Hepatitis C in Cameroon: What is the progress from 2001 to 2016?

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ABSTRACT

Chronic hepatitis C is a major public health problem in sub-Saharan countries and particularly in Cameroon where the prevalence rate is around 7.6% in the age group of 55–59 years. Recent investigations into this infection allowed defining a national seroprevalence, characterizing virological and biological profiles of infected patients and identifying medicinal plants of potential interest in hepatitis C therapy. However, in Cameroon, no existing report currently presents a good overview of hepatitis C research in relation to these parameters. This review seeks to discuss major findings published since 2001 that have significantly advanced our understanding of the epidemiology and treatment of hepatitis C in Cameroonian patients and highlight the major challenges that remain to overcome. We performed a systematic search in Pubmed and Google Scholar. Studies evaluating prevalence, treatment, coinfection, and genetic diversity of HCV infection in Cameroon were included. Studies suggest that HCV prevalence in Cameroon would be low (around 1.1%) with a lot of disparities according to regions and age of participants. Elders, pregnant women, blood donors, health care workers, patients on hemodialysis, and homozygous sickle cell patients have been identified as risk groups. Moreover, HCV/HBV coinfection was found more prevalent than HCV/HIV coinfection. Phylogenetic studies reported circulation of three main genotypes such genotypes 1, 2, and 4 but little is known about antiviral candidates from the Cameroonian pharmacopeia. In conclusion, some epidemiological data prove that hepatitis C in Cameroon is well known but efforts are still necessary to prevent or control this infection.

Key words: hepatitis C, Cameroon, prevalence, antiviral agents, public health

INTRODUCTION

Hepatitis C is a global issue that mostly affects developing countries. Among the 170 million people chronically infected by hepatitis C virus (HCV) worldwide, 32.5 millions are found in Africa[1]. In Cameroun, hepatitis C is endemic. Nzereniet et al. performed a serological study conducted in 2003 on 1,434 individuals in Yaounde and other HCV seroepidemiological studies were carried out on 2,066 sera from four geographically distinct rural areas of Cameroon, which reported high seroprevalence rates for Yaounde (6.9%), Ntem (14.4%), and Meka (16.6%) and low seroprevalence rates for Nditém (2.9%) and Yokadouma (3.3%)[2]. Later, analysis of sera samples from the 2011 Health Demographic Survey indicated a national prevalence of 1.1%. Unlike the first study that was only based on three regions, the demographic survey included all the 10 regions of the country. The elders group (55–59 years old) in this study emerged as the most vulnerable with a seroprevalence rate of 7.6%. Meanwhile, prevalence was higher in rural communities than urban areas (1.4% vs 0.9%, respectively, $P < 0.001$) and significantly different regionally across the country with the highest prevalence in the Central region (2.9%) and the lowest in the Far North region (0.4%)[3].
Up to now, little is known about the clinical, virological, and immunological profiles of Cameroonian-infected patients and several cases of coinfection with human immunodeficiency virus (HIV) or hepatitis B virus (HBV) were reported. Some molecular phylogeny studies were conducted to characterize circulating HCV strains and these studies highlighted three main genotypes (1, 2, and 4) with genotype 1 as the most prevalent and heterogeneous [4]. Moreover, cirrhosis and hepatocellular carcinoma (HCC), which are some severe HCV-related complications, were also found, especially in males aged older than 60 years [3].

During the last 20 years, treatment of hepatitis C in Cameroon was only based on the combination of α-pegylated interferon/Ribavirin (PEG-IFN/RBV), accessible to a low number of patients because of relatively high costs. A partnership signed between the Cameroonian government and the pharmaceutical laboratory Gilead offers HCV-infected patients an opportunity to access the new direct antivirals at low cost, especially the combination of Sofosbuvir/RBV, and Sofosbuvir/RBV/Ledispavir. As part of the agreement, a discount of 50–80% will be imposed on the cost of new antiviral molecules. However, many challenges remain to be overcome. Only a limited number of patients are estimated to benefit from this measure. Also, the effect of antivirals on HCC development is not well known. Medicinal plants represent an alternative for the management of hepatitis C; however, Cameroonian medicinal plants are poorly investigated for their beneficial effects against HCV and liver cancer. Besides these, it is quite difficult to know if these plants can prevent reinfection of liver after transplantation or if they can be used to manage oxidative damage associated with HCV infection. The lack of studies on potentially active vaccines is also important.

In general, these challenges strongly demonstrate that our understanding of HCV infection in Cameroon remains incomplete and that efforts are still necessary to expand it. The aim of the current work is to discuss the advances of HCV infection recorded in Cameroon since 2001.

In 2011, a total of 15,000 subjects (men and women) spread through the 10 administrative regions of Cameroon were screened in the framework of the national health demographic survey. This is the most important and recent epidemiology study conducted on infectious diseases in Cameroon. In a study published in 2015, Njouom et al. screened the sera samples of these participants in order to evaluate the seroprevalence to different viral hepatitis including hepatitis C and their distributions through the country. The results of this study showed that Cameroon is a low endemic zone to hepatitis C with a national rate of 1.1% (IC95%: 1–1.3%). The prevalence of hepatitis C was found to significantly increase with age ranging from 1% in people less than 45 years, more than 3% for 45-55 years and more than 7% for elderly people (≥55 years). Similarly, a previous study by Pepin et al. also reported high rates of seroprevalence (more than 50%) in this elder group (>60 years old)[6]. Another interesting finding of this national survey was the vulnerability of populations from rural zones compared to those from urban zones (1.2% vs. 0.9%). These seroprevalence rates also greatly differed according to the administrative regions with the central region as being the most affected (2.4%). High rates of hepatitis C (17.9%) were found, for instance, in elderly inhabitants of a remote village in South Cameroon [7].

A Bayesian analysis of the epidemic history of HCV in Cameroon indicates that the elderly would have contracted this infection during mass medical campaigns just before 1960[3]. Some ritual procedures such as circumcision, scarification, blood transfusions, sharing of razor blades or knives, and the use of intravenous antimalarial treatments like quinine might have disseminated the virus [6]. Also, quinine injections were reported to be responsible for more than 33% of cases of HCV transmission in South Cameroon during the colonial era. These situations and continuous exposure might partly explain the increase in seroprevalence with age.

**Seroprevalence of HCV in some risk population Groups**

**Pregnant women**

It has been previously demonstrated that vertical transmission among HCV-RNA positive pregnant women was about 5%. Based on data from two relevant studies published by Njouom et al. in 2003 and 2005, the prevalence of HCV infection in pregnant women was estimated around 1.85% in Yaoundé [8,9]. However, in one of these studies, none of the screened children born from these women were HCV-positive, meaning that the
mother-to-child transmission is not a major route of HCV transmission in Cameroon.

**Blood donors**
The regular screening of blood is systematic in clinic routine to prevent transfusion-transmittable infections. However, the risk for nonimplementation of this practice remained high in some underdeveloped areas and health formations. Four studies published between 2003 and 2016, grouping more than 1200 participants, have tried to estimate the HCV seroprevalence in blood donors in Cameroon. These studies were conducted in the central and littoral regions while no data exists for other regions. The prevalence of HCV was shown to vary from 4.8% in Edea \[10\], 1.3% in Douala \[11\], to 3.2–4.8% in Yaoundé \[12,13\]. In addition, several cases of co-infection with HIV and HBV were reported \[11,14,15\].

**Health care workers**
Health care workers (HCW) represent an important risk group in HCV transmission. However, HCV infection in this population was poorly studied in Cameroon. Regular screening is therefore necessary to avoid patient’s contamination. Birguel *et al.* evaluated the viral markers of hepatitis C in 93 HCW in the Sahelian district of Tokombere (Far North Cameroon). About 6.3% were HCV-antibody positive \[19\]. Because of limited information on the study, it is quite difficult to conclude whether the prevalence is due to the epidemic history of HCV or due to contamination by the patient.

**Homozygous sickle cell patients**
Blood transfusion is very often an essential tool for the management of complications in sickle cell patients. However, it can also increase the chances of being infected by viral hepatitis. Indeed, previous studies demonstrated that parenteral transmission of hepatitis C by blood donors is relatively important in some Cameroonian towns, even though secured diagnosis tests currently exist. In a study published in 2013, Ngo Sack *et al.*, investigated the prevalence of HCV infection among 108 homozygous sickle cell patients collected at the Central Hospital of Yaoundé. The results of this study demonstrated that 16.67% of these patients were HCV-antibodies positive and 86.1% (93) have experienced blood transfusion during their lives, with about 14 persons having received more than 10 blood transfusion \[17\].

**Patients on Maintenance Hemodialysis**
Maintenance hemodialysis (HD) is a high-risk milieu for nosocomial HCV infection. Ashuntantang *et al.* have evaluated the rate and potential risk factors of seroconversion to anti-HCV positivity in maintenance HD patients in a tertiary hospital in Cameroon and have found that 10 of the 40 patients developed anti-HCV antibodies on dialysis (cumulative seroconversion rate 25%). A longer duration on dialysis (14 vs. 27 months, *P*=0.003) and a higher number of blood units received (19.5 vs. 5 units, *P*<0.001) were significantly associated with seroconversion \[18\].

**Genetic diversity of viral strains**
Recent advances in the characterization of HCV strains allowed identifying seven genotypes worldwide with some specificity in their geographical distributions. In Cameroon, molecular phylogenetic studies reported circulation of three main genotypes such genotypes 1, 2, and 4 \[8,19–21\]. By sequencing the NS5B and E2 regions of 156 HCV isolates collected from patients in Yaoundé, Pasquier *et al.* found that genotype 1 was more frequent than genotypes 4 and 2. Genotypes 1 and 4 were highly heterogeneous, containing many subtypes described previously (1b, 1c, 1e, 1h, 1l, 4f, 4t, 4p, 4k) \[21\] and unsubtype groups. Furthermore, there was a systematic phylogenetic concordance between NS5B and E2 sequence clustering \[21\]. Further characterization of the full-length genome sequences of seven hepatitis C virus (HCV) isolates belonging to genotype 1 by Li *et al.* revealed nine genotype 1 subtypes among which four were described for the first time. Subsequent phylogenetic analysis of 141 partial NS5B sequences further differentiated 13 subtypes (1a–1m) and six additional unclassified lineages within genotype 1. As a result of this study, there are now seven HCV genotype 1 subtypes (1a–1c, 1e, 1g, 1h, 1l) and two unclassified genotype 1 lineages with full-length genomes characterized \[17\].

In contrast to these studies highlighting the predominance of genotype 1, the characterization of the viral genotypes by Njouom *et al.* in a Bantou population from the south region of Cameroon indicated that most of the HCV strains were of genotype 4 (76%), while genotype 2 (16%), and 1 (8%) were marginally represented \[17\]. Likewise, another study conducted by the research group indicated the predominance of genotype 4 (38–45%) on the other genotypes in pregnant women from Yaoundé. These results suggest the fact that there are still some disparities in the geographical localizations of HCV strains in Cameroon.

The mechanisms underlying the genetic diversity of HCV are not totally understood and the role played by the recombination in this diversity and particularly in HCV evolution is currently uncertain and poorly explored in Cameroon. Recently, Iles *et al.* reported the occurrence of some intergenotypic (4/1) recombinants in samples collected in South Cameroon using a number of approaches, including standard Sanger sequencing, genotype-specific PCR amplification, and non-HCV-specific Illumina RNA
sequencing (RNA-seq) [23]. Furthermore, in a comparative evolutionary analysis, Pouillot et al. demonstrated that HCV-genotype 2 strains from Cameroon were deriving from the West African strains and have undergone different epidemic stories. HCV-genotype 2 appeared to have spread relatively slowly within the West African population from 1630 to 1900, while the Cameroon lineages exhibited rapid, exponential spread from 1920 to 1960 [23].

Hepatocellular carcinoma
Data on HCV-related hepatocellular carcinoma (HCC) in Cameroon are very rare. Andoulo et al. analyzed the epidemiological characteristics of this cancer in 26 patients surveyed at the Yaounde General Hospital and Yaounde University Hospital and having both HCV and HCC [8]. These patients were between 30 and over 60 years old.

The results obtained showed that most of these patients were males (18/26) and aged older than 50 years (53.8% were ≥60 years and 38.5% between 50 and 59 years). Also, 69.2% of patients had cirrhosis while 30.8% were cirrhosis-free. Patients with cirrhosis were relatively younger than those without cirrhosis (mean age ± SD, 59.05 ± 10.05 vs. 66.87 ± 8.72 years, P=0.066). The presence of cirrhosis diminished gradually with increasing age (100% at 30–39 years to 57.0% at ≥60 years), cirrhosis-free patients were more frequent as from 50 years old. Moreover, cirrhosis was more frequent among women (87.5%), relative risk (RR) (RR 1.43 CI 95%:0.91–2.25), among alcoholics (100%) (RR 1.5 CI 95%: 1.13–1.99) and nonsmokers (70.0%) (RR 0.95 IC 95%:0.51–1.80 for the smoker). In general, 23.1% (6/26) of patients were smokers while 7.7% (2/26) of patients were alcoholics. The prevalence of HCC with respect to age was 0% among those aged < 0 years; 3.8% (95%CI: 0.1–19.6) in 30–39 years; 3.8% (95%CI: 0.1–19.6) in 40–49 years; 38.5% (95%CI: 20.2–59.4) in 50–59 years and 53.8% (95%CI: 33.4–73.4) in age=≥60 years. Parenteral exposition other than injection drug usage was encountered in 84.6% (22/26) of patients.

Taken altogether, these results suggest that cirrhosis, age, alcohol, sex, and parental exposition are risk factors to HCC development in Cameroonian HCV-infected patients.

Coinfection of HCV with HIV and HBV
Between 2001 and 2016, some studies were done to determine the profile of the HCV/HIV or HCV/HBV coinfection in Cameroon. The results tend to prove the HCV/HBV coinfection is more frequent than HCV/HIV coinfection.

Luma et al. [24] analyzed the prevalence of this coinfection in 524 patients sampled from January 2008 to December 2014 at the Gastroenterologic Clinic of the General Hospital of Douala (Littoral Region). The surveyed subjects had a mean of age of 56 years and 53% of them were female. The study results showed that HCV coinfection with HBV and HIV were 3.6% and 3.4% respectively.

In a recent study by Noubiap et al. [14], 531-HIV infected patients were screened for the presence of antibodies to HCV (HCV-Ab) and HBV surface antigen (HBsAg) in order to estimate the seroprevalence and identify risk factors associated with HBV or HCV coinfection in HIV-infected subjects. The analysis was carried out in five regions including Center, North West, East, South, and South West in persons aged between 14 and more than 50 years. The results by region indicated that the Central region had the highest rate of HCV/HIV coinfection (5.46%) followed by East (2.82%), South East (2.07%), North West (1.13%), and South (0.00%). Moreover, the age-specific prevalence in HCV/HIV coinfection was highest (4%) in the 31–40 years group and lowest (2%) in the elderly group (>50 years). This situation can be explained by the fact that people from the first age group are very sexually active. When analyzing the influence of the residence place on the chance of being co-infected, the authors showed that people living in cities had fewer chances to be co-infected than those from rural villages, although no statistical difference was found. Likewise, people with single sexual partners were more a group at risk than those with multiple sex partners, but this result was also not significant statistically. Although some limitations were pointed out, the authors suggested that their study opened new doors for the understanding of HCV/HIV coinfection in Cameroon and to elaborate more structured studies in some targeted populations, including risk groups.

In 2012, Ymele et al. [15] analyzed the prevalence of the HCV/HBV and HCV/HIV coinfections in 4650 blood samples collected at the Blood Bank of the Central Hospital of Yaoundé between January and June 2008. These samples were obtained from a population mostly made of males (sex ratio: 14/1) with a median age of 28 years old (range: 16 to 69 years). The results of this study showed that coinfections were not very common in blood donors. A prevalence of 0.22% was reported for the HBV/HCV coinfection, 0.06% for HCV/HIV coinfection, and 0.04% for the coinfection with the three viruses. HCV/HIV coinfection, in particular, was found to increase with the age of donors. Following this study, the authors suggested the need to review policies for blood collection from donors, by modifying the algorithm of blood donor testing and by pretesting potential donors, using rapid tests.

In a study published in 2007 [25], Laurent et al. investigated the prevalence of HIV/HCV coinfection in 484 participants from East Cameroon. The age of participants ranged from...
15 to 75 years with a median age of 38 and women were the most represented group. Even though high rates of HCV (13.04%) and HIV were found in this population, HCV/HIV coinfection was rather scarce. A rate of 8.6% of HCV coinfection was found in HIV-infected subjects. The authors hypothesized that this finding could be related to the dissimilar epidemiologic patterns of the two infections. Indeed, HIV infection mainly affected young persons, especially young women, while HCV infection was more frequent in older persons of both sexes.

Besides these studies reporting the coinfection of HCV with other viruses in different regions of Cameroon, some authors also analyzed the effect of some antiviral treatments in the framework of this coinfection. Mbougua et al. [25] compared the hepatotoxicity and the immunological, virological, and clinical effectiveness of a nevirapine-based antiretroviral therapy between patients infected with HIV only and patients coinfected with hepatitis B or C virus in Cameroon. A retrospective cohort study was conducted among HIV-1-infected patients. Of the 169 HIV-1-infected subjects, 21% were coinfected with HBV or HCV. In coinfected patients, the median viral load was 928 000 IU/mL for HCV. Multivariate analyses found that the risk of hepatotoxicity was two-fold higher in co-infected patients ($P < 0.01$) than in the mono-infected group. The response to antiretroviral therapy was, however, comparable between mono-infected and co-infected patients in terms of CD4 cell count increase ($P = 0.8$), HIV-1 viral load below 400 copies/mL ($P = 0.9$), death ($P = 0.3$) and death or new AIDS-defining event ($P = 0.1$). Therefore, the authors concluded that nevirapine-based antiretroviral therapy could be used safely as the first-line treatment in patients with low CD4 cell count in Africa despite frequent coinfections with HBV or HCV.

These findings clearly indicate that the effect of antiviral treatments on HCV coinfection is still poorly investigated in Cameroon and further investigations are necessary to determine and better understand potential drug interactions that might affect their efficiency.

TREATMENT

Modern treatments against hepatitis C in Cameroon

The treatment of hepatitis C in Cameroon for more than 10 years was only based on the combination of pegylated interferon alpha and Ribavirin (PEG-IFNα/RBV) administrated for a period of 6 months. A study conducted by Njouom et al. on the efficiency of this treatment in HCV-infected patients in Cameroon revealed a higher sustained virological response for HCV-2 patients (80%) compared to HCV-1 and HCV-4 (30–40%) [27]. However, a recent study by Njoya et al. in 2013, recently reported some relapses in these very sensitive patients (genotype 2) [28]. In January 2016, the Cameroonian government, through the Minister of Public Health, announced the arrival of new anti-HCV molecules in the market at relatively low cost, thanks to a program initiated with Gilead Laboratories. The cost of treatment of hepatitis C will be 230 euros/month for genotype 2 and 530 euros/month for genotypes 1 and 4 for a period of 3 months. This treatment will mostly include the combination Sofosbuvir/RBV for genotype 2 patients and Sofosbuvir/RBV/PEG-IFNα for genotypes 1 and 4. Another combination (Sofosbuvir/Ledispavir) was also expected during 2016, at 1% of its European price. However, some questions arise in the mind of the national health community. The number of patients who will benefit from this program is evaluated at 500 in the 10 administrative regions of the country and a great number of these patients will not have access to these treatments. Moreover, there are no solutions proposed to patients infected by other genotypes.

Cameroonian medicinal plants of potential interest against hepatitis C

A very few numbers of HCV-infected patients currently have access to the new treatments against hepatitis C in Cameroon because of relatively high costs. The use of medicinal plants in the management of this infection and other liver-related diseases occupies a great place in rural communities. An ethnobotanical survey conducted in the Noun Division from West Cameroon by Njayou et al. reported the use of 53 plants used in traditional medicine for the management of jaundice and viral hepatitis [29]. Some of these plants were screened for their antiviral effects against hepatitis C. Table 1 summarizes the most important results obtained during these studies.

From the surveyed plants, only seven plant families were found in the literature search to have an anti-HCV effect. Their action on HCV infection mostly rested on entry and replication. A fermented papaya preparation and caffeine were reported, in particular, to delay fibrosis and cirrhosis.

NEW CHALLENGES

Instead of the genetic diversity of HCV in Cameroon, there are no studies intended to develop vaccines and the reasons explaining this diversity are not totally understood. In addition, the efficiency of the current antiviral molecules against HCV does not predict their effect on HCC. Further investigations are necessary to examine the effect of natural products or many antiviral molecules in this process. Moreover, some traditional medicinal plants have shown their efficacy in vitro against HCV infection. It would be very interesting for further studies to investigate the biological
properties of these plants in HCV-infected patients, especially in coinfected patients. This might significantly help Cameroonian to manage their hepatitis C.

CONCLUSION

Data collected between 2001 and 2016 suggest that HCV prevalence is decreasing in Cameroon at a rate of 1.1%, which is a drastic drop from 13.9% reported by Nerrienet et al. This prevalence is visible largely in some population groups including elders, pregnant women, blood donors, and especially sickle cell patients and some cases of coinfection with HIV and HBV were reported. Genotypes 1, 2, and 4 identified as the main circulating genotypes and do not have the same distributions in different populations strata. While genotype 1 is more expanded in the general population and marked by a great genetic diversity, genotype 4 is highly predominant in pregnant women. The arrival of second generation antivirals from 2016 is a hope for many patients. Their combinations with PEG-IFN/RBV will significantly increase the virological response in most infected patients. However, even the reduced cost of these treatments is still high for the modest Cameroonian. In addition, the effect of these antivirals on HCC and transplanted patients is still unknown. Furthermore, there is no vaccine to prevent hepatitis C and little is done to investigate the potential of medicinal plants against HCV infection and the related liver diseases.

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Conflict of Interest

Authors declare no conflict of interests for this manuscript.
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