International Scholars Journals

International Journal of Public Health and Epidemiology ISSN: 2326-7291 Vol. 11 (9), pp. 001-010, September, 2022. Available online at www.internationalscholarsjournals.org © International Scholars Journals

Full Length Research Paper

Chronic viral HBeAg-negative hepatitis B: therapeutic characteristics in an outpatient descriptive cohort

Eric Nagaonlé Somé[1*], Issaka Zongo[1], Félicité Nana[1], Daouda Sané[2], Maxime Drabo[1], Roger Sombié[2]

[1]Institut de Recherche en Sciences de la Santé (IRSS) Ouagadougou, Burkina Faso.
[2]Département de gastro-entérologie ; UFR/SdS ; Université Joseph Ki-Zerbo, Ouagadougou, Burkina Faso.

Accepted 20 September, 2022

Abstract

In Burkina Faso, the prevalence of HBs antigen is estimated at 9.1%. We aimed to describe the therapeutic and evolutionary aspects of chronic HBeAg-negative viral hepatitis B outpatients at the University Hospital Yalgado Ouédraogo. Methods: It was a cross-sectional descriptive study including 325 participants with a retrospective data collection from January 2004 to April 2016. Results: The mean age was 38.7 years and the sex ratio, 1.5. The mean concentration of HBsAg and HBV Viral load was 7861.6 IU/mL and 32 237.20 IU/mL, respectively. A total of 84 participants were on antiviral therapy; 73 (86.9%) and six (7.1%) patients were on tenofovir and lamivudine, respectively. Under tenofovir, the virological response was complete and ALT was normal in 44.4% and 77.7% of the patients after one year. HBV DNA was undetectable and ALT normal under Lamivudine in 50% of the patients after four years. The adherence to the treatment was high, moderate or low in 71.4%, 21.4% and 7.2% of the cases, respectively. In high adherent group, HBV DNA was undetectable and ALT normal in 91.6% and 95% of cases, respectively. Under tenofovir and lamivudine, we noted an HBsAg seroconversion after 2 and seven years of treatment, respectively. CONCLUSION: The prevalence of chronic HBeAg negative hepatitis B patients is currently increasing. The HBs seroconversion is still low. The sensitization of the population to avoid the viral hepatitis infection mainly by a systematic immunization of the population remains the most effective weapon to fight this disease.

Key words: hepatitis B infection, HBs antigen, HBe antigen, antiviral treatment, adherence, sub Saharan Africa.

BACKGROUND

Viral hepatitis can be caused by five types of agents including A, B, C, D and E hepatitis viruses (https://www.who.int/news-room/q-a-detail/hepatitis). The chronic hepatitis caused by the B virus is the most frequent among the series, the A virus being involved more frequently in the acute forms (1). Viral hepatitis B (VHB) is an inflammatory disease of the liver caused by the hepatitis B virus (HBV). It constitutes a major public health problem both in terms of its seriousness and its evolution towards chronicity, as well as the number of affected subjects and the diversity of its clinical forms. Indeed, the World Health Organization (WHO) estimated that two billion people including ten to thirty million infections per year, would be infected during their life-course. Also according to the WHO in 2015, around 257 million people suffered from chronic hepatitis B worldwide with a high frequency in African countries and more than 800,000 people died from it (2, 3).

In Burkina Faso, the prevalence of Hepatitis B surface antigen (HBsAg) is estimated at 9.1% (4). The HBV transmission is predominantly vertical (mother-to- child) or horizontal (sexual and other close contact) (5, 6). Despite the existence of an effective vaccine recommended by the WHO, the number of patients chronically infected with the HBV is still important in Sub Saharan Africa. In this area, the infection is often acquired

Corresponding author e-mail: eric.some@gmail.com

at birth leading easily to the chronic carriage because of the immune-tolerance (7)**.** Following the immune-tolerance phase the immune reactivation with a negativation of the Hepatitis Be Antigen (HBeAg) with or without appearance of the anti-HBe antibodies (anti-HBeAb) corresponds to the infection control phase. However, due to a pre-C /mutation, HBeAg may no longer be secreted despite the presence of anti-HBeAb. This situation has become very frequent (87% in Europe and 50 to 80% in Asia and the Mediterranean zone) (8, 9)**.**

In Burkina Faso, Sombié (10) in 2010 found a prevalence of 77.7% for HBeAg-negative chronic hepatitis B patients. This form is at risk of a long-term progression toward serious fibrosis, cirrhosis or hepatocellular carcinoma (HCC) [3]. It should prompt a discussion on an antiviral treatment initiation with the objective to obtain a HBs seroconversion (11-13)**.** Our study aims to describe the therapeutic and evolutionary aspects of chronic HBeAg-negative viral hepatitis B outpatients at the University Teaching Hospital Yalgado Ouédraogo.

METHODS

Our study took place in the hepato-gastroenterology department of the University Teaching Hospital Yalgado Ouédraogo. It was a cross-sectional descriptive study with retrospective data collection from January 2004 to April 2016.

We included patients aged at least 15 years, with positive HBsAg for more than six months and a negative HBeAg and whose latest laboratory tests including the transaminases (alanine-amino-transferase: ALT) and / or the HBV DNA, were ≤ one year. Patients with decompensated cirrhosis or primary liver cancer were excluded. The sample size was 325 chronic HBV carriers with negative HBeAg.

A monthly, then quarterly and semi-annually check of the ALT was carried out. Serum creatinine and serum phosphorus were performed every six months in patients taking treatment. A lab analysis for HBsAg, HBeAg and HBV-DNA was performed every six months or one year. HBsAg was detected by the Determine ^{TM} technique (Abbott) and Elisa (Vidas®). The HBsAg was quantified using HBs Ag II quant II Cobas: 0.05 IU / mL to 52,000 IU / mL (log $_{10:}$ 2.11). Quantification of HBV-DNA was performed by real-time PCR (Roche Cobas Taq Man, sensitivity threshold 20 IU / mL)**.** An ultrasound and / or abdominal CT scan were performed annually in the absence of cirrhosis and every six months otherwise. Liver activity and fibrosis were assessed by a liver biopsy or a liver fibrosis blood test (FibroMeter®). Antiviral therapy was indicated in patients with a liver activity and / or fibrosis ≥ 2. In the event of an increase in ALT greater than twice the upper limit of the normal range in a patient with a detectable viral load, treatment was started regardless of the status of hepatic fibrosis. The complete virological response was defined as undetectable HBV-DNA obtained within one year of treatment. Using a questionnaire, the treatment compliance was assessed over the last three months by a visual analogue scale (VAS) from 0 to 10 (0: no treatment taken at all, to 10: no treatment skipped). Three adherence groups were defined including a high adherence group (where no dose was missed, mean VAS score of 10 over the last four weeks), moderate adherence group (overall compliance over the last 4 weeks between mean VAS score 8.1 to 9.9) and the low adherence group (with a mean VAS score ≤ 8 over the last four weeks). The data was analysed with Epi Info 7, SPSS and Microsoft Office Excel 2013 software.

Operational definitions

- HBV Chronic carrier: a subject whose HBsAg test is positive for more than 6 months and the anti-HBc (total IgG) antibody test is positive.
- Chronic active hepatitis: a chronic hepatitis B carrier whose ALT quantification is twice above the superior threshold of the normal range of values, continuously or in a fluctuating manner and the HBV-DNA is detectable.
- Chronic inactive carrier: a chronic hepatitis B carrier whose ALT quantification is still within the normal range and the HBV-DNA is less than 2000 IU / ml.
- Duration of HBsAg carriage: this is the time interval between the date of HbsAg detection and the end of our study.
- Immune-tolerance: a patient whose HBV-DNA > 20,000 IU / ml with its ALT still within the normal range
- HBs seroconversion: it is the loss of the HBsAg with or without the detection of the Anti-HBs antibody (Ab) and the Anti-HBcAb is negative.
- HBe seroconversion: it is the loss of the HBeAg with or without the detection of the anti-HBe Ab.

We categorized five biochemical and virological profiles:

- first profile: HBV-DNA < 2000 IU / ml and ALT still within the normal range (inactive carriage);
- second profile: a high HBV-DNA > 20,000 IU / ml and ALT consistently above the normal range;
- third profile: a fluctuating viral replication and ALT values without any normalization window;
- fourth profile: a succession of periods of elevated ALT followed by spontaneous normalization and a fluctuating viral replication;
- fifth profile: the immune-tolerance phase with an HBV-DNA > 20,000 IU / ml and ALT consistently within the normal range.

RESULTS

We recruited a total of 1133 patients with chronic viral hepatitis B. Among them, 325 (28.7%) patients were HBeAg negative and were included in the study.

Sociodemographic characteristics

Men represented 60% of all participants, meaning a sex ratio of 1.5. The mean age was 38.7 years (range from 16 to 74 years). The 25 - 44 year age group represented 67% of the sample. Employees from the formal sector (public or private), were the most represented professional group with 60.6 % of the participants; 61.8% of the participants were married. With

Table I. Basic sociodemographic Characteristics.

	Frequency	Percent (%)
Gender : male	195	60
Age group		
16-24	19	5.8
25-34	101	31.1
35-44	117	36.0
45-54	63	19.4
≥ 55	25	7.7
Occupation		
Pupils / Students	62	19.1
Formal sector	197	60.6
Informal sector	66	20.3
Marital status: Married	210	61.8
Lifestyle		
Alcohol consumption	134	41.2
Smoking	17	5.2
Neither alcohol nor tobacco	174174	53.6
Family history HBsAg+ or HCC	53	16.3
Circumstance of HBsAg diagnostic		
Health check up	177	54.5
Blood donation	109	33.5
Antenatal visit	16	4.9
Symptoms investigation	23	7.1

regards to the lifestyle, occasional alcohol consumption was declared by 41.2% patients and smoking by 5.2 % of the patients. Family history of HBsAg carriage or primary liver cancer were found in 16.3% of the patients (Table 1).

Table I HERE

Clinical and paraclinical aspects

The physical examination was normal in 319 (98.2%) patients and suggestive of cirrhosis in the other patients. Overall, 188 (57.8%) patients completed the HBsAg quantitative analysis. The mean concentration was 7861.6 IU/mL with a range from 2IU/mL to≥ 52,000 IU/mL. The viral hepatitis C (VHC) and D (VHD) test was positive in 4/310 and 1/184 patients, respectively, while the human immunodeficiency virus (HIV) test was positive in 3/305 people. Viral load was performed in all participants. The mean value was 32 237.20 IU/mL with a range from 0 to 91 086 744 IU/mL. HBV DNA was detectable (greater than 20IU/ml) in 258 (79.4%) patients. ALT, controlled every month for six months in 241 untreated patients, was consistently normal, fluctuating or consistently abnormal in 188 (78%), 42 (17.4%), 11(4.6%) of them, respectively.

Other paraclinical analyses

The abdominal ultrasound was performed in all participants and was normal for 276 (84.9%) patients. The liver biopsy (PBH) was performed in 25 patients (Table II). Minimal or moderate inflammatory activity was found in 44% and 24% of the patients, respectively and 32% presented a portal fibrosis with some septa (F2). Overall, 132 (40.6%) patients performed the hepatic fibrosis blood test (Table II) and 43.9% and 41.6% had minimal (A1) or moderate (A2) inflammatory activity while 59.1% and 20.4% had minimal (F1) or moderate (F2) fibrosis, respectively.

Table II HERE

Therapeutic aspects

A total of 84 participants were on antiviral therapy and 73 (86.9%)

Table II. Distribution of the participants having performed a pathology analysis and / or the hepatic fibrosis blood test according to the METAVIR score of the activity grade and fibrosis stage.

Results	Frequency	Percentage (%)
Histology (n = 25)		
Activity grade		
A0	3	12
A1	**11**	**44**
A2	6	24
A3	5	20
Fibrosis stage		
F0	4	16
F1	**8**	**32**
F2	**8**	**32**
F3	4	16
F4	1	4
Fibrometer ® (n = 132)		
Activity grade		
A0	13	9.8
A1	**58**	**43.9**
A2	**55**	**41.6**
A3	6	4.5
Fibrosis stage		
F0	10	7.6
F1	**78**	**59.1**
F2	**27**	**20.4**
F3	12	9.1
F4	5	3.8

patients were on tenofovir, of which 15 (21.9%) had received initial treatment with lamivudine; six patients (7.1%) received treatment with lamivudine alone; two patients were on effavirenz-emtricitabine-tenofovir combination; two patients were on other nucleotide analogues combinations and one patient was on pegylated interferon. The virological response was complete (within one year) and ALT was normal in 44.4% and 77.7% of the patients. HBV DNA was undetectable in 83.3% of the patients and ALT normal in all cases after 2 years of treatment using tenofovir (figure 1).

HBV DNA was undetectable and ALT normal under Lamivudine in 2/4 patients after four years. HBV DNA was detectable in 1/4 patient within seven years and 1/4 patient after seven years.

Figure 1 HERE

Adherence and resistance to treatment

The adherence to the treatment was high, moderate or low in 71.4%, 21.4% and 7.2% of the 84 assessed patients, respectively. The most poorly adherent groups included the traders and the students with 14 and 11% of non-adherent participants respectively (figure 2B). A total of 22 patients started their antiviral treatment with lamivudine. Mutant strains emerged in 12 (54.5%) patients causing resistance to the treatment; after more than seven years of treatment, a preventive switch to tenofovir was implemented in four (18.2%) patients on lamivudine to avoid an emergence of resistant strains; 6 (27.3%) patients remained on lamivudine. Resistance to lamivudine appeared in 9 (75%) patients after seven years of treatment. No resistance has been observed in patients taking tenofovir.

Although fluctuating, the adherence over the years was generally satisfactory. Poor adherence was mostly observed during the first year with a period of relapse again around the fourth year (Figure 2B).

Figure 2 HERE

In high adherent group, HBV DNA was undetectable and ALT normal in 91.6% and 95% of cases, respectively. These proportions were 55.5 and 100%, 33.3% and 66.6% in moderate or low adherent groups, respectively.

Under tenofovir, we noted an HBsAg seroconversion after 2 years of treatment without any detection of anti-HBs antibodies, at the opposite of the only patient taking lamivud-

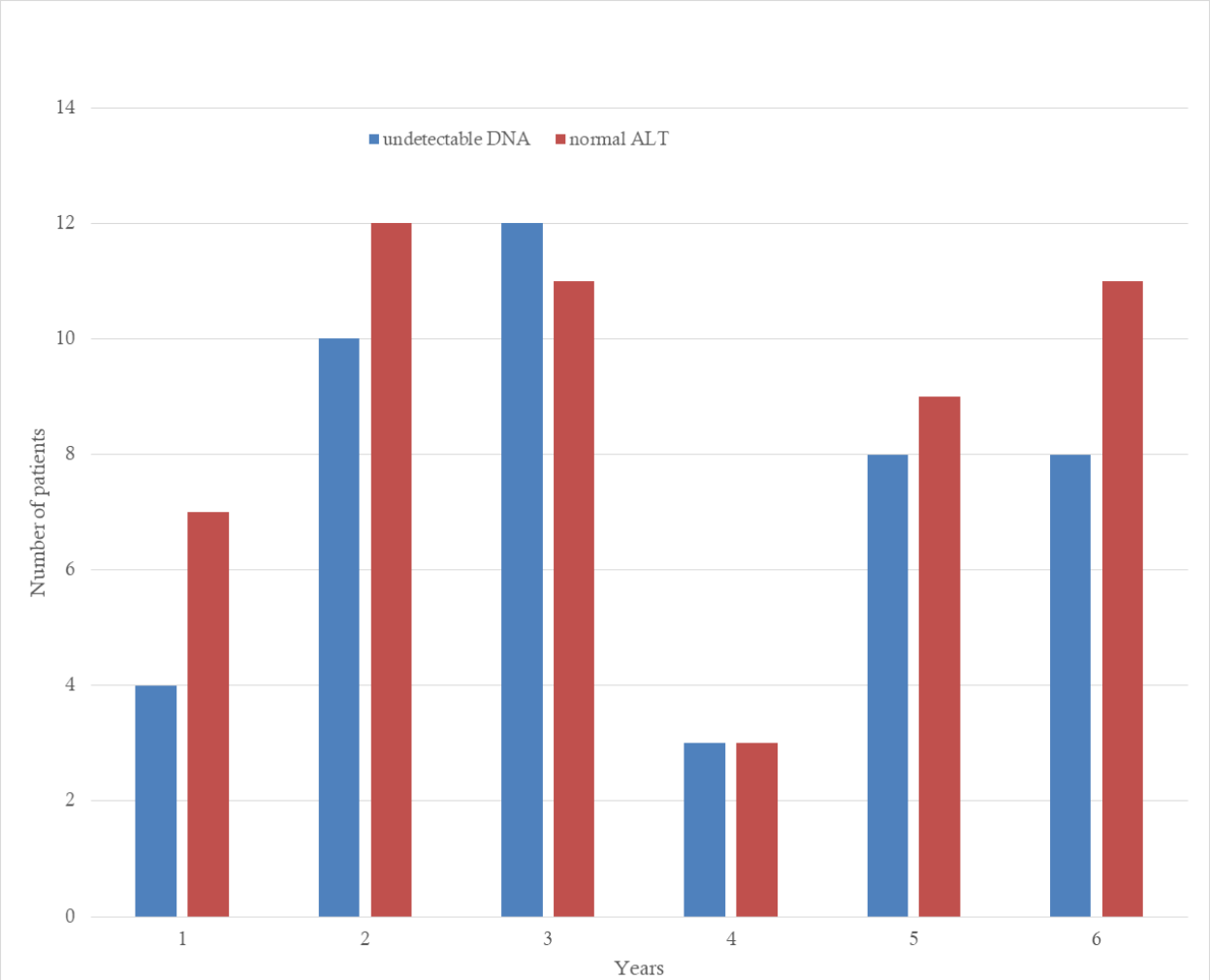


Figure 1: Distribution of patients on tenofovir according to the duration of treatment, the virological and biochemical response

dine whose HBsAg seroconversion occurred after seven years of treatment accompanied with the detection of anti-HBs antibodies. When the two molecules (tenofovir and lamivudine) were associated, no case of negativation was observed.

DISCUSSION

Limitations of the study

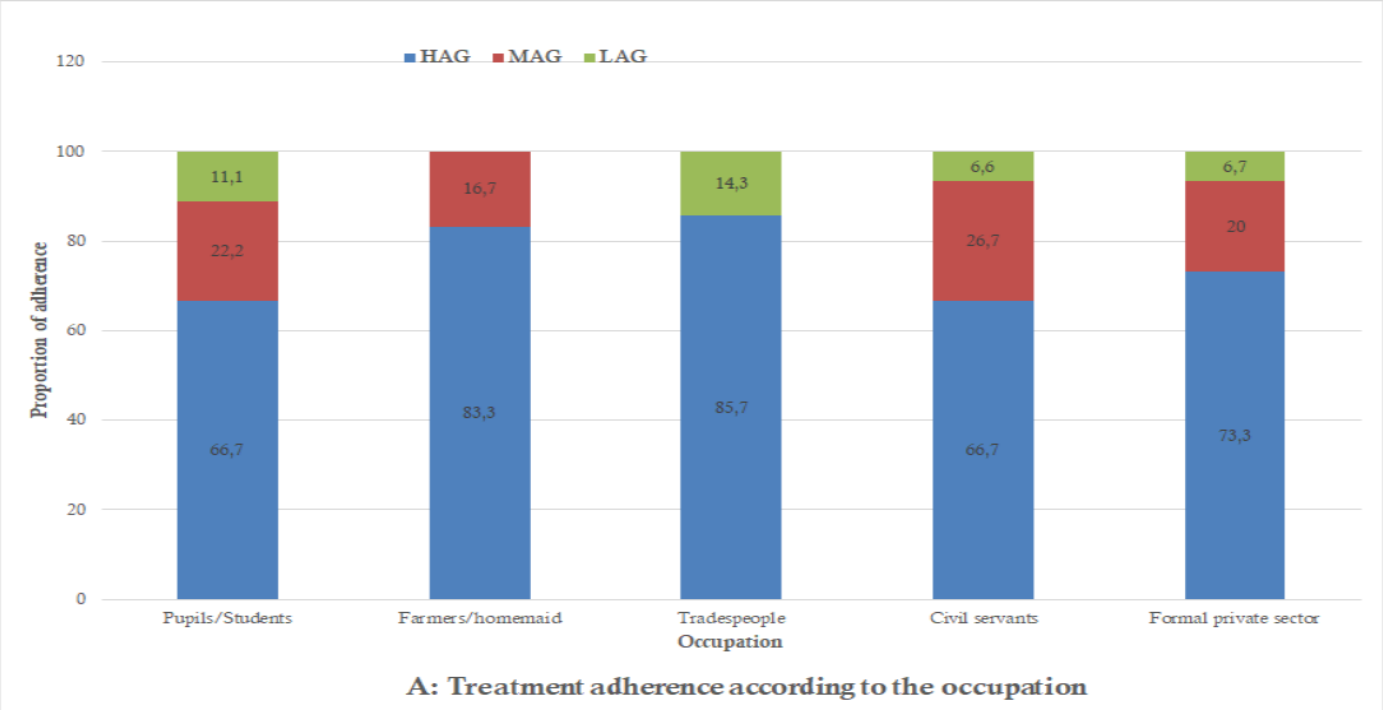
A significant number of patients lacked biological and ultrasound monitoring data. Financial reason seemed to be behind this, as the study was designed to analyse routine data. We therefore believe that the description given in this work does not present the whole reality of our cohort. However, what is observed in this work gives us a fairly objective picture of the evolution of a HBsAg-positive HBeAg-negative patient regularly monitored.

HbsAg and viral load

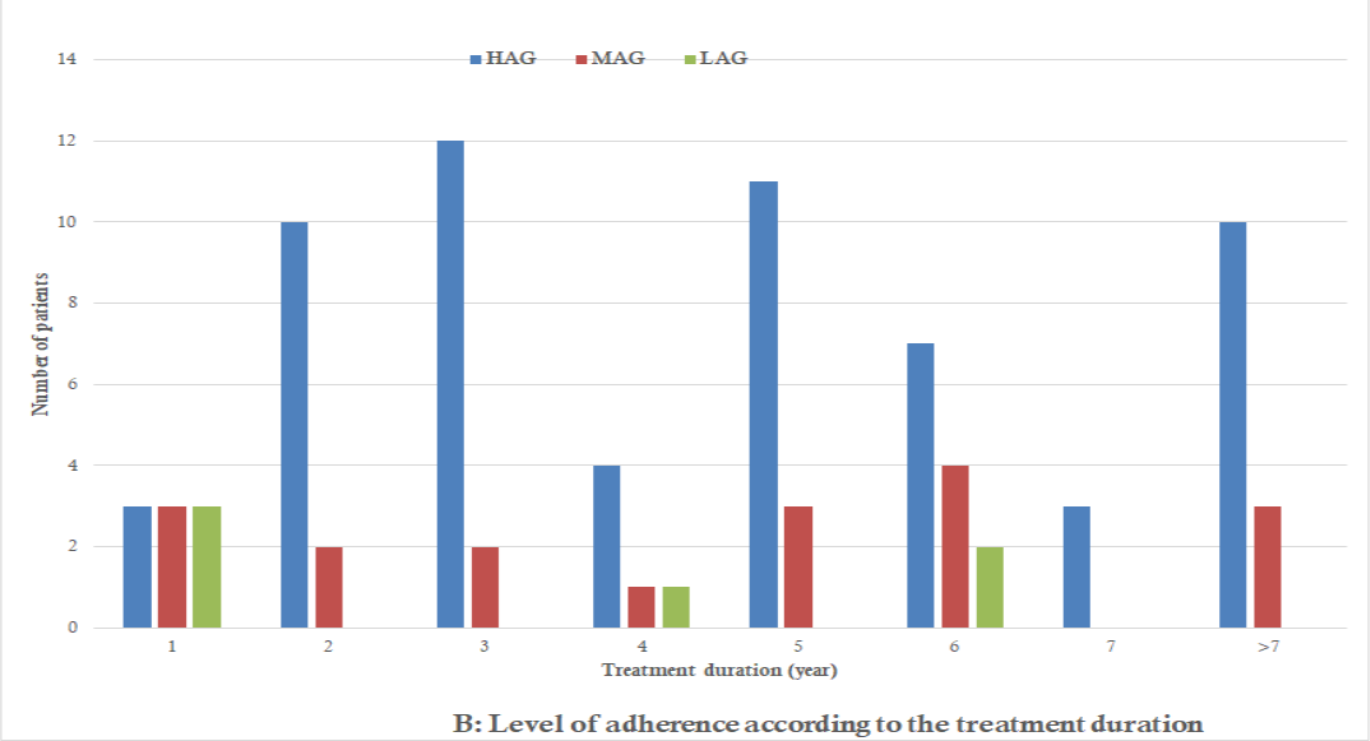
Eighty-four (25.8%) patients were on treatment in our study. Among patients with HbsAg>1000 IU/mL, 42/46 (91.3%) had an undetectable viral load; while 13/18 (72.2%) patients with HbsAg<1000 IU/mL, had undetectable viral load. There is a correlation between viral load and HbsAg concentration. The quantification of the HBsAg is becoming, along with the viral load, an essential tool for the evaluation and monitoring of the effectiveness of the treatment of patients with chronic viral hepatitis B (14-17).

Antiviral drugs

Tenofovir was used in 86.9% of the patients. Among these patients, 21.9% were switched from lamivudine. Tenofovir is a nucleotide analogue which blocks the viral replication without inducing mutation in the DNA polymerase. Although developed



A: Treatment adherence according to the occupation



B: Level of adherence according to the treatment duration

to treat resistant HIV infections, tenofovir shows greatly efficacious in the situations of HBV-HIV co-infections. It also proved efficacious when resistant strains emerge under lamivudine or entecavir treatment (18-21).

Lamivudine was used in 7.1% of the patients. It was the first oral antiviral drug. It is well tolerated and efficacious in the majority of patients. However, its main drawback is the emergence of mutations and resistance, responsible for a loss of efficacy with more severe viral reactivation in patients with underlying cirrhosis. Randomized controlled trials with lamivudine assessed virological response rates of 50%, 32% and 29% after one, two and three years of treatment,

respectively. The gradual decline in efficacy would be related to the development of a resistance mutation which incidence gradually increases to reach about 60% by the end of the 3rd year (19-21). This progressive resistance to lamivudine led us to switch it with tenofovir in 15 patients (21.9%) after 4 to 7 years of treatment. The lower proportion of switched patients could be explained by the lamivudine being the only drug available and prescribed in our country for long time because of its lower cost. Tenofovir has been introduced in the country recently.

Virological and biochemical response

Under tenofovir, the HBV DNA was undetectable in 86.9% of the cases. The complete virological response was 44.4% and 83.3% within one and two years, respectively. This virological response rate was comparable to Kabore's reported rates of 89.5% within one year and 79% within two years [unpblished data]. Asselah (22) in France reported a rate of 93% after one year and 92% after two years. In general, the virological response is around 91% in HBeAg negative patients within one year of tenofovir treatment (23-25). ALT normalized in 77.7% of cases in our study. The same rate is reported in the literature after one year of treatment (23, 24). Actually, the biochemical response rate would increase according to the duration of the treatment.

Under lamivudine, the viral DNA was undetectable in 50% of cases after four years and 25% of cases beyond seven years of treatment. This decreasing proportion could be explained by the risk of high resistance to lamivudine and therefore increasingly limiting its use as a monotherapy. At the period of our study, only 7.1% of patients were still taking lamivudine. ALT normalized in 50% of cases. This proportion was lower than Sia's finding(26) in Burkina, Yao's (27) in China, who reported biochemical response rates of 71.8% and 79.1%, respectively. In general, the literature (23, 24) also reports a rate of 74% in one year of treatment with lamivudine. Other studies have shown that when patients is treated for several years with lamivudine as a monotherapy and followed up, the complete virological (undetectable HBV DNA) and biochemical (normal ALT levelS) response rates decreased over time due to the selection of lamivudine mutant and resistant HBV (28).

Adherence to treatment

Overall, 71.4%, 21.4% and 7.2% of the participants were assessed as high, moderate or low adherent group's patients, respectively. Kaboré [unpblished data] reported in 2014, a cumulated rate of 31.6% for moderate to low adherent groups. In our study, non-adherence to the treatment could be justified by the cost of the drugs which was not affordable to many patients, the forgetfulness, mainly at the beginning of this long-lasting treatment and finally the frequent countrywide shortages of the drugs.

The adherence to the treatment varied according to the patient's occupation. Among civil servants, 62.5% were poorly adherent versus only 12.5% among students. Why these differences in the adherence by different groups of occupation? Our data did not allow us to give an answer. In general, the number of times you forget to take a medicine decreases as the treatment continues. Actually, the number of treatment skipped in the low adherent group decreased over the course of treatment. As the patient lives with the disease, he learns to accept it and integrate the medication into his daily life.

The virological and biochemical response varies depending on whether the patient is fully compliant with the treatment or not. Indeed, the therapeutic efficacy rate decreases as the compliance decreases. Adherence to treatment would therefore be a predictor of the detectability of the HBV DNA as well as the normalization of ALT.

Tolerance and resistance to the treatment

Clinical and biological safety were excellent for all our patients treated with tenofovir or lamivudine. The nephrotoxicity associated with tenofovir and described by several authors (29-32) was not observed in our series. In general the nucleotide analogues were well tolerated. The mean values of serum creatinine and serum phosphoremia were 84.4 micromoles / L and 1.1 millimoles / L, respectively, with respective ranges from 22 to 177 micromoles / L and 0.6 to 1.8 millimoles / L. Monthly monitoring of serum creatinine and phosphoremia during the first six months of treatment followed by a quarterly monitoring did not show significant variations.

In our study, the rate of viral resistance to lamivudine was 8.3% at six years; 16.6% at seven years; a cumulated 75% beyond seven years of treatment. Sia (26) reported a frequency of resistance to lamivudine of 6.6% for four years of treatment. Studies showed that the viral resistance rates increases over years, from 24% within one year, 38% within two years, 49% within three years, 67% within four years to 70% within five years (28, 33). Our relatively low rate of resistance could be explained by an underestimation of the resistance rate, many patients being unable to afford the cost of the treatment monitoring lab analyses, or the small size of our cohort.

No cases of resistance to tenofovir was observed in our study. This finding confirms the data of the literature which has not reported any case of resistance to tenofovir to date (23, 24, 33).

HBs seroconversion

In our study, two cases of HBsAg seroconversion were diagnosed, including one patient on tenofovir after two years and one on lamivudine after seven years. Sia (26) in Burkina Faso did not diagnose any case of HBsAg seroconversion in treated patients. However, six cases of spontaneous HBsAg negativation in untreated patients were observed. In the literature, HBs seroconversion is reported to be seldom and could occur under treatment or spontaneously. This is the ultimate goal of any treatment against chronic viral hepatitis,

spontaneous negativation being more seldom and estimated at only 0.5-1% versus0.5-5% with treatment(23, 24).

CONCLUSION

Viral hepatitis B is one of the most common infectious diseases in the world and is a serious worldwide public health threat. The prevalence of chronic hepatitis B patients with HBeAg negative is currently on the rise. Our study confirms the predominance of this form of hepatitis in our context. The HBs seroconversion, which is the ultimate goal of any treatment, is still low despite of the treatment. Currently, the issue of resistance to antivirals seems to be fairly well controlled. The therapeutic means were recently enriched with new molecules which offer new possibilities to patients. However, in our context where the general population is poor, the cost of the treatment is a challenge. The sensitization of the population to avoid the viral hepatitis infection mainly by a systematic immunization of the population remains the most effective weapon to fight this disease.

ACKNOWLEDGEMENT

We are much grateful to the staff of the gastro-enterology department who contributed greatly to and facilitated the data collection. We want also to thank the administration of the university teaching hospital Yalgado Ouedraogo who provided all permission to make possible the data collection.

Competing interest

The authors report no competing interest

Authors'contributions:

ENS, IZ, FN, DS, and RS: analysed and interpreted the data;
ENS: drafted the paper
IZ, FN, DS, RS and MD: reviewed the manuscript

What is already known on the topic?

- Viral hepatitis B is a global public health issue
- Primary prevention remains today the most effective strategy to eradicate the disease
-

What this study adds

- The prevalence of chronic hepatitis B patients with HBeAg negative is currently on the rise
- The ultimate goal of any treatment of the hepatitis B infection is seldom achieved probably because of the challenges related to the adherence to the treatment and the accessibility to the medicines

REFERENCES

1. Behzadi MA, Leyva-Grado VH, Namayandeh M, Ziyaeyan A, Feyznezhad R, Dorzaban H, et al. Seroprevalence of viral hepatitis A, B, C, D and E viruses in the Hormozgan province southern Iran. BMC infectious diseases. 2019;19(1):1027. doi: 10.1186/s12879-019-4661-4. PubMed PMID: 31795979; PubMed Central PMCID: PMCPMC6889522.
2. World Health Organization. Global hepatitis report. World Health Organization 2017. 2017;Global Hepatitis Programme, Geneva 83.
3. World Health Organization. Hepatitis B vaccines: WHO position paper – July 2017. Weekly epidemiological record. 2017;27(92):369–92.
4. Meda N, Tuaillon E, Kania D, Tiendrebeogo A, Pisoni A, Zida S, et al. Hepatitis B and C virus seroprevalence, Burkina Faso: a cross-sectional study. Bull World Health Organ. 2018;96(11):750-9. Epub 2018/11/21. doi: 10.2471/BLT.18.208603. PubMed PMID: 30455530; PubMed Central PMCID: PMCPMC6239015.
5. Lisker-Melman M, Khalili M, Belle SH, Terrault NA, Lin HS, Smith CI, et al. Maternal knowledge of the risk of vertical transmission and offspring acquisition of hepatitis B. Ann Hepatol. 2020;19(4):388-95. doi: 10.1016/j.aohep.2020.04.006. PubMed PMID: 32507734; PubMed Central PMCID: PMCPMC7738313.
6. Lin Y, Liu Y, Ding G, Touqui L, Wang W, Xu N, et al. Efficacy of tenofovir in preventing perinatal transmission of HBV infection in pregnant women with high viral loads. Sci Rep. 2018;8(1):15514. doi: 10.1038/s41598-018-33833-w. PubMed PMID: 30341345; PubMed Central PMCID: PMCPMC6195597.
7. Lee HA, Lee HW, Kim IH, Park SY, Sinn DH, Yu JH, et al. Extremely low risk of hepatocellular carcinoma development in patients with chronic hepatitis B in immune-tolerant phase. Aliment Pharmacol Ther. 2020;52(1):196-204. doi: 10.1111/apt.15741. PubMed PMID: 32452564.
8. Wang XL, Ren JP, Wang XQ, Wang XH, Yang SF, Xiong Y. Mutations in pre-core and basic core promoter regions of hepatitis B virus in chronic hepatitis B patients. World J Gastroenterol. 2016;22(11):3268-74. doi: 10.3748/wjg.v22.i11.3268. PubMed PMID: 27004005; PubMed Central PMCID: PMCPMC4790003.
9. Kheirabad AK, Farshidfar G, Nasrollaheian S, Gouklani H. Prevalence and Characteristics of Precore Mutation in Iran and Its Correlation with Genotypes of Hepatitis B. Electron Physician. 2017;9(4):4114-23. doi: 10.19082/4114. PubMed PMID: 28607644; PubMed Central PMCID: PMCPMC5459281.
10. Sombié R, Bougouma A, Diallo O, Bonkoungou G, Cissé R, Sangare L, et al. Hépatite B chronique: aspects épidémiologique, diagnostique, thérapeutique et évolutif au centre hospitalier universitaire Yalgado Ouédraogo de Ouagadougou. Journal Africain d'Hépato-Gastroentérologie. 2010;4(1):3-10. doi: 10.1007/s12157-009-0137-2.
11. Lee HW, Kim SU, Baatarkhuu O, Park JY, Kim DY, Ahn SH, et al. Progression of Untreated Minimally Active Chronic HBV Infection Compared to Inactive Infection. Clin Gastroenterol Hepatol. 2019;17(13):2808-10 e2. doi: 10.1016/j.cgh.2019.01.002. PubMed PMID: 30639778.

12. Kuhns MC, Holzmayer V, McNamara AL, Anderson M, Cloherty GA. Hepatitis B seroconversion revisited: new insights into the natural history of acute hepatitis B virus (HBV) infection from quantitative and highly sensitive assays and novel biomarkers. Virol J. 2021;18(1):235. doi: 10.1186/s12985-021-01706-w. PubMed PMID: 34844619; PubMed Central PMCID: PMCPMC8628455.
13. Zhong YW, Shi YM, Chu F, Liu J, Shi C, Xu JJ, et al. Prediction for HBsAg seroconversion in children with chronic hepatitis B. BMC infectious diseases. 2021;21(1):1211. doi: 10.1186/s12879-021-06883-1. PubMed PMID: 34863101; PubMed Central PMCID: PMCPMC8645145.
14. Cornberg M, Wong VW, Locarnini S, Brunetto M, Janssen HLA, Chan HL. The role of quantitative hepatitis B surface antigen revisited. J Hepatol. 2017;66(2):398-411. doi: 10.1016/j.jhep.2016.08.009. PubMed PMID: 27575311.
15. Martinot-Peignoux M, Lapalus M, Asselah T, Marcellin P. HBsAg quantification: useful for monitoring natural history and treatment outcome. Liver Int. 2014;34 Suppl 1:97-107. doi: 10.1111/liv.12403. PubMed PMID: 24373085.
16. Chang KC, Lee CY, Chang TS, Hung CH, Chen WM, Chen MY, et al. Usefulness of quantitative hepatitis B surface antigen testing in hepatitis B community-based screening. J Formos Med Assoc. 2021;120 (2):847-53. doi: 10.1016/j.jfma.2020.08.031. PubMed PMID: 32896456.
17. Chung KH, Kim W, Kim BG, Lee HY, Jin E, Cho Y, et al. Hepatitis B Surface Antigen Quantification across Different Phases of Chronic Hepatitis B Virus Infection Using an Immunoradiometric Assay. Gut Liver. 2015;9(5):657-64. doi: 10.5009/gnl14188. PubMed PMID: 25717049; PubMed Central PMCID: PMCPMC4562784.
18. Tacke F, Kroy DC. Treatment for hepatitis B in patients with drug resistance. Ann Transl Med. 2016;4(18):334. doi: 10.21037/atm.2016.09.19. PubMed PMID: 27761438; PubMed Central PMCID: PMCPMC5066043.
19. Hermans LE, Svicher V, Pas SD, Salpini R, Alvarez M, Ben Ari Z, et al. Combined Analysis of the Prevalence of Drug-Resistant Hepatitis B Virus in Antiviral Therapy-Experienced Patients in Europe (CAPRE). J Infect Dis. 2016;213 (1):39-48. doi: 10.1093/infdis/jiv363. PubMed PMID: 26136470.
20. Tamandjou Tchuem CR, Brandt L, Nel ER, Cotton MF, Matthews P, Kaindjee-Tjituka F, et al. Hepatitis B virus drug resistance mutations in HIV/HBV co-infected children in Windhoek, Namibia. PloS one. 2020;15(9):e0238839. doi: 10.1371/journal.pone.0238839. PubMed PMID: 32915862; PubMed Central PMCID: PMCPMC7485811.
21. Mokaya J, McNaughton AL, Bester PA, Goedhals D, Barnes E, Marsden BD, et al. Hepatitis B virus resistance to tenofovir: fact or fiction? A systematic literature review and structural analysis of drug resistance mechanisms. Wellcome Open Res. 2020;5:151. doi: 10.12688/wellcomeopenres.15992.1. PubMed PMID: 33869791; PubMed Central PMCID: PMCPMC8033640.
22. Asselah T, Lada O, Boyer N, Martinot M, Marcellin P. [Treatment of chronic hepatitis B]. Gastroenterol Clin Biol. 2008;32(8-9):749-68. doi: 10.1016/j.gcb.2008.07.001. PubMed PMID: 18775613.
23. Heathcote EJ, Marcellin P, Buti M, Gane E, De Man RA, Krastev Z, et al. Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. Gastroenterology. 2011;140(1):132-43. doi: 10.1053/j.gastro.2010.10.011. PubMed PMID: 20955704.
24. Buti M, Tsai N, Petersen J, Flisiak R, Gurel S, Krastev Z, et al. Seven-year efficacy and safety of treatment with tenofovir disoproxil fumarate for chronic hepatitis B virus infection. Dig Dis Sci. 2015;60(5):1457-64. doi: 10.1007/s10620-014-3486-7. PubMed PMID: 25532501; PubMed Central PMCID: PMCPMC4427621.
25. Lovett GC, Nguyen T, Iser DM, Holmes JA, Chen R, Demediuk B, et al. Efficacy and safety of tenofovir in chronic hepatitis B: Australian real world experience. World J Hepatol. 2017;9(1):48-56. doi: 10.4254/wjh.v9.i1.48. PubMed PMID: 28105258; PubMed Central PMCID: PMCPMC5220271.
26. Sia R. Les hépatites virales chroniques au Centre hospitalier Universitaire Yalgado Ouédraogo: aspects épidémiologiques, diagnostiques, thérapeutiques et évolutifs. [Thèse] Ouagadougou (PA): . 2009;Univ de Ouagadougou.:1-77.
27. Yao GB, Zhu M, Cui ZY, Wang BE, Yao JL, Zeng MD. A 7-year study of lamivudine therapy for hepatitis B virus e antigen-positive chronic hepatitis B patients in China. J Dig Dis. 2009;10(2):131-7. doi: 10.1111/j.1751-2980.2009.00375.x. PubMed PMID: 19426396.
28. Han Y, Gu L, Zhu T, Li T, Song X, Huang Y, et al. Emergence of lamivudine-resistant hepatitis B virus during combination antiretroviral therapy that includes lamivudine for patients co-infected with HIV and hepatitis B virus in China: a 2-year pilot cohort study. The Lancet. 2015;386(S32):1. doi: 10.1016/S0140-6736(15)00613-3.
29. Lopez Centeno B, Collado Borrell R, Perez Encinas M, Gutierrez Garcia ML, Sanmartin Fenollera P. Comparison of the effectiveness and renal safety of tenofovir versus entecavir in patients with chronic hepatitis B. Farm Hosp. 2016;40(4):279-86. doi: 10.7399/fh.2016.40.4.10492. PubMed PMID: 27571496.
30. Thu AM, Poovorawan K, Kittitrakul C, Nontprasert A, Sriboonvorakul N, Phumratanaprapin W, et al. Nephrotoxicity caused by oral antiviral agents in patients with chronic hepatitis B treated in a hospital for tropical diseases in Thailand. BMC Pharmacol Toxicol. 2015;16:38. doi: 10.1186/s40360-015-0037-6. PubMed PMID: 26651337; PubMed Central PMCID: PMCPMC4677430.
31. Yang YM, Choi EJ. Renal safety of tenofovir and/or entecavir in patients with chronic HBV monoinfection. Ther Clin Risk Manag. 2017; 13:1273-85. doi: 10.2147/TCRM.S143286. PubMed PMID: 29033575; PubMed Central PMCID: PMCPMC5628694.
32. Koklu S, Gulsen M, Tuna Y, Koklu H, Yuksel O, Demir M, et al. Differences in nephrotoxicity risk and renal effects among anti-viral therapies against hepatitis B. Aliment Pharmacol Ther 2015;41:310 - 9. doi: 10.1111/apt.13036.
33. Wang HL, Lu X, Yang X, Xu N. Antiviral Therapy in Lamivudine-Resistant Chronic Hepatitis B Patients: A

Systematic Review and Network Meta-Analysis. Gastroenterol Res Pract. 2016;2016:3435965. doi: 10.1155/2016/3435965. PubMed PMID: 27672391; PubMed Central PMCID: PMCPMC5031861.