Hepatitis C Continuum of Care in a Treatment Center in Sub-Saharan Africa

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Background: **Hepatitis C virus (HCV) infection is a major public health challenge in Cameroon with over three million people infected. Government efforts to improve care and treatment are unsatisfactory and need to be assessed. We aimed at studying the several steps along the HCV continuum of care in one of two hepatitis treatment centers in Cameroon.** ***Methods:*** **We undertook a retrospective chart review of anti-HCV positive individuals, who attended the Douala general hospital between 2008 and 2015. We defined the HCV treatment cascade as follows: step 1—HCV RNA testing, step 2—complete pre-therapeutic evaluation (genotyping and liver fibrosis markers), step 3—initiation of treatment, step 4—treatment completion, and step 5—sustained virological response (SRV). Each successive step in the HCV care continuum was dependent on passing through the previous step.** ***Results:*** **The mean age of the 669 anti-HCV antibody positive individuals was 57 (sd: ±13) years. Females were 52.8% of the study population. 410 (61.3%) were tested for HCV RNA. Three hundred and sixty-six (54.7%) were confirmed to have viral replication (HCV RNA positive). One hundred and eighty (26.9%) did a complete pre-therapeutic evaluation (both HCV genotyping and liver fibrosis assessment included). Eighty-one (12.1%) initiated treatment with pegylated interferon/ribavirin. Seventy-two (10.8%) completed treatment and 44 (6.6%) had SVR. Sociodemographic characteristics including age, gender, marital status, having medical insurance, and profession were associated with attaining later steps in the care cascade.** ***Conclusion:*** **This study shows that HCV continuum of care and treatment is less optimal at the Douala general hospital and is highly impacted by socio-economic factors. Continued efforts are needed to improve HCV care. (J Clin Exp Hepatol 2018;8:335–341)**

More than an estimated 185 million people worldwide are infected with the hepatitis C virus (HCV), of whom 90% reside in low and middle income countries.[1] One-third of those who become chronically infected would progress to chronic liver disease including end-stage liver disease and hepatocellular carcinoma.[1–3] In Cameroon, the prevalence of anti-HCV antibody positivity is estimated at about 13%.[4] This corresponds to an estimated population of about 3.12 million. Hepatitis C infection is therefore, relatively, a major public health problem in Cameroon,[5] yet, there is no comprehensive strategy to address the problem.

Recent reports suggest that, screening rates for chronic HCV infection among eligible subjects varies anywhere from 1% to 16% (12). Additionally, less than half of those who tested anti-HCV positive underwent HCV-RNA testing.[6–9] Even more troubling is the fact that only a very small proportion of individuals with chronic HCV infection (15%) have received any form of antiviral treatment.[10,11] We therefore need a comprehensive public health program that prioritizes effective interventions, and promotes efficient service delivery strategies with a sustained impact at the population level. It is imperative to examine effective strategies to improve treatment outcomes along the entire chronic HCV care continuum from diagnosis through cure.[12] An evaluation of the current HCV management process can provide a useful frame work that will allow the development of an effective and efficient public health intervention program.[12]

Treatment for chronic HCV has undergone tremendous transformation in the past several years with the introduction of direct acting antiviral therapy (DAA). In Cameroon, interferon based treatment was the standard of care prior to January 2016. However, in 2014, because of low treatment uptake predominantly due to costs, the Ministry of Public Health and the Cameroon Society of Gastroenterology and Hepatology went into an agreement

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Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; DAA: direct acting antiviral therapy; DGH: Douala General Hospital; ELISA: enzyme linked immunosorbent assay; HCV: hepatitis C virus; HIV: human immunodeficiency virus; RNA: ribonucleic acid; SVR: sustained virological response
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with a pharmaceutical firm regarding lowering cost with the hope of improving access to screening and treatment. As a result of this agreement, Peg-interferon was subsequently sold at 67% of the market price while ribavirin was provided free of charge. Two treatment centers were created and eligibility criteria for HCV treatment were set.

Generic DAA which have high efficacy, limited side effects and short duration of treatment became available in Cameroon in January 2016. This meant that a considerable uptake in HCV treatment was anticipated. To ensure an effective implementation of a strategic HCV management program in Cameroon, there is need to evaluate the current care progress to identify areas for improvement. The results will allow for the development of a comprehensive pathway that leads to the identification and treatment of eligible individuals with improved outcomes. This will help to put in place well-executed action plans, appropriate resource allocation and comprehensive public health policies.[12,13] Unfortunately, there is very limited data on access to HCV screening and treatment services in most resource limited settings including Cameroon. The main objective of this study was to assess the HCV care process (continuum) in one of two treatment centers in Cameroon. We hope to provide evidence-based data that will help establish and evaluate a comprehensive HCV management program in Cameroon.

METHODOLOGY

Study design and setting

We conducted a retrospective cross sectional study based in the Douala General Hospital (DGH). This is a tertiary health facility in Douala, the largest city and economic capital of Cameroon. Douala has an estimated population of over 3 million inhabitants. This health care facility has a dedicated outpatient gastroenterology clinic where most patients with liver diseases in Douala and around the country are referred for evaluation and management.[14] It is one of the two hepatitis C treatment centers in Cameroon.

Data Collection

Patient files were reviewed. Included were all patients tested and declared positive for anti-HCV antibody. The study period was from January 1, 2008 to December 31, 2015. Excluded were subjects with decompensated cirrhosis and hepatocellular cancer at the time of diagnosis. Information abstracted from each chart included: (1) socio-demographic characteristics—age, sex, marital status, profession, care support; (2) laboratory test results—anti-HCV antibody, HCV-RNA at baseline, and at week 4, 12, 24, 48 and 24 weeks following treatment completion depending on the protocol and genotype, HCV genotype, fibrosis scores and treatment characteristics (initiation and completion).

Laboratory Analysis

In the DGH, there is a fully functional laboratory (subjected to periodic quality control and validation) where most baseline tests relevant to HCV diagnosis and management are done.

Anti-HCV testing was done first using a rapid test on plasma, and for those who were positive, confirmation was carried out using a third generation solid phase enzyme-linked immuno-sorbent assay (ELISA): Recombi LISA HCV antibody test (Ref E0511, CTK Biotech, San Diego, California, USA) according to manufacturer's instructions. This test which qualitatively detects IgG and IgM for HCV is highly sensitive and specific (100%). In the last four years, HCV serology is done directly using Elisa methods but as most referred patients were diagnosed using rapid tests, we continued to follow the above protocol on them.

Following anti-HCV positive testing, all individuals were recommended an HCV RNA test, HCV genotyping and liver fibrosis assessment. Liver fibrosis was evaluated using non-invasive tests with FibroTest (BioPredictive, Paris, France) or ultrasound elastography (Fibroscan). HCV RNA quantification and genotyping were done by real time polymerase chain reaction (RT-PCR). Given that these tests are not routinely done in Cameroon, blood samples from HCV positive patients were collected in EDTA tubes and processed as specified by respective test sample collection procedures, frozen and transported in temperature controlled thermochip containers to the accredited laboratory in Paris, France where they were analyzed. Results were usually available within 10 days and communicated by fax or email.

HCV Continuum of Care

We used three core indicators to monitor and evaluate the global health sector strategy on viral hepatitis B and C based on World health organization (WHO) recommendations. These included: (1) testing, (2) treatment and (3) cure.[15] This was modified and studied as follows:

The entry port into the cohort was HCV antibody positivity. Several steps in the continuum of care were assessed. Step 1: HCV-RNA testing. Step 2: complete pre-therapeutic eligibility evaluation which included genotype and fibrosis assessment. Step 3: treatment initiation. Step 4: treatment completion. Step 5: sustained virological response (SVR).

The study was approved by the DGH ethics committee for research.

Definitions: Participants described as insured were those who had full or partial compensation for medical expenses.

METAVIR score assessed fibrosis in chronic hepatitis C according to a 5-stage classification from F0 (no fibrosis), F1 (portal and peri-portal fibrosis without

septa) F2 (portal and peri-portal fibrosis with rare septa) F3 (numerous septa without cirrhosis) and F4 (cirrhosis).

Treatment with pegylated interferon alpha 2a and weight-based/genotype specific dosing of ribavirin was standard treatment. Duration of treatment was 24 weeks for genotype 2 and 48 weeks for non 2 genotypes (1 and 4).

Statistical Analysis

Results are presented as proportions (percentages of individuals who attained the highest level in the HCV continuum of care. Bivariate analysis using the Chi-squared tests were used to identify demographic factors associated with reaching each step in the HCV continuum of care process. The level of significance was set at 5%. All analyses were done using stata 13 (Stata Corp, College Station, Texas, USA).

RESULTS

Sociodemographic Characteristics

A total of 669 individuals tested positive for antibodies to HCV. The mean age of these individuals was 57 (sd: ±13) years with the majority being 50–69 years old. Female gender represented 52.8% of the study cohort. The vast majority of the patients were married (64.8%). Ninety five percent of the patients had no form of health insurance (Table 1).

Table 1 Socio-Demographic Characteristics of the Population.

Characteristics	Value
Mean (±SD) age	57 (±13)
Age groups	
<30	36 (5.4)
30–49	116 (17.4)
50–69	408 (61.1)
≥70	108 (16.2)
Gender	
Male	315 (47.2)
Female	353 (52.8)
Marital status	
Single	88 (13.2)
Married	433 (64.8)
Divorced	14 (2.1)
Widowed	133 (19.9)
Care support	
Personal	641 (95.9)
Insurance	24 (3.6)
Family	3 (0.45)
Profession	
Paid worker	362 (54.2)
Non-paid worker	94 (14.1)
Jobless	212 (31.7)

Results are presented as count (percentage) or otherwise stated.

Continuum of HCV Care and Treatment

Table 2 shows the proportion of individuals who reached each checkpoint in the HCV continuum care process. Out of the 669 patients with a positive HCV antibody test result, 61.3% (410) underwent HCV RNA testing. Three hundred and sixty-six (54.7%) were confirmed to have viral replication (HCV RNA positive) and 108 (26.9%) had a complete treatment eligibility evaluation. A total of 286 completed HCV genotyping. The most common genotype was genotype 1 in 40.2% (115) of the subjects. One hundred and ninety-two had done transient elastography, or fibrotest/fibrometer. Eighty-one (12.1%) initiated treatment with pegylated interferon/ribavirin. Seventy-two (10.8%) completed treatment and 44 (6.6%) had undetectable HCV RNA levels at 24 weeks after treatment completion (SVR). This made up 54% (44/81) of those who initiated treatment.

Continuum of HCV Care by Socio-Demographic Characteristics

In Table 3 we cross-tabulated the baseline characteristics of the individuals by the stages of continuum of care and treatment. People aged 30–49 and 50–69 had higher proportions in initiating treatment when compared to those aged <30 and >70 ($P = 0.0003$). Similarly, the proportion of men who attained treatment initiation was higher when compared to women ($P = 0.03$). People who had insurance had higher proportions in late stages of care compared to those who were supported by themselves or by the family. Profession and marital status too were significantly associated to attending late stages in continuum of care.

DISCUSSION

We aimed at studying the several steps along the care continuum which involved screening, diagnosis, pre-therapeutic evaluation and treatment[15] with the hope of providing a useful framework to discuss new strategies for intervention at each stage.[12] From our study, we found out that of the 669 anti-HCV antibody positive individuals, 61.3% did HCV RNA testing, 26.9% had a complete Pre-therapeutic evaluation (which included both genotyping and fibrosis assessment), 12.1% initiated treatment with pegylated interferon and ribavirin, 10.8% completed treatment and 6.7% achieved SVR. Socio-demographic characteristics which included age, gender, marital status, having care support and profession were associated with attaining the later steps in the care continuum.

It is strongly recommended that HCV serological testing be offered to individuals who are part of a population with a high prevalence or who have a history of HCV risk

Table 2 Steps of Continuum of HCV Care and Treatment.

Total HCV antibody positivity	669 (100)
Step 1—HCV RNA testing	410 (61.3%)
HCV RNA confirmation	366 (54.7)
Median HCV viral load ($\times 10^5$ UI/ml)	6.96 (1.39–23.1)
Step 2—pretherapeutic evaluation (genotype + liver fibrosis assessment)	180 (26.9)
Genotype	286 (42.8)
1	115 (40.2)
2	69 (24.1)
4	98 (34.3)
1/4	2 (0.70)
1/5	1 (0.35)
2/4	1 (0.35)
Liver function evaluation (fibroscan/fribrometer/fibrotest)	192 (28.7)
Fribrometer ($N = 201$)	35 (17.4)
Fibroactitest ($N = 201$)	151 (75.1)
Fibroscan ($N = 201$)	32 (15.9)
Score fibrosis ($N = 187$)	
F0-1	71 (37.8)
F2-4	116 (62.5)
Step 3—treatment initiation	81 (12.1)
Step 4—treatment completion	72 (10.8)
Step 5—sustained virological response (SVR)	44 (6.6)
Genotype 1 ($n = 31$)	13 (41.9)
Genotype 2 ($n = 28$)	23 (82.1)
Genotype 4 ($n = 22$)	8 (36.3)

Percentages for each step are calculated on the total of HCV antibodies positivity (669). SVR is defined as having viral load undetectable at 24 weeks after the end of treatment.

exposure/behavior.[1] In this study, we reviewed patients who were already tested and positive for anti-HCV antibody. The circumstances of anti-HCV testing in this setting were mainly self-request for routine medical check-up, systematic screening in different high risk population groups and for a smaller group who presented with symptoms of chronic liver disease.[14] Universal or voluntary HCV screening, as for HIV, is not common practice in Cameroon though known for its high prevalence of HCV. We need to encourage health provider awareness and enforce screening for groups perceived to be at highest risk for HCV infection (HIV, haemodialysis, past history of blood transfusion, injection drug use and previous surgery).[16] There is no doubt that rapid diagnostic testing for anti-HCV antibodies has eased and improved the rate of diagnosis of HCV especially as it does not require capital investment and can be performed by any trained person.[17] Following anti-HCV antibody positivity patients are then referred for specialist care and follow up in tertiary centers where there are gastroenterologists, infectious diseases specialists and internists. Referral to a specialist presents an opportunity to be evaluated for treatment and to receive preventive and risk reduction counseling.[1,18]

The next step is HCV-RNA testing which is not routinely available in Cameroon whereas, this is a crucial step in the care continuum as it confirms viral replication. Inaccessibility to HCV-RNA is a major barrier in engaging chronically infected individuals in HCV care. In our treatment center, all tests were carried out in a reference laboratory in France with inherent disadvantages of costs, delay and a possibility for loss to follow up. 61.3% had HCV-RNA testing, of which 89.5% (366/410) confirmed viral replication. In agreement with other studies, 30–50% of individuals do not receive confirmatory testing.[10,18,19] Previous studies have shown that when adequate measures are taken such as increasing awareness and strong recommendations to that effect, there is an increase in confirmatory HCV-RNA testing.[10]

Similar difficulties apply to the next step in the care continuum which is the pre-therapeutic evaluation, of which genotyping and fibrosis assessment are most important. Genotype testing is also only done abroad while markers of liver fibrosis used were expensive. In this center we used FibroTest/Fibrometer and transient elastography which require more resources. This is unfortunate because APRI and FIB4 should be the preferred test in this low income setting.[1] 28.7% of the study population had an adequate pre-therapeutic evaluation.

Staging of liver fibrosis at present still remains important for determining the urgency and timing of HCV therapy and for identification of cirrhosis, which should prompt screening for HCC and monitoring for the development of hepatic decompensation.[11,20,21] Current guidelines call for HCV-RNA, HCV genotyping and fibrosis assessment to inform treatment decisions whereas they are out of reach in this setting due to inadequate infrastructure and cost. Low cost methods for identification of HCV-RNA is essential[22] and point of care tests are currently under investigation.[23] Also, we hope that in the future, the new DAA will provide an opportunity to simplify the laboratory requirements for HCV therapy.

Standard of care was based on ribavirin/peg-interferon combination. Government intervention and funding enabled patients to pay for 33% of the real cost of treatment. This was still not affordable for the majority of the population. Only a small proportion of individuals, 12.1% in the care continuum (22.1% of HCV-RNA positive) received antiviral treatment. This is consistent with other studies showing low rates of treatment uptake.[16,24] Infact, in 2015, it was estimated that less than 1% of people with chronic HCV were receiving treatment.[5] In other studies carried out in high risk groups for acquiring HCV such as sex workers in Canada and IDU in India, only 1% and 1.4% respectively of anti-HCV positive individuals received treatment.[16,22] Physician and patient factors may have

Table 3 Continuum of HCV Care and Treatment by Socio-Demographic Characteristics.

Characteristics	HCV positive	Stage 1 HCV RNA testing	Stage 2 Pretherapeutic evaluation	Stage 3 Treatment initiation	*P* value
Age groups					
<30	36 (5.4)	11 (3.0)	3 (1.7)	2 (2.5)	
30–49	116 (17.4)	74 (20.2)	34 (18.8)	18 (22.2)	0.0003
50–69	408 (61.1)	248 (67.8)	130 (72.2)	57 (70.4)	
≥70	108 (16.2)	33 (9.0)	13 (7.2)	4 (4.9)	
Gender					
Male	315 (47.2)	170 (46.5)	87 (48.3)	52 (64.2)	
Female	353 (52.8)	196 (53.5)	93 (51.7)	29 (35.8)	0.03
Marital status					
Single	88 (13.2)	43 (11.8)	16 (8.9)	5 (6.2)	
Married	433 (64.8)	259 (70.7)	141 (78.3)	68 (83.9)	
Divorced	14 (2.1)	7 (1.9)	1 (0.6)	3 (3.7)	0.002
Widowed	133 (19.9)	57 (15.5)	22 (12.2)	5 (6.2)	
Care support					
Personal + family[a]	644(96.3)	346 (94.5)	166 (92.2)	66 (81.5)	
Insurance	24 (3.6)	20 (5.5)	16 (8.8)	15 (18.5)	<0.0001
Profession					
Paid worker	362 (54.2)	219 (59.8)	126 (70.0)	55 (67.9)	
Non-paid worker	94 (14.1)	56 (15.3)	21 (11.7)	15 (18.5)	0.0002
Jobless	212 (31.7)	91 (24.9)	33 (18.3)	11 (13.6)	
History of alcohol					
No	340 (51.5)	189 (51.8)	87 (48.6)	32 (39.5)	
Yes	322 (48.5)	176 (48.2)	92 (51.4)	49 (60.5)	0.20
History of smoking					
No	605 (91.4)	327 (89.3)	160 (88.9)	68 (83.9)	
Yes	57 (8.6)	39 (10.7)	20 (11.1)	13 (16.1)	0.16
Diabetes					
No	532 (80.2)	285 (77.9)	139 (77.2)	62 (76.5)	
Yes	131 (19.8)	81 (22.1)	41 (22.8)	19 (23.5)	0.68
Hypertension					
No	452 (68.3)	241 (66.1)	116 (64.8)	58 (72.5)	
Yes	210 (31.7)	124 (33.9)	63 (35.2)	22 (27.5)	0.56

[a]We combined personal + family because of very small cell count.

played a role in low treatment rates.[25] Patient factors may have included; absence of symptoms of liver disease until advanced stages, fear of adverse drug effects, longer duration of treatment (24–48 weeks) and management costs.[16,24,26] Physician factors included guidelines for treatment which included moderate to severe fibrosis (≥F2), anticipation for arrival of newer DAA especially as from 2014 thereby deferring treatment to await new HCV therapies.[24,27]

Our treatment outcomes (SVR) were comparable with those published in trials of patients treated with peg IFN/ribavirin (82.14% of patients with genotype 2, 41.9% genotype 1 and 36.3% genotype 4 achieved SVR).[28,29] Experience on this treatment and its outcome is sparse in this sub-region.

From this study, 6.6% of anti-HCV antibody positive patients achieved SVR. This finding was similar to other reports. In the US for example, only 5–6% of all people with chronic HCV were shown to have successfully progressed from detection of HCV infection to achievement of SVR.[11,19]

This study also showed significant differences between age, gender, marital status, care support and profession and profiles of individuals at each stage of the care continuum. Similar findings have been previously reported.[10,25] As regards age, it was found to be higher for individuals in each stage of the continuum. Older people have had more time to be exposed, tested, and receive care and because disease severity increases with age.[10] Lack of health insurance as well as limited access to regular healthcare have been known to limit patients' health seeking behavior.[10] In the United States, lack of

health insurance was found to be a major barrier to pursuing downstream HCV care.[30]

With the arrival of these new direct-acting antiviral agents, HCV treatment duration will be shortened, cure rates will be increased and the number of people offered treatment will also rise considerably.[11,31,32] However, to maximize the benefits of these new treatments, issues related to treatment access, that is technical, logistical and financial challenges must be overcome. These should include: (1) education of care providers and the general public about HCV prevention, care, and treatment. (2) Increased access to HCV testing, ensuring affordable and adequate laboratory capacity for specialized investigations. (3) Expansion of HCV therapy services from specialized centers to general practice and other healthcare workers as is the case for HIV presently. (4) Ensuring affordability of treatment.[5,11,22,33]

LIMITATIONS

This data was obtained by reviewing patient's files and registers which are susceptible to missing data and misclassification errors. More to that, the files were not conceived to answer the question on continuum of care, therefore, we had little flexibility on variables that could be used for analytical purposes (to stratify stages of continuum of care). That notwithstanding, this is the first data that shows a clear picture of the problem of continuum of HCV care and treatment in a major HCV treatment center in Cameroon. This hospital being a referral one, patients attending may be different from those attending other hospitals in the country, thus making our results less generalizable. Nonetheless we strongly believe that this result will raise the alarm on HCV care in Cameroon and will stand as strong evidence to support HCV care and treatment policy in the future.

CONCLUSION

In one of two hepatitis treatment centers in Cameroon, we have clearly shown decreasing numbers of individuals at all steps in the continuum of care in the era of IFN/Ribavirin as standard of care. This was highly impacted by socio-economic factors. This result we hope, will provide a framework for identifying gaps in the HCV care continuum. While newer treatments are becoming available, their benefits can be maximized only by comprehensively addressing all issues related to improving access to treatment.

AUTHORS' CONTRIBUTION

Designing and planning the study: HNL, DNN, SAFBE, NAG, OSD, ICD. Data collection: HNL, SAFBE, AM, TTS, EBA. Data analysis and interpretation: HNL, SAFBE, DNN, OSD, NAG, EBA. Preparing and writing the unpublished study: HNL, SAFBE, DNN, EBA, Critical review: ICD, AM, TTS. Final approval: HNL, DNN, SAFBE, NAG, OSD, ICD, AM, TTS, EBA.

CONFLICTS OF INTEREST

The authors have none to declare.

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