Seroprevalence, Genotyping, and Monitoring of Hepatitis C Viral Loads in Patients on Antivirals in Burkina Faso

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Keywords

Hepatitis C virus · Genotype · Viral load · Pan-genotypic drugs · Burkina Faso

Abstract

Introduction: Hepatitis C virus (HCV) infection remains a major public health problem worldwide. In Burkina Faso, nearly 720,000 people are living with HCV, and each year about 900 people die from complications of cirrhosis or hepatocellular carcinoma. This study was planned to determine the HCV seroprevalence, characterize circulating genotypes, and monitor HCV viral loads in patients under treatment with antivirals. **Methods:** A total of 4,124 individuals and 167 patients in the pre-therapy program were recruited. The “SD Bioline HCV” kit was used for rapid screening of anti-HCV an-

tibodies. Viral load and genotyping were performed in 167 HCV patients on antivirals using the “Iontek HCV Quant” and “Iontek genotyping” kits. **Results:** Prevalence of HCV was 1.65% (68/4,124), and the median viral load of participants was 5.37 log₁₀/mL (1.32–7.67 log₁₀/mL). Genotype 2 was predominant with a frequency of 86.23% (144/167) and appeared to be more active with higher viral load compared to 13.77% (23/167) for genotype 1 ($p < 0.001$). After 24 weeks of pan-genotypic direct-acting antivirals, such as sofosbuvir/daclatasvir and sofosbuvir/velpatasvir, the viral loads of all patients became undetectable. **Conclusion:** The responses to antivirals by the circulating genotypes indicate that the results are very satisfactory. Therefore, the prevalence of HCV in the population can be reduced through identification of cases and treatment.

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Introduction

Hepatitis C virus (HCV) infection remains a major public health problem worldwide. It is one of the causes of high morbidity and mortality in the working population with significant socioeconomic consequences [1]. Several studies have shown that chronic infection of HCV is the leading cause of cirrhosis and hepatocellular carcinoma worldwide [2–4]. According to the WHO, close to 71 million people worldwide are chronic carriers of HCV with 399,000 deaths each year from complications such as cirrhosis and hepatocellular carcinoma [5].

Africa is one of the continents with a high prevalence rate with 19 million people chronically infected by HCV [6]. In Burkina Faso, nearly 720,000 people are living with HCV [4]. The number of deaths due to complications such as cirrhosis and primary liver cancer is about 900 per year in Burkina Faso [7]. The Fifth General Census of Population and Housing (fifth ERGPH) of Burkina Faso, which took place at the end of 2019, gives a total population of 20,487,979 composed of 9,894,028 or 48.3% men and 10,593,951 or 51.7% women [8]. In Burkina Faso, as in other African countries, the available data show that HCV is endemic with various prevalences. Antiviral drugs can cure 95% of HCV-infected people, but access to diagnosis and treatment remains limited in resource-limited countries including Burkina Faso [9]. Rapid diagnostic tests for anti-HCV antibodies show high prevalences among blood donors with levels of 3.9% [10–12] and low rates in the general population in Burkina Faso [13].

The HCV has several genotypes and subtypes, including 7 genotypes from 1 to 7 and 84 subtypes [14, 15]. In Burkina Faso, the molecular epidemiology of HCV is poorly documented, and most of the existing data relate to seroprevalence based solely on HCV antibody testing of blood donors and pregnant women [16–18]. Determining HCV genotypes is very important for identifying infected patients who are at increased risk of disease progression in order to optimize treatment and identify possible mutations [19]. To date, hepatitis C has no vaccine, and therefore treatment is essential. In developing countries, for the treatment of HCV, interferon is commonly used, with all its several side effects such as fever, headache, fatigue, arthralgia, and myalgias. Direct-acting antivirals (DAAs) are molecules that treat all genotypes of the HCV with document cure rate above 95% [20, 21]. In developed countries, pan-genotypic DAAs have shown their effectiveness in the treatment of HCV. However, the efficacy of these pan-genotypic DAAs has not yet been demonstrated in patients from Burkina Faso with chronic hepatitis C.

In 2017, Burkina Faso developed a strategic plan to fight against viral hepatitis C that did not consider specific protocols for the treatment of viral hepatitis C. The treatment is allowed for free choice to clinicians and patients [22]. In 2019, the standards and protocols for the management of viral hepatitis were established with the introduction of pan-genotypic molecules at subsidized cost. The diagnosis, which is the first means of fighting against HCV infection, remains at the patient's expense, as well as the follow-up tests before and during treatment. Among the molecules used in the treatment against HCV, first-line combination of sofosbuvir/velpatasvir is used in cirrhotic and noncirrhotic patients without addition of ribavirin, and for second line, the combination sofosbuvir/daclatasvir. In case of first-line treatment failure, the combinations of sofosbuvir/velpatasvir/voxilaprevir as the first option and glecaprevir/pibrentasvir as the second option are recommended [23]. The aim of this research work was to evaluate the prevalence of hepatitis C in Burkina Faso, to characterize the circulating genotypes, and finally to follow the evolution of viremia in HCV-positive patients under pan-genotypic DAA treatment.

Materials and Methods

Study Design and Population

A cross-sectional descriptive study took place from June 2016 to June 2019 at the Pietro Annigoni Centre for Biomolecular Research (CERBA) and the Laboratory of Molecular Biology and Genetics (LABIOGENE) of the Joseph KI-ZERBO University in Ouagadougou, Burkina Faso. The study included 4,124 individuals who came for HCV antibody screening on their own initiative or following medical instruction. In addition, 99 HCV-positive patients receiving care at CERBA/LABIOGENE were recruited. Viral load and genotyping were performed in all the HCV identified positives cases.

Laboratory Methods

Eight milliliters of venous blood was collected from the participants for the various serological and molecular tests. The SD Bioline HCV kit in a multi-cassette box/100 tests (Borahagal-Ro, Giheung-Gu, Yongin-Si, Gyeonggi-Da, South Korea) was used for the rapid diagnosis of HCV by qualitative detection of HCV-specific antibodies in serum or plasma.

Extraction of HCV RNA

HCV RNA was extracted using the kit “ABIOpure™ Viral DNA/RNA Extraction” (Alliance Bio, Bothell, WA98021, USA) following the recommendations or instructions of the manufacturer. Viral load and HCV genotyping were performed, respectively, using the kits “Iontek HCV Quant (Istanbul, Turkey)” and “Iontek genotyping Real Time PCR (Istanbul, Turkey) on the ABI 7500 Fast Real-Time PCR System” (Applied Biosystems, Waltham, MA, USA) following the protocol provided by the manufacturer.

Table 1. Population serological status according to the sociodemographic characteristics of the 4,124 subjects of the study

Variables	N = 4,124	HCV positive (n = 68)	Prevalence of HCV	p value
Women, years				
<20	403	2	0.50	<0.001
20–35	1,353	12	0.89	
35–50	537	8	1.49	
>50	181	13	7.18	
Subtotal	2,474	35	1.41	
Men, years				
<20	299	2	0.67	<0.001
20–35	732	11	1.50	
35–50	454	8	1.76	
>50	165	12	7.27	
Subtotal	1,650	33	2	
General population, years				
<20	702	4	0.57	<0.001
20–35	2085	23	1.10	
35–50	991	16	1.61	
>50	346	25	7.23	
Total	4,124	68	1.65	
Profession				
Civil servants	1,284	22	1.71	0.999
Pupils/students	420	7	1.67	
Informal sector	766	12	1.57	
Housewives/cultivators	1,284	21	1.64	
Retired	370	6	1.62	
Marital status				
Married	3,334	55	1.65	0.921
Singles	642	10	1.56	
Widows/widowers	148	3	2.02	
Level of education				
No formal education	1,235	21	1.7	0.997
Primary	469	8	1.7	
Secondary	1,432	23	1.6	
Post-secondary	988	16	1.6	
Residence				
Urban	2,889	30	1.04	<0.001
Rural	1,235	38	3.07	

HCV, hepatitis C virus.

Statistical Analysis

The results of this study were recorded in Excel 2016 and analyzed using SPSS version 17.0 and Epi info version 7.0. The χ^2 test was used for proportion comparisons, and the difference was considered significant for $p < 0.05$.

Results

Prevalence of HCV

Table 1 shows the general characteristics of the 4,124 subjects included in the study. Figure 1 shows the distribution of HCV prevalence according to patient's residence across Burkina Faso.

The age range of these individuals was between 18 and 75 years with an average of 44 ± 0.19 years. HCV RNA was detected in 68 subjects, giving a prevalence of 1.65% (68/4,124). The age group most infected with HCV was over 50 years of age with a frequency of 7.23%. Female patients of the study population had a low HCV prevalence of 1.41% compared to males with an HCV prevalence of 2%.

According to the sociodemographic characteristics, there was no statistically significant difference between HCV antibody prevalence by occupation ($p = 0.999$), marital status ($p = 0.921$), and education level ($p = 0.997$). However, there was a statistically significant difference

Fig. 1. HCV-positive/screening subjects according to the different zones of Burkina Faso. HCV, hepatitis C virus.

between urban and rural HCV antibody prevalence ($p < 0.001$) (Table 1).

Viral Load Assessment and Genotyping

Table 2 shows the distribution of viral load according to sex and HCV genotype. The total HCV-positive cases in this study was 167 patients made up of the 68 identified through the general screening and the 99 receiving care at CERBA. These 167 patients completed the HCV viral load testing before and at the end of treatment. The results showed that before treatment >88.62% of patients had a viral load >1000 IU/mL with a median of 5.39 log₁₀ (1.32–7.74 log₁₀/mL) for men and 5.26 log₁₀ (1.32–7.40 log₁₀/mL) for women ($p < 0.001$).

One hundred and sixty-seven HCV-positive patients including 106 men (63.47%) and 61 women (36.53%) with detectable viral load (before treatment) were genotyped. In this study, only 2 genotypes were found: genotypes 1 and 2. The genotyping results showed that genotype 2 was the most predominant with a frequency of

86.23% versus 13.77% of genotype 1 ($p < 0.001$). Similarly, the median viral load was higher in subjects with genotype 2 at 5.63 log₁₀ (1.75–7.67 log₁₀/mL) compared to those with genotype 1 at 4.93 log₁₀ (3.80–6.48 log₁₀/mL), and the difference was statistically significant ($p < 0.001$) (Table 2).

Medical Treatment according to HCV Genotype and Viral Load

One hundred and sixty-seven participants with known genotypes, namely, genotype 1 and genotype 2, were put under antiviral therapy. Depending on the molecule used and the level of viral load before the start of treatment (W0), the evolution of viral load was evaluated at 12 weeks (W12) and 24 weeks (W24) after the start of treatment (W0). The median viral load during the different periods and the number of patients ($n = 167$) are shown in Table 3.

After 12 and 24 weeks of treatment, respectively, 91.02% and 100% of patients had undetectable viral loads.

Table 2. Distribution of HCV viral load before treatment by sex and genotype for 167 subjects of the study

	N	Genotypes			HCV viral load, log10/mL				
		genotype 1	genotype 2	p value	<50	50–1,000	>1,000	VL* median, log10/mL	p value
Gender, n (%)									
Men	106 (63.47)	15 (14.15)	91 (85.85)	<0.001	7 (6.6)	4 (3.8)	95 (89.7)	5.39 (1.32–7.74)	<0.001
Women	61 (36.53)	8 (13.11)	53 (86.89)		2 (3.3)	6 (9.8)	53 (86.9)	5.26 (1.32–7.40)	
Genotype, n (%)									
1	23 (13.77)	–	–	–	1 (4.3)	2 (8.7)	20 (87.0)	4.93 (3.80–6.48)	<0.001
2	144 (86.23)	–	–	–	8 (5.6)	8 (5.6)	128 (88.8)	5.63 (1.75–7.67)	
Total	167	23	144		9	10	148		

HCV, hepatitis C virus. * VL, viral load.

Table 3. Median viral load results of patients presented according to the regimen and at weeks 0, 12, and 24 on treatment

Treatment regimen	Viral load results, UI/mL					
	genotype 1			genotype 2		
	W0	W12	W24	W0	W12	W24
Daclatasvir + ribavirin (n)	61.945 (8)	Undetectable	Undetectable	Molecule not used for this genotype		
Interferon (n)	Molecule not used for this genotype			1,387.331 (10)	Undetectable	Undetectable
Ledipasvir + sofosbuvir (n)	1,444.201 (10)	Undetectable	Undetectable	1,141.602 (15)	512.340 (10)	Undetectable
Sofosbuvir + daclatasvir (n)	Molecule not used for this genotype			719.436 (5)	Undetectable	Undetectable
Sofosbuvir + ribavirin (n)	Molecule not used for this genotype			1,124.987 (46)	12 (5)	Undetectable
Sofosbuvir + velpatasvir (n)	8.011 (5)	Undetectable	Undetectable	2,163.767 (68)	Undetectable	Undetectable

W0, median viral load before the start of treatment; W12, median viral load 12 weeks after treatment; W24, median viral load 24 weeks after treatment; n, number of individuals.

DAAAs such as sofosbuvir/daclatasvir and sofosbuvir/velpatasvir induced undetectable viral load after only 12 weeks of treatment.

Discussion

In this research, the prevalence of anti-HCV antibody was 1.65% (68/4,124). However, it is important to specify that this rate varied according to the sociodemographic characteristics of our study population: from 1.57% among individuals in the informal sector to 3.07% among rural dwellers, singles (1.5%), civil servants (1.71%), and widows/widowers (2.02%). The high prevalence in rural areas (3.07%) compared to urban areas (1.04%), with $p < 0.001$, could be explained by the fact that most of the patients were from the southwestern region of Burkina

Faso, which is the area with a high prevalence of viral hepatitis: 9.1% for HBV and 3.6% for HCV [6].

Our study population was between 18 and 75 years of age (44 ± 0.19 years). The age range most represented was between 20 and 35 years of age, or 49.42% of the population. The most infected age group was over 50 years of age with a prevalence of HCV infection of 7.23% versus 1.65% in the overall population. This high prevalence in the over-50 age group could be explained by risk behaviors. The overall prevalence of the study of 1.65% is similar to those found by other studies [11, 17, 24] among blood donors in Ouagadougou: 1.8%, 2.1%, and 2%, respectively. However, the prevalence of this study is lower than the 3.6% found by Meda et al. [6] in the general population, the 6.5–8.7% among blood donors by Nagalo et al. [10], and the 5.4% among pregnant women in Ouagadougou by Simporé et al. [13]. This could be explained by in-

creased sensitization, screening, and treatment over the years through World Hepatitis Days. Likewise, the prevalence in this study is higher than the 1% found by Tao et al. [25] in the general population.

In our study, women were the least affected with a prevalence of 1.41% compared to 2% for men. Our results corroborate those of Meda et al. [6] which showed that HCV seroprevalence was higher in men (3.9%) compared to women (3.2%) and could be attributed to health-seeking behaviors of females compared with males.

After diagnosis, we performed viral load testing of all HCV antibody-positive individuals and determined HCV genotypes in 167 individuals. In both males and females, 80% had a viral load >1000 IU/mL, with a significantly higher median in males ($5.39 \log_{10}$ [1.32–7.74 $\log_{10}$ /mL]) than in females ($5.26 \log_{10}$ [1.32–7.40 $\log_{10}$ /mL]). Several studies have already shown that high viral load is a risk factor for the progression of hepatitis C to cirrhosis and hepatocellular carcinoma [26, 27]. Our results would suggest that men were at increased risk of developing liver cancer or cirrhosis following chronic HCV infection. Our results corroborate those found by El-Serag and Rudolph [28] which showed that advanced age and male sex are risk factors for the development of hepatocellular carcinoma. It was also demonstrated by White [29] that elevated testosterone levels were linked to advanced liver fibrosis in men with chronic hepatitis C and HCC in hepatitis B carriers.

Genotyping showed that HCV genotype 2 was the most common in our study population. Besides genotype 1 and genotype 2, no other genotypes were detected in our study population, suggesting that these genotypes are those commonly encountered in Burkina Faso. Our results corroborate those of Assih et al. [30] who found that HCV genotypes 1 and 2 accounted for 96.4% of HCV infections in West African countries. Genotype 2 (2a) is predominantly represented in Benin, Burkina Faso, Ghana, Guinea Bissau, and Mali while genotype 1 is predominant in Côte d'Ivoire, Senegal, and Nigeria [31]. However, there was no correlation between the genotype and the geographical location of the subjects in our study.

Among the molecules used, we have interferon- α (IFN- α) which is an antiviral molecule produced naturally by immune cells allowing a decrease in viral replication in a nonspecific manner by activating natural killer cells and CD8 T lymphocytes [32]. Sofosbuvir is an NS5B polymerase inhibitor that acts by blocking the replication of the virus [33]. For genotypes 1 and 2, and after 12 weeks of treatment, 88.62% of patients had undetectable viremia and 100% had an undetectable viral load at 24 weeks of

treatment regardless of the molecule used. For effective patient follow-up, quantification of viral RNA would be the most appropriate means [20]. In addition, pan-genotypic DAA drugs, such as sofosbuvir/daclatasvir and sofosbuvir/velpatasvir, would be more effective against HCV infection, hence the need to subsidize their cost to facilitate their prescription by Burkinabe clinicians.

In our study, the following molecules (ribavirin + daclatasvir, sofosbuvir + ledipasvir, and sofosbuvir + velpatasvir) were used in the treatment of genotype 1. For genotype 2, interferon, sofosbuvir + daclatasvir, sofosbuvir + ledipasvir, sofosbuvir + ribavirin, and sofosbuvir + velpatasvir were used. The pan-genotypic molecules (sofosbuvir + daclatasvir and sofosbuvir + velpatasvir) resulted in an undetectable viral load after 12 weeks of treatment regardless of the genotype (1 and 2). Also, daclatasvir + ribavirin for genotype 1 and interferon for genotype 2 gave an undetectable viral load after 12 weeks of treatment, while the other molecules like sofosbuvir + ledipasvir and sofosbuvir + ribavirin gave detectable viral loads after 12 weeks of treatment for genotype 2. These results corroborate those of Sakr et al. [34] who showed that pan-genotypic molecules were very effective in the treatment of HCV infection with a success rate of 95–100% regardless of the genotype. The detectable viral load after 12 weeks of treatment with genotype 2 could be explained by the fact that these patients had a very high viral load prior to treatment, and sofosbuvir + ledipasvir and sofosbuvir + ribavirin were better indicated for treatment of genotype 1. Studies have shown that genomic RNA has different lengths among HCV genotypes, and these differences may affect some properties of the virus, such as pathogenicity, clinical manifestations, response to treatment, and inability to produce HCV vaccines [35, 36].

According to Zuberi et al. [37], genotypes 2 and 3 have poor response to treatment compared to genotypes 1 and 4, which respond well to IFN plus ribavirin combination therapy. In general, in genotypes 2 and 3, the response to treatment is poor compared to genotypes 1 and 4; therefore, the treatment period is longer [38, 39].

Also, in addition to the genotype, several important factors, such as interleukin 28B (IL28B) polymorphism, cirrhosis status, coinfection with other infectious diseases [40], and drug susceptibility testing of HCV strains, need to be considered for effective treatment of HCV infections [41–43]. We found a difference in treatment response between genotype 1 patients with undetectable viral load after 12 weeks and genotype 2 patients with detectable viral load after 12 weeks with the sofosbuvir/ledipasvir combination.

Our results show that this treatment gives a rapid response with genotype 1 and a slower response with genotype 2. These results could be explained by the fact that genotype 1 is more sensitive to sofosbuvir/ledipasvir compared to genotype 2 thus prolonging the duration of treatment to 24 weeks to achieve an undetectable viral load [44]. This result would not be related to the initial viral load because all patients of genotype 1 and 2 had a similar high viral load in this study. However, other authors have shown that host factors, such as the presence of cirrhosis, social criteria, adherence to treatment, and drug interactions, influence the sustained viral response, particularly in older patients [44]. In addition, viral factors, such as viral load, genotype, and presence of baseline resistance, affect the response rate [45].

In Burkina Faso, screening for hepatitis is not routine, except among blood donors and some HIV-infected individuals. HIV-induced immunosuppression affects immunity to HCV, increasing HCV plasma viral load, but these and other risk factors for HCV acquisition were not the focus of this study. Although Burkina Faso complies with blood safety standards, residual risks associated with transfusion exist, but HBV/HCV/HIV coinfections were not studied in this research. This represents a limitation of our study because these infections influence the natural history of these viruses, the evolution of these diseases, and the response to treatment [46].

With the arrival of DAAs in 2019, Burkina Faso has adopted a protocol for the management of HCV, which allows for the effective fight against HCV from diagnosis to treatment. However, there is a lack of awareness, and the subsidized treatment is still not affordable to the majority of patients. Screening and the various other follow-up laboratory tests for screen positives are not subsidized, and this impacts care and requires attention. Routine screening for HCV for pregnant women should also be considered, and the national guidelines must be revised periodically to respond to new strategies in the fight against viral hepatitis.

Conclusion

This study found HCV prevalence of 1.65% and demonstrated that genotype 2 remains the most prevalent in Burkina Faso. DAAs were also shown to be effective in the treatment of HCV-infected persons in Burkina Faso. However, the costs of DAAs are very expensive for most African countries. Nevertheless, it is necessary to continue to follow patients who have recovered from the infection

but whose liver damage, such as severe fibrosis, significantly increases their risk of cancer. In order to detect the risks of this liver tumor at an early stage, a large-scale epigenetic study on cancerous liver tissue would be necessary in the West African subregion, including in Burkina Faso.

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Statement of Ethics

The Ethics Committee for Health Research (CERS) of Burkina Faso has approved this study (Deliberation No. 2013-7-065 of July 11, 2013). All participants have given their free and written informed consent to participate in the study. Anonymity and confidentiality with respect to the information collected was scrupulously respected.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

E.T.Y., F.W.D., T.M.Z., A.A.Z., and J.S. contributed to study concept and design; E.T.Y., H.S., A.S., A.Y., P.B., and M.K. contributed to sample collection and processing; A.K.O., I.T.K., A.Z., and E.T.Y. contributed to statistical analysis and interpretation of data; E.T.Y., F.W.D., A.A.Z., M.Z., M.K., and D.O.-Y. contributed to drafting of the manuscript; I.K., A.K.O., T.M.Z., A.A.Z., M.Z., F.W.D., I.T., and J.S. contributed to critical revision of the manuscript for important intellectual content; A.K.O., I.T., and J.S. contributed to administrative, technical, and material support; J.S., F.W.D., and D.O.-Y. contributed to study supervision.

Data Availability Statement

Data sharing is not applicable to this article.

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