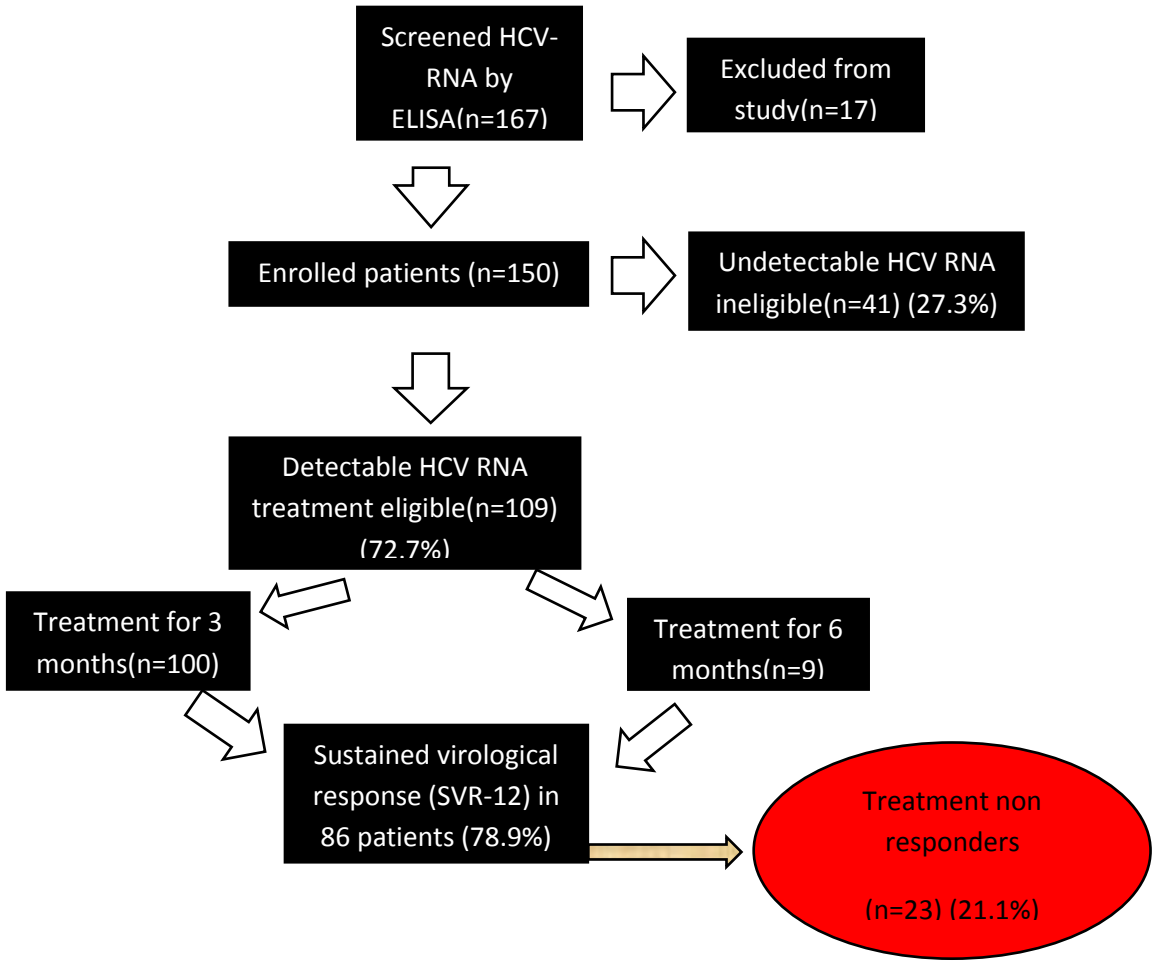

Chart 1. Algorithm of the study design

Classifying the treatment eligible patients into high (HCV RNA>800,000) and low (HCV RNA<800,000) 38 (34.9%) patients had a high viral load and 71 (65.1%) were classified as having a low viral load. Patients with low viral load were more likely to achieve SVR at 12 weeks (OR=2.52, 95%CI=0.985 to 6.436, p=0.050) see Table 7.

3.3 Safety Outcomes

The most reported adverse effects were abdominal discomfort (n=5,4.6%), fatigue (n=1,0.92%) and insomnia (n=1,0.92%) which was reported in 6.44% of our study population. There were however no reports of treatment discontinuation following this observed adverse events.

4. DISCUSSION

This was a prospective open label non-randomized interventional trial of pangenotypic HCV therapy with DAAs- sofosbuvir and daclatasvir in 150 HCV antibody positive patients. Our preliminary screening test for HCV

was done using third generation ELISA that detects HCV antibody in both patients with active infection and those who have been “cured” either spontaneously or by treatment. In our study, out of 150 anti-HCV positive recruited patients, 109 (72.7%) had PCR detectable HCV RNA and where thus eligible to receive the DAAs after meeting our inclusion criteria while forty-one (27.3%) of the recruited patients were able to clear the virus spontaneously. This surmises that the use of the more affordable ELISA as a screening test for hepatitis C overestimates the burden of the disease. Furthermore, spontaneous viral clearance was more likely to occur in males (OR=2.14, 95%CI=1.002-4.462, p=0.047) and young adults (x2 =16.416, p<0.001).

In our study, there were more males 79 (52.7%) than females 71 (47.3%) and this same pattern of a higher male population has been reported by other Nigerian investigators [25–27]. We also observed that a majority of our study population were young to middle-aged patients and this may reflect the tendency for “at risk” behaviors commoner to these population.

The reported efficacy of Sofosbuvir/daclatasvir combination for the treatment of hepatitis C varies depending on the prevalent genotype. Leroy et al. [28] reported an efficacy of 96% (SVR-12) though their study was conducted in a predominantly HCV genotype 1 patients population and some of the participants received a Sofosbuvir/Ribavirin Regimen. Furthermore, a prospective study of 10 patients with HCV genotype 3 treated for 3 months with Sofosbuvir/ Daclatasvir combination reportedly achieved a 100% sustained virological response at 12 weeks post treatment (SVR-12) and an accompanying significant reduction in liver transaminases [29].

The efficacy of Sofosbuvir/Daclatasvir combination as observed in this pangenotypic observational cohort is 78.9% as 86 of 109 patients who received the stated combination had undetectable HCV RNA at 12 weeks after completion of therapy. Several studies have demonstrated the safety and efficacy of sofosbuvir/daclatasvir combination therapy for HCV in comparison to other DAAs. In the ENDURANCE 3 trial- a randomized, open-label, multicenter study to compare efficacy and safety of Glecaprevir + Pibrentasvir (ABT-493/ABT-530) to SOF/DAC in treatment-naïve chronic HCV genotype 1&3-infected patients, SOF/DAC was reported to be superior to ABT-493/ABT-530 as they achieved a 97% ‘cure’ compared to 95% [30]. Additionally, the REDEMPTION trials of over 1000 patients presented at the 2016 International Liver Conference recorded a 93-100% ‘cure’ for all genotypes of HCV [31,32]. Ultimately, SOF/DAC is the cheapest, most effective pangenotypic HCV treatment especially in non-cirrhotic patients [32].

This is in variance to previously obtained virological response of 40-50% (33) observed with the use of Pegylated Interferon and Ribavirin despite the longer duration of therapy, myriad side effects and the stringent conditions attached to Pegylated interferon/Ribavirin administration including the obligatory requirement for genotyping, pre-treatment histological assessment in genotype 1 or 4 and the prolonged nature of therapy [33]. However, we did not observe a significant response in the subgroup of patients who had Decompensated Cirrhosis notwithstanding the extension of their antiviral therapy from 3-6 months as only 33.3% achieved SVR-12.

Notably, cumulative therapy for HCV increases the chance of viral clearance as observed in our study as one hundred percent of those that had been previously treated for HCV with pegylated interferon and Ribavirin with treatment failure were able to achieve SVR at 12 weeks post treatment. This is similar to findings obtained by other studies which reported SVR-12 of 94.8% [34], 98.7% [35], and 99% [36].

Additionally, patients with low viral load were more likely to achieve SVR at 12 weeks post treatment (OR=2.52, 95%CI=0.985 to 6.436, p=0.050).

Low viremia (HCV RNA<800,000) has been widely recognized as a predictor of "çure" in HCV patients receiving antiviral medications especially in patient with genotype 1 and 2 [37,38].

Interestingly, we observed that persistence of viral activity was tied to the finding of an abnormal abdominal ultrasound scan in our study population as 86% of the participants with detectable HCV RNA had abnormal findings on their abdomina USS report (OR=3.37, 95%CI=1.426 to 7.958, p=0.004).

5. CONCLUSION

Direct acting antivirals are highly effectual and tolerable in the treatment of HCV. Our observed

efficacy of approximately 80% though modestly lower when compared to previously reported values in studies with known HCV genotypes is a remarkable improvement notwithstanding the nescience of the genotypes of our study population. We believe that achieving the WHO 2030 viral hepatitis elimination target will require more programmes such as this Pilot project with increased risk based and universal screening as well increased linkage to care and affordable treatment.

CONSENT AND ETHICAL APPROVAL

Informed written consent was obtained from the participants and ethical approval was obtained from the ethical committee of the RSUTH with REC number RSUTH/REC/2022161.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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