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Chronic Carriage of Hepatitis B Virus at the University Teaching Hospital Yalgado Ouedraogo: Therapeutic Aspects and Outcome in a Cohort of HBeAg+ Outpatients

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Abstract

Introduction: The HbsAg prevalence in Burkina Faso was 9.1%. We aimed at describing the therapeutic features and the clinical outcome for the patients taking antiretroviral treatment. **Materials and Methods***:* We implemented a cross-sectional study from January 1st, 2004 to December 31st, 2015. Patients aged more than 15 years with positive hepatitis B surface antigen for over six months and positive hepatitis B e-antigen were included. **Results:** We analyzed the data of 148 participants for a sex ratio of 3; sixty-three patients including 49 men (77.8%) were on treatment. and 81.5% had inflammatory activity greater than one. Under tenofovir, the normalization of ALT was observed in 42 (84%) patients while HBV-DNA became undetectable in 24/33 patients. HBeAg negativation was observed in 16/25 (64%) patients after seven years of treatment. With lamivudine, 2/9 patients had a complete virologic response and six had a normalization of their ALT. Two and 9 patients lost HBeAg after 7 and 9 years of treatment, respectively. Overall 63% and 27% of the patients were in the high or low-adherence group, respectively. In the low-adherence group, all patients had normal or abnormal ALT, but detectable HBV DNA. Ten patients taking lamivudine developed resistance including primary resistance in three patients. No resistance has been observed with tenofovir. **Conclusion**: The management of the viral hepatitis B includes often a long follow up period without any medication. When antiviral is indicated, the adherence to the treatment is crucial to a long-term control of the virus. In our setting, the low purchase power of the patients may jeopardize their therapeutic future and there is a need to support this group of patients with free-of-charge medicines as it is provided for the HIV infected people.

Keywords

Viral Hepatitis B, HBe Antigen, Antiretroviral Therapy, Adherence, Resistance

1. Introduction

Chronic viral hepatitis B refers to an inflammatory disease of the liver caused by the hepatitis B virus (HBV) which has been active for more than six months. It is a major public health problem, since the prevalence of chronic HBV carriage, is over 7% or even 20% in sub-Saharan African countries [1]. According to the World Health Organization (WHO) in 2015, around 257 million people suffered from chronic hepatitis B worldwide with a higher frequency in African countries and more than 800,000 people died from it [2] [3].

Despite the effective vaccine recommended by WHO against hepatitis B since 1991 and introduced in the Expanded Program of Immunization in Burkina Faso since 2006, the number of patients infected with HBV still remains high. Burkina Faso is ranked as a highly endemic area [3] with a prevalence of the hepatitis B surface antigen (HBsAg) estimated at 9.1% [4]. This situation is explained by the fact that in sub-Saharan Africa, the HBV infection, most often acquired at birth, promotes chronic carriage due to the immunotolerance reaction of the body [5].

The HBV replication may be due to the wild virus excreting the hepatitis B e-antigen (HBeAg) or the preC/C mutant preventing the excretion of HBeAg. Although HBeAg is associated with high contagiousness, it is the detection and quantification of HBV-DNA that remains the best test for viral replication. This phase of viral replication, when uncontrolled by the body, could progress to cirrhosis or primary liver cancer. It should prompt doctors to discuss the indication of an antiviral treatment. In the management of chronic viral hepatitis B (VHB) in HbeAg+ patients, whether or not under medication, the objective is to obtain the HBe seroconversion which most often allows the control of the infection, especially by the immune system. We collected the data in the context of a medical doctorate thesis with the general objective to gather baseline data in an HbsAg positive cohort, for future follow-up. The decision to publish the data was made lately in order to feed the global knowledge on the topic and mainly to allow comparison with other future studies in Sub-Saharan Africa. The aim of the current paper was to describe the therapeutic aspects and the treatment's outcomes in HbeAg+ patients in the hepato-gastroenterology department of the University Teaching Hospital Yalgado Ouédraogo (CHU-YO).

2. Materials and Methods

We implemented at the hepato-gastroenterology department of the University Teaching Hospital Yalgado Ouédraogo (CHU-YO), a cross-sectional descriptive

study with a retrospective data collection from January 1st, 2004 to December 31st, 2015. The study population consisted of 1) HbsAg+ patients screened by the national blood transfusion center and referred to the hepato-gastroenterology department of CHU-YO for treatment and 2) chronic VHB HbeAg+ patients who were followed-up as outpatients in the same department. Patients aged more than 15 years with HbsAg+ for over six months and HbeAg+ were included. Patients who had a decompensated cirrhosis or a primary liver cancer were excluded. Data were collected using a data collection form.

2.1. Study Overview

Once recruited, the patients' paper medical files were used to collect information on civil status, weight, height, telephone number, lifestyle, risk factors and clinical, biological, radiological and histological data. A monthly, quarterly and bi-annual check of the transaminases (alanine aminotransferase (ALT)) was carried out. Tests for HBsAg, HBeAg and HBV-DNA were performed every six months or every year. HBsAg was detected using the rapid diagnostic test (the Determine TM Abbott) or the Elisa method (Vidas®). The quantification of HBsAg was carried out by the HBs Ag II quant II Cobas method: 0.05 IU/mL to 52,000 IU/mL (log10: 2.11) and the quantification of HBV-DNA by a real-time PCR (Roche Cobas Taq Man, sensitivity threshold 20 IU/mL). An abdominal ultrasound and/or an 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 using a FibroMeter®.

Antiviral treatment was indicated in patients with activity and/or fibrosis ≥ 2. When ALT concentration was twice the superior margin of the range in a patient with detectable viral load, antiviral treatment was also initiated regardless of the activity or the fibrosis. A family history of primary liver cancer and the ability to adhere to the treatment were also considered before the treatment initiation. Using a questionnaire and a visual analogue scale (VAS) from 0 to 10 (0: the patient stopped any medication and 10: the patient takes regularly its drugs at the right time), the adherence to the treatment was assessed over the last three months. Three categories were defined with regard to the adherence: The high adherence group (no missed dose, VAS score of 10), moderate adherence group (overall good adherence over the last three months, VAS score from 8.1 to 9.9), and low or non-adherence group (seldom drug intake or treatment completely stopped over the last three months, VAS score ≤ 8). The statistical analysis was carried out using Epi Info software.

2.2. Operational Definitions, Biochemical and Virological Profiles

- HBV chronic carrier: a subject whose HBsAg test is positive for more than 6 months and the anti-hepatitis B core antibodies (anti-HbcAb; total IgG) test is positive.
- Chronic active hepatitis: a chronic hepatitis B carrier whose ALT quantifica-

tion 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.
- Primary non-response: was defined as a <1-log drop after 3 months of treatment as per EASL's (European Association for the Study of the Liver) definition [6].
- Complete virological response: decrease of serum HBV DNA to PCR-undetectable levels after 1 year of treatment.
- Resistance: It corresponds to the rise in serum HBV DNA levels of at least 1 − $\log_{10}$ IU/mL compared with the lowest value during therapy (nadir value), in 2 consecutive samples 1 month apart, in patients who have previously responded and have a good treatment compliance [7].
- Primary resistance: when viral DNA remains unchanged after three months of treatment.
- Immunotolerance: 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-HBsAb and the Anti-HBcAb is negative.
- HBe seroconversion: it is the loss of the HBeAg with or without the detection of the anti-HBeAb.

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 immunotolerance phase with an HBV-DNA > 20,000 IU/ml and ALT consistently within the normal range.

3. Results

From January 1st, 2004 to December 31st, 2015, we recruited a total of 1264 patients with chronic VHB including 148 (11.7%) carriers of HBeAg.

3.1. Sociodemographic Characteristics

The sample included 148 participants for a sex ratio of 3; 69% of the participants were ≤34 years old. There were 66 (44.6%) students, and 63 (29%) workers in the

formal public or private sectors. Singles or widows represented 93 (62.8%) participants. Blood donation 66 (44.6%) and routine check-up 43 (29%) were the most frequent circumstances for diagnosing HBV infection.

Abdominal ultrasound was normal in 126 (85.1%) patients. A fatty or dysmorphic liver was observed in 9 (6.1%) and 7 (4.7%) cases, respectively.

The hepatic fibrosis blood test showed an activity A ≥ 2 in 25 (83.3%) patients and fibrosis F ≥ 2 in 23 (76.7%) patients. The liver biopsy was performed in 8 (5.4%) patients; 2 patients showed no inflammatory activity (A0); 5 had a minimal activity (A1). A portal fibrosis without septa (F1) was found in three patients and three others had portal fibrosis with some septa (F2).

3.2. Therapeutic Features

Sixty-three patients including 49 (77.8%) men were on treatment. The remaining participants were not taking any drug either because antiviral drugs were not yet indicated for their disease status, or because they were not able to complete the biological investigations to make the decision to start a treatment. The mean age for those under treatment was 33.8 years (range: 21 to 62). The most represented occupations were pupils or students 45 (30.2%), civil servants 42 (28.6%) and private employees 33 (22.2%). Fibrometer testing was performed in 27 patients and 14 (81.5%) had inflammatory activity greater than one.

Tenofovir was administered to 50 (79.4%) patients and lamivudine to 9 (14.3%) patients (Figure 1).

The duration of the treatments with tenofovir ranged between 1 and 9 years. Normalization of ALT was observed in 42 (84%) patients while HBV-DNA became undetectable in 24/33 patients. HBeAg negativation was observed in 16 (64%) patients after seven years of treatment.

Of the nine patients on Lamivudine, two had a complete virologic response and six had a normalization of their ALT (Table 1). Two and 9 patients lost HBeAg after 7 and 9 years of treatment, respectively. No case of HBsAg seroconversion has been observed under lamivudine treatment.

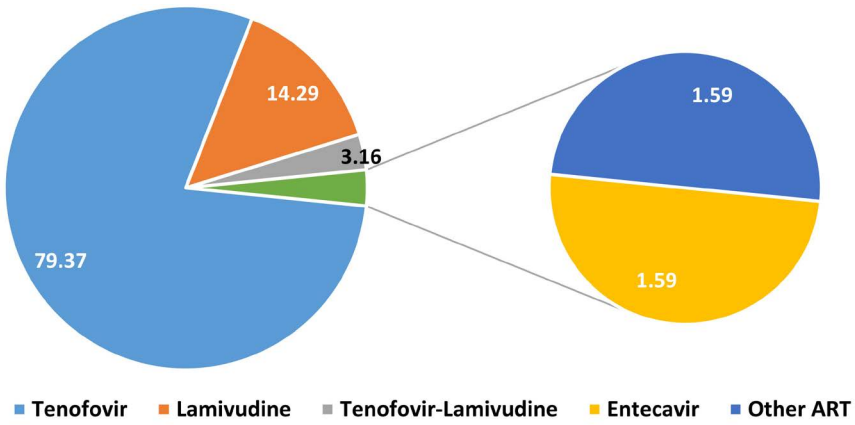

Figure 1. Distribution of patients according to the antiretroviral treatment. *Anti-retroviral treatment.

Table 1. Changes in ALT concentrations and HBV DNA load according to the treatment duration.

Treatment duration (year)	Tenofovir treatment				Lamivudine treatment			
	Normal ALT	Abnormal ALT	Undetectable Viral DNA	Detectable Viral DNA	Normal ALT	Abnormal ALT	Undetectable Viral DNA	Detectable Viral DNA
<1	8	2	1	3				
1	2	0	2	0				
2	5	0	1	1				
3	6	1	4	1				
4	5	1	4	0	1	0	0	1
5	2	2	2	0	0	0	0	0
6	11	2	7	3	2	1	0	0
7	2	1	2	1	1	1	1	1
8	1	0	1	0	1	1	1	0
9	8	2	1	3	1	0	0	0
Total	**42**	9	**24**	9	**6**	3	**2**	2

3.3. Therapeutic Adherence

Overall 40 (63%) patients were highly adherent, 17 (27%) were in the low adherence group and 6 (10%) were moderately adherent (Figure 2). According to the occupation, religious people and housewives were the most adherent (Figure 3), followed by the private sector employees, the civil servants and the students/pupils and tradespeoples at the same proportion of 50%. The highly adherent group among farmers represented 33%. The 15 - 24 age group was the least adherent (20% of the group was adherent) while the group of the 45 - 54 years old was highly (100%) adherent. The other age groups (25 - 34; 35 - 44 and 55 - 64) had an adherence level of over 60%. After three years of treatment, 72.2% of the patients were adherent against 76.3% at 5 years; 11% and 13.2% were moderately adherent at respectively 3 and 5 years, and 16.8% and 10.5% were not at all adherent still at the same time period. Among highly or moderately adherent patients, ALT were normal and viral DNA undetectable in 76.5% and 33.3% of cases, respectively. In the low adherent group, all patients had normal or abnormal transaminases, but detectable HBV DNA.

3.4. Resistance to Treatment and Disease Progression

Lamivudine was initiated in 21 patients, 9 of whom were still under the molecule at the time of our study. Ten had developed resistance including primary resistance in three patients. In two patients, lamivudine was switched to tenofovir after 4 years of treatment to prevent the development of resistance. The resistance in one year was 14.3% and 47.6% in 5 years of treatment, meaning a mean increase of 12% per year. No resistance has been observed with tenofovir. Progressively, 4/41 patients with active VHB had become stable (inactive carriage with normal ALTs and HBV-DNA < 2000 IU/mL) over a follow-up period of 1 to 6

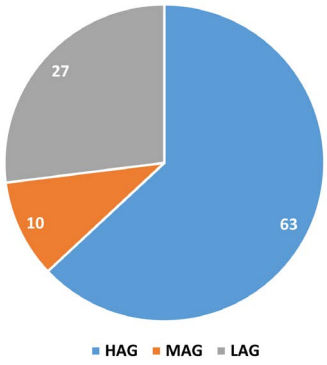

Figure 2. Distribution of the patients according to the adherence category. HAG: high adherence group; MAG: moderate adherence group; LAG: low adherence group.

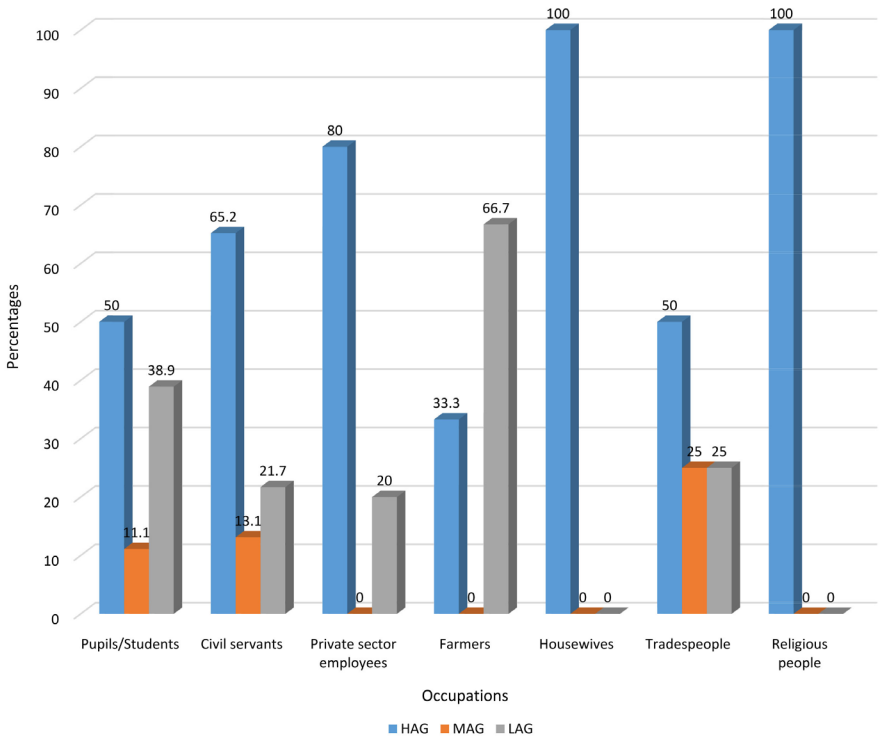

Figure 3. Distribution of the patients according to the occupation and the adherence category. HAG: high adherence group; MAG: moderate adherence group; LAG: low adherence group.

years. HBeAg seroconversion was observed in two inactive carriers. HBeAg negativation was found in 9 patients (22% of active carriers). Thirty-seven (90.2%) patients with chronic active hepatitis were observed among the untreated population.

4. Discussion

4.1. Sociodemographic Characteristics

With a sex ratio = 3, our results were comparable to those of other studies on the topic [8] [9] and clearly indicated that VHB became chronic more often in men

than in women.

The mean age was 33 years and 85.8% of the participants were younger than 40. Bougouma and Khelifa found a mean age of 37.5 and 35 years, respectively among patients with positive HBeAg. Other studies found a mean age as low as 33 years [8] [10]. In the literature [11], patients with HBeAg are generally < 40 years.

Pupils and students represented 45% of our sample, followed by civil servants and private sector employees (**Figure 3**). These groups used to be the target population of blood collection campaigns and/or the yearly health check-up as part of occupational medical visits. The education level of these groups was undoubtedly also a contributing factor to the high rate of representativeness

A family history of HBsAg carriage, cirrhosis or primary liver cancer was found in 12.8% of cases. The weakness of HBV screening in the general population may be the explanation here.

4.2. Therapeutic Features

The virological response to tenofovir was complete in 72.7% of cases. This rate is comparable to the virological response reported in the literature, which fluctuates between 72% and 76% [12] [13]. Furthermore, the ALT normalized in 84% of our patients taking tenofovir over a period of 1 to 6 years (**Table 1**) versus 69% in the literature [12] for a follow-up of one year.

According to the defined categories of therapeutic adherence, 40 (63%) patients were highly adherent; 6 (10%) patients were moderately adherent and 17 (27%) patients were in the low-adherence group (**Figure 2**). In other countries, the high adherence level was similar. Besides, 32% and 7% of cases were in the moderate or low-adherence group [14] [15]. The high proportion of low-adherent patients in our survey could be explained by the skipped doses because of the lack of habit at the beginning of the treatment and the consecutive forgetfulness, a lack of money to supply drugs [16], the drugs shortage at the level of the unique national supplier of antiretroviral drugs including lamivudine and tenofovir.

Adherence is the main factor associated with the viral suppression and its maintenance over time; conversely, non-adherence is a risk factor for the emergence of resistant strains [17]. The 15- to 24-year age group was 80% low-adherent. The adherence to a long-term medication is usually a challenge in young subjects. Generally speaking and in relation to the HBV infection, there is no need to rush to initiate antiviral treatment for young people; rather, the emphasis should be put on the clinical follow-up.

The rates of biochemical and virological responses decreased with decreasing adherence [15] [16] [17]. Adherence to treatment would therefore be a predictor of the viral suppression and normalization of transaminases. Consequently, the biochemical and virological responses were better in the context of high adherence.

In our study, 47.6% of the participants under lamivudine molecule developed a resistant strain of the virus by five years of treatment. In the literature, the frequency of the resistance to lamivudine is 70% by five years [12]. In our setting, only a small number of patients could afford to get a laboratory viral load assessment and the proportion of resistance to lamivudine may have been underestimated. No case of resistance to tenofovir has been detected in our study and this finding is confirmed by other studies that did find no or very rare cases of resistance to tenofovir [7] [13].

4.3. Study Limits

A significant number of patients participating in the study, lacked laboratory and ultrasound data. Financial reason seemed to be behind this, as the study was designed to analyze 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 gives us a fairly objective picture of the evolution of a regularly monitored VHB patient.

5. Conclusion

The viral hepatitis B is a silent infection with a small proportion of patients experiencing viral replication activity. The management includes often a long follow up period without any medication. When antiviral is indicated, the adherence to the treatment is crucial to a long-term control of the virus. In our setting, the virological and biochemical responses were in general better or similar to other cohorts'. However, the low purchase power of the patients may jeopardize their therapeutic future and there is a need to support this group of patients with free-of-charge medicines as it is provided for the HIV-infected people.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Schweitzer, A., *et al.* (2015) Estimations of Worldwide Prevalence of Chronic Hepatitis B Virus Infection: A Systematic Review of Data Published between 1965 and 2013. *The Lancet*, **386**, 1546-1555. https://doi.org/10.1016/S0140-6736(15)61412-X

[2] World Health Organization (2017) Global Hepatitis Report. Global Hepatitis Programme, World Health Organization, Geneva, 83.

[3] World Health Organization (2017) Hepatitis B Vaccines: WHO Position Paper—July 2017. *Weekly Epidemiological Record*, **27**, 369-392.

[4] Meda, N., *et al.* (2018) Hepatitis B and C Virus Seroprevalence, Burkina Faso: A Cross-Sectional Study. *Bulletin of the World Health Organization*, **96**, 750-759. https://doi.org/10.2471/BLT.18.208603

[5] Lee, H.A., *et al.* (2020) Extremely Low Risk of Hepatocellular Carcinoma Development in Patients with Chronic Hepatitis B in Immune-Tolerant Phase. *Alimentary Pharmacology & Therapeutics*, **52**, 196-204. https://doi.org/10.1111/apt.15741

[6] Yang, Y.J., *et al.* (2014) Assessment of Current Criteria for Primary Nonresponse in Chronic Hepatitis B Patients Receiving Entecavir Therapy. *Hepatology*, **59**, 1303-1310. https://doi.org/10.1002/hep.26910

[7] Zoulim, F. and Locarnini, S. (2009) Hepatitis B Virus Resistance to Nucleos(t)ide Analogues. *Gastroenterology*, **137**, 1593-1608 e1-2. https://doi.org/10.1053/j.gastro.2009.08.063

[8] Bermingham, S.L., *et al.* (2015) Cost-Effectiveness Analysis of Alternative Antiviral Strategies for the Treatment of HBeAg-Positive and HBeAg-Negative Chronic Hepatitis B in the United Kingdom. *Value Health*, **18**, 800-809. https://doi.org/10.1016/j.jval.2015.05.007

[9] Nita, M.E., *et al.* (2009) Patterns of Viral Load in Chronic Hepatitis B Patients in Brazil and Their Association with ALT Levels and HBeAg Status. *Annals of Hepatology*, **8**,339-345. https://doi.org/10.1016/S1665-2681(19)31747-8

[10] Khelifa, F. and Thibault V. (2009) Characteristics of Hepatitis B Viral Strains in Chronic Carrier Patients from North-East Algeria. *Pathologie Biologie* (*Paris*), **57**, 107-113. https://doi.org/10.1016/j.patbio.2008.07.031

[11] Kondili, L.A., *et al.* (2005) Clinical and Molecular Characterization of Chronic Hepatitis B in Albania: A Country That Is Still Highly Endemic for HBV Infection. *Journal of Medical Virology*, **75**, 20-26. https://doi.org/10.1002/jmv.20231

[12] European Association for the Study of the Liver (2009) *EASL Clinical Practice Guidelines: Management of Chronic Hepatitis B. Journal of Hepatology*, **50**, 227-242. https://doi.org/10.1016/j.jhep.2008.10.001

[13] Yao, G.B., *et al.* (2009) A 7-Year Study of Lamivudine Therapy for Hepatitis B Virus E Antigen-Positive Chronic Hepatitis B Patients in China. *Journal of Digestive Diseases*, **10**, 131-137. https://doi.org/10.1111/j.1751-2980.2009.00375.x

[14] ANRS and AFEF (2014) Prise en charge des personnes infectées par les virus de l'hépatite B ou de l'hépatite C. EDK/Groupe EDP Sciences,. Paris, 527 p.

[15] Abu-Freha, N., *et al.* (2020) Adherence to Anti-Viral Treatment for Chronic Hepatitis B. *Journal of Clinical Medicine*, **9**, 1922. https://doi.org/10.3390/jcm9061922

[16] Xu, K., *et al.* (2018) Adherence and Perceived Barriers to Oral Antiviral Therapy for Chronic Hepatitis B. *Global Health Action*, **11**, 1433987. https://doi.org/10.1080/16549716.2018.1433987

[17] Lieveld, F., *et al.* (2013) Patient Adherence to Antiviral Treatment for Chronic Hepatitis B and C: A Systematic Review. *Annals of Hepatology*, **12**, 380-391. https://doi.org/10.1016/S1665-2681(19)31000-2

List of Abbreviations

Abbreviation	Definition
ALT	Alanine amino Transferase
CHU-YO	Centre Hospitalo-Universitaire Yalgado Ouédraogo (University Teaching Hospital Yalgado Ouédraogo)
HBeAg	Hepatits B e-Antigen
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HIV	Human Immuno-deficiency Virus
IU	International Unit
VHB	Viral Hepatitis B
WHO	World Health Organization