Scientific Research Publishing

Open Journal of Gastroenterology, 2023, 13, 299-312
https://www.scirp.org/journal/ojgas
ISSN Online: 2163-9469
ISSN Print: 2163-9450

Antiviral Therapy Eligibility and Low Treatment Coverage among Hepatitis B Virus Infected Patients in Tanzania

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How to cite this paper: Kilonzo, S.B., Nkandala, I., Jaka, H. and Marmo, L. (2023) Antiviral Therapy Eligibility and Low Treatment Coverage among Hepatitis B Virus Infected Patients in Tanzania. *Open Journal of Gastroenterology*, **13**, 299-312.
https://doi.org/10.4236/ojgas.2023.1310027

Received: August 23, 2023
Accepted: October 23, 2023
Published: October 26, 2023

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Abstract

Introduction: Limited access to treatment is a crucial factor contributing to the suboptimal control of hepatitis B virus (HBV) infection, especially in sub-Saharan African countries such as Tanzania. The eligibility for antiviral therapy is typically determined based on the extent of HBV replication and liver damage. However, there is insufficient data available regarding the actual treatment needs and the overall characteristics of HBV-infected individuals in Tanzania. Therefore, the aim of this study is to fill this knowledge gap and provide valuable insights to aid in the planning of treatment programs. **Materials and Methods:** We conducted a cross-sectional study at Bugando Medical Centre in northwest Tanzania, examining the data of 340 patients who were diagnosed with chronic HBV infection and attending the hepatitis clinic. Data on sociodemographic, clinical, and investigation details were collected through electronic files and subsequently analyzed. The eligibility for HBV antiviral treatment was assessed using the criteria established by the World Health Organization (WHO). **Results:** Out of the 340 patients included in the study, the majorities were males 252 (74.1%) and had a median age of 36 years. Most patients came from outside of Mwanza city. Twenty-percent had significantly elevated alanine transaminase, and over one-third had high DNA levels (>2000 IU/L). The prevalences of liver cirrhosis and significant liver fibrosis were 15% and 15.3%, respectively. None of the patients were on antiviral therapy for hepatitis B. A total of 64 (18.8%) patients met the criteria for treatment eligibility. Male sex, older age, residing outside Mwanza city, and anemia (all with $p < 0.05$) were factors associated with treatment eligibility in the multivariate analysis. **Conclusion and Recommendations:** The significant number of HBV-infected patients is suitable for antiviral therapy but none of them have initiated the treatment. The significance of these findings is to emphasize the need for enhancing hepatitis B services in Tanzania.

Keywords

Hepatitis B, Treatment, Eligibility, Coverage, Tanzania

1. Introduction

Hepatitis B virus (HBV) infection is highly prevalent in sub-Saharan Africa (sSA) and is associated with a significant burden of chronic liver disease. To reach a global target of its elimination as a public health threat by 2030 [1], greater access to treatment is desirable.

According to several international guidelines such as those provided by the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), the Asian Pacific Association for the Study of the Liver (APASL), and the World Health Organization (WHO), antiviral therapy should be given to eligible patients with HBV infection in order to reduce the progression of liver disease, decrease mortality rates, and improve the overall quality of life. The eligibility to antiviral treatment is determined by the level of HBV replication measured by HBV DNA, and the degree of liver injury measured by ALT, noninvasive methods or liver biopsy [2]. Therefore, only a portion of HBV-infected patients are usually eligible for antiviral therapy.

The WHO antiviral treatment criteria provide simpler diagnostic tests that are mostly feasible in low-income countries which are its main focus. The criteria recommend initiating treatment for individuals 1) with clinically diagnosed decompensated liver cirrhosis, 2) with an APRI score above 2, and 3) who are 30 years or older with persistently elevated ALT levels (>UNL) and a viral load exceeding 20,000 IU/l [3]. Contrarily, the AASLD, EASL, and APASL guidelines are more meticulous and hence are considered superior to the WHO criteria in identifying patients in need of treatment. For instance, in one African study, WHO criteria failed to identify half of the patients who needed treatment that were determined by the EASL criteria [4]. Recent studies suggest on the shifting from the WHO criteria to other simplified scoring systems such as The Treatment Eligibility in Africa for the Hepatitis B Virus (TREAT-B) and the Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B (REACH-B) which have better discrimination capabilities in African and Asian populations respectively, compared to the WHO criteria [5] [6]. However, clinical utilization of these scores is impending subject to further validation. Therefore, despite this drawback, the WHO criterion is still widely used by several low-income countries to identify patients who require antiviral treatment, including Tanzania [7].

Nevertheless, the proportion of patients eligible for treatment in the African region remains largely unknown. A recent meta-analysis that included data from all WHO regions reported that 8% of patients with HBV infection were eligible for treatment according to AASLD criteria (2018), 18% according to EASL criteria (2017), and 10% according to the WHO criteria (2015). However, in this

analysis, only two studies were from Africa (West Africa) [8]. Thus, obtaining this data would allow for a better understanding of the actual treatment needs and support the planning of treatment programs in the country, where HBV therapy is largely inaccessible [9]. Therefore, this study was designed to address this knowledge gap by first describing the population of patients attending the hepatitis clinic and to identify the ratio of those who need antiviral treatment.

2. Materials and Methods

2.1. Study Design, Population and Setting

This cross-sectional study was conducted on 340 patients from July to October 2021 at the hepatology clinic of Bugando Medical Centre (BMC) in northwest Tanzania. BMC is a tertiary and teaching hospital in the lake zone of Tanzania, serving approximately 13 million people. The hospital provides inpatient and outpatient services with an approximate bed capacity of 1000. The participants in this study were patients diagnosed with chronic hepatitis B infection with complete investigations who were attending the clinic.

2.2. Sample Size Determination

The sample size was calculated using the Taro Yamane formula for a given population [10];

$$n = \frac{N}{1 + N\left(e^2\right)}$$

where n = estimated sample size, N = Population under study, e = margin error (0.05).

There are 861 patients with chronic hepatitis B (CHB) infection attending hepatology clinic at BMC by the time of data collection. The minimum sample size was 273, and we recruited 340 participants with complete clinical data.

2.3. Data Collection

The patient's details were obtained from electronic files and recorded on a structured data collection form (**Appendix**). The information collected included sociodemographic data, clinical data, and investigations. The hepatitis B test was conducted using the rapid HBsAg (Meriscreen HBsAg, Gujarat, India). Routine analysis of alanine aminotransferase (ALT), aspartate aminotransferases (AST), total bilirubin, and full blood picture was performed in the hospital laboratory using an automatic biochemical analyzer (COBAS Integra 400 Plus, Roche, Basel, Switzerland) according to the manufacturer's instructions. Anemia was defined as hemoglobin less than 12 g/dl in females and 13 g/dl in males. The HBV deoxyribonucleic acid (DNA) titer was measured using the Cobas Taq Man HBV Test assay (Roche Diagnostics, Shanghai, China) with a linear detection range of 20 to 1.7×10^8 IU/ml.

Our definition of terms was solely derived from the WHO guidelines [3].

Treatment eligibility was defined as follows: 1) All patients with CHB with compensated or decompensated liver cirrhosis based on the clinical evidence or the Aspartate aminotransferase Platelet Ratio Index (APRI) score > 2, regardless of ALT or HBV DNA levels 2) Adults aged more than 30 years with CHB who do not have clinical evidence of cirrhosis or based on APRI score ≤ 2, and have abnormal ALT levels and high-level HBV replication (HBV DNA > 20,000 U/mL). Clinical features of cirrhosis were defined as the presence of portal hypertension (ascites, variceal hemorrhage, and hepatic encephalopathy), coagulopathy, liver insufficiency (jaundice), hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema, or edema. The APRI score was determined using the formula:

$$\text{APRI} = \frac{\left(\text{AST}\middle|\text{UNL}\right)\times 100}{\text{Patelet count}\left(10^9/\text{L}\right)}$$

Significant liver fibrosis was diagnosed when the Fibrosis-4 (FIB-4) score was greater than 3.25. FIB-4 score was determined using the formula:

$$\text{FIB-4} = \frac{\text{Age}\left(\text{years}\right)\times \text{AST}\left(\text{IU}\middle|\text{L}\right)}{\left[\text{Platelet count}\left(10^9\middle|\text{L}\right)\times \text{ALT}\left(\text{IU}\middle|\text{L}\right)\right]1/2}$$

2.4. Statistical Analysis

The analysis was conducted using Microsoft Excel and Stata/IC version 13 (College Station, Texas). Categorical variables were described as proportions and compared using the chi-square test, while continuous variables were summarized by medians with interquartile ranges or means with standard deviation depending on the distribution pattern. All variables that showed an association ($p < 0.05$) in the univariable analysis were subjected to multivariable logistic regression analysis to identify the factors independently associated with treatment eligibility.

3. Results

During the study period, all 861 patients registered in the hepatitis clinic were examined for eligibility. Of these, 521 (60.5%) participants were excluded due to incomplete investigations, leaving 340 patients for analysis.

3.1. Baseline Characteristics of the Study Population

Out of the 340 patients recruited for the study, the majority were males (252, 74.1%). The median age was 36 (30 - 44) years. Many (75.3%) of the study participants came from outside the Mwanza city. Twenty percent of the patients had significantly elevated ALT level. More than 90% of the participants had detectable DNA levels, and more than one-third had high DNA levels (>2000 IU/ml). The prevalence of liver cirrhosis was 51 (15%) and that of significant liver fibrosis was 18 (5.3%). None of the patients were on antiviral therapy for hepatitis B treatment (Table 1).

Table 1. Baseline characteristics of the study population (n = 340).

Variable	Frequency (number or CI)	Percentage (%) or IQR
Median age	36	30 - 44
Age (years)		
18 - 30	72	21.2
30 - 40	146	42.9
41 - 50	78	22.9
51 - 60	35	10.3
>60	9	2.7
Gender		
Male	252	74.1
Female	88	25.9
Residence		
Mwanza city	84	24.7
Mwanza region	38	11.2
Outside Mwanza	218	64.1
Comorbidities		
Diabetes	8	2.4
Hypertension	3	0.9
Anti-HCV positivity	4	1.2
Alanine transaminase > 2 × UNL (U/L)	71	20.9
Aspartate aminotransferase > 2 × UNL (U/L)	85	25.0
Total bilirubin > 5 × UNL (μmol/L)	156	45.9
Albumin (g/L)	43.1	19.0 - 45.5
Alfa fetoprotein (ng/mL)	3.5	0.8 - 6.3
Platelets (10^9/L)	206	166 - 205
Total white blood count (10^9/L)	4.8	4.0 - 6.0
Anemia	56	16.5
HBV viral load (IU/mL)		
Undetectable (<20)	34	10
20 - 2000	197	57.9
2001 - 20,000	67	19.7
>20,000	42	12.4
Liver cirrhosis	51	15.0
APRI score > 2	19	5.6
Clinical diagnosis	42	12.4
Both criteria	10	2.9
Significant fibrosis	18	5.3

CI: Confidence interval; IQR: Interquartile range; HCV: Hepatitis C virus; UNL: Upper normal limit; HBV: Hepatitis B virus; DNA: Deoxyribonucleic acid; UNL: Upper normal limit; APRI: Aspartate aminotransferase platelet ratio index.

3.2. Treatment Eligibility

A total of 64 (18.8%) patients fulfilled at least one WHO criterion for hepatitis B therapy. Of these, majority 42 (65.6%) had clinical evidence of decompensated liver cirrhosis, 19 (29.7%) had APRI score more than 2, and 17 (26.6%) had elevated ALT, HBV DNA > 20,000, and were aged more than 30 years.

A total of fourteen (21.9%) patients out of 64 fulfilled at least two criteria together. Among them, 10 patients (71.4%) fulfilled the criteria of decompensated cirrhosis and APRI > 2, while 4 (28.6%) fulfilled the criteria of decompensated cirrhosis and elevated ALT and HBV DNA. None of the patients fulfilled all three criteria for treatment eligibility (**Figure 1**). There was a high predominance of males compared to their female counterparts in all eligibility criteria; 84.2% vs. 15.8% for decompensated cirrhosis, 85.7% vs. 14.3% for APRI score > 2, and 88.2% vs. 11.8% for elevated ALT and HBV DNA (**Figure 2**). Moreover, the age group of 41 to 50 comprised majority (42.1%) of patients in decompensated cirrhosis criterion while in other two criteria, predominated age group was 30 to 40 years in 35.3% and 30.9% among those with elevated ALT with HBV DNA and those with APRI score > 2, respectively. Notably, the elderly patients (>60 years) were only observed in decompensated cirrhosis criterion (**Figure 3**).

3.3. Factors Associated with Treatment Eligibility

In multivariate analysis, HBV treatment eligibility was significantly associated with male sex ($p = 0.01$), older age ($p = 0.009$), residing outside the Mwanza city ($p = 0.008$), and anemia ($p < 0.001$) (**Table 2**).

4. Discussion

The purpose of this study was to analyze the population of registered patients in a hepatitis clinic at a tertiary-level hospital in Tanzania and determine the proportion of individuals who meet the WHO criteria for antiviral therapy for HBV.

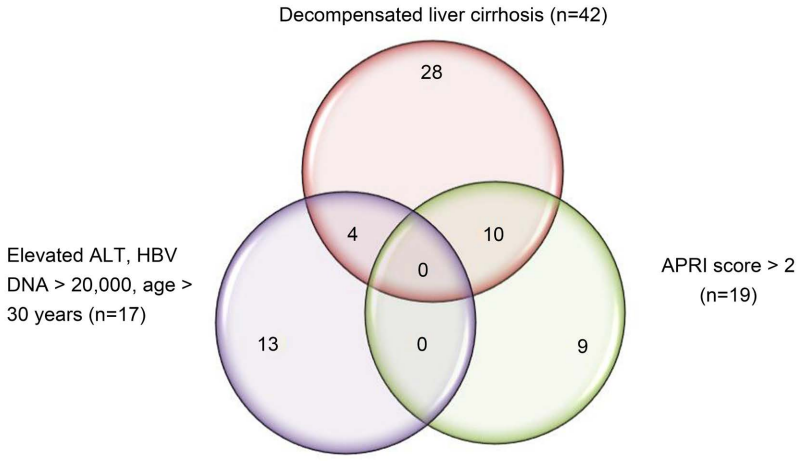

Figure 1. Distribution of patients meeting different criteria of WHO guidelines for hepatitis B virus antiviral therapy. ALT: Alanine transaminase; APRI: Aspartate aminotransferase to platelets ratio index; DNA: Deoxyribonucleic acid; HBV: Hepatitis B virus.

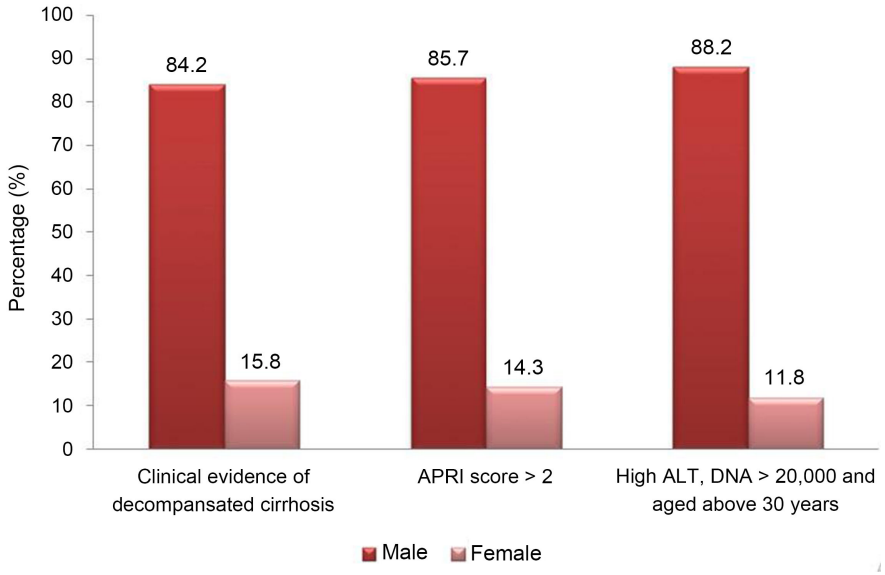

Figure 2. Distribution of eligible patients for hepatitis B virus treatment by gender. ALT: Alanine transaminase; APRI: Aspartate aminotransferase to platelets ratio index; DNA: Deoxyribonucleic acid; HBV: Hepatitis B virus.

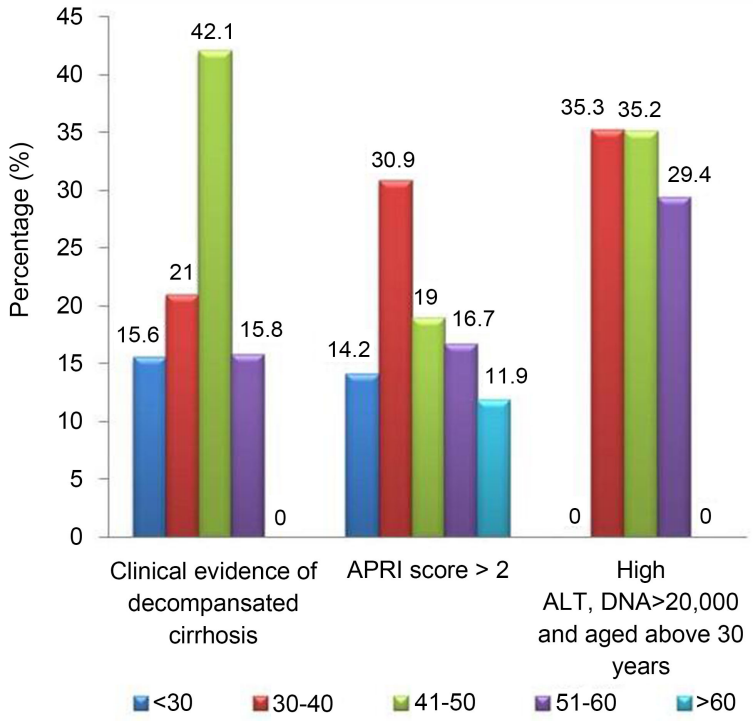

Figure 3. Distribution of eligible patients for hepatitis B virus treatment by age. ALT: Alanine transaminase; APRI: Aspartate aminotransferase to platelets ratio index; DNA: Deoxyribonucleic acid; HBV: Hepatitis B virus.

The majority of our sample comprised of younger males, specifically those aged between 30 and 40 years, who had detectable HBV DNA. About 20% of the participants required therapy, with a higher likelihood of being males, older and anemic.

Table 2. Multivariate analysis on the factors associated with HBV treatment eligibility.

	Eligible for treatment		Crude OR	*p* value	Adjusted OR	*p*-value
	Yes	No				
Male sex	55 (85.9)	197 (71.4)	2.4 (1.1 - 5.2)	0.02	3.0 (1.3 - 7.2)	0.01
Advanced age (>40 years)	44 (68.7)	124 (44.9)	2.7 (1.5 - 4.8)	0.001	2.3 (1.2 - 4.4)	0.009
Residing out of Mwanza city	54 (84.4)	204 (73.9)	1.9 (0.9 - 3.9)	0.08	3.2 (1.3 - 7.3)	0.008
Diabetes	1 (1.6)	7 (2.5)	0.6 (0.07 - 5.0)	0.65	[a]	
Hypertension	1 (1.6)	2 (0.7)	2.2 (0.2 - 7.3)	0.52	[a]	
HCV	1 (1.6)	3 (1.1)	1.5 (0.1 - 6.4)	0.73	[a]	
High WBC	15 (23.4)	68 (24.6)	0.93 (0.5 - 1.8)	0.84	[a]	
High alpha-fetoproteins	40 (62.5)	151 (54.7)	1.4 (0.8 - 2.4)	0.26	[a]	
Anemia	28 (43.7)	28 (10.1)	6.9 (3.7 - 12.9)	<0.001	8.4 (4.2 - 16.9)	<0.001

[a]: Not included in multivariate analysis. OR: odds ratio; HCV: hepatitis C; WBC: white blood count.

Our study found a higher rate of eligibility for antiviral therapy for HBV compared to previously reported rates in other African countries. Three different studies that were conducted in various settings, observed a prevalence of 10%. These studies included a multivariate analysis conducted among African outpatients [8], a cross-sectional study among high-risk populations such as female sex workers, prisoners, and men who have sex with men in three Western African countries [11], and a large survey of the general population in Zambia [12]. Conversely, studies conducted in Europe have found much higher rates of eligibility. In Austria, for example, nearly one-quarter of all evaluated patients with CHB were found to be eligible for antiviral therapy according to the WHO guidelines [13]. It appears that WHO criterion is less employed in high-income countries, leading to limited comparable studies. The discrepancies found in the proportion of patients needing therapy could potentially be attributed to different HBV genotypes. Genotype A, which is commonly found in Tanzania [14], is associated with more severe disease compared to genotype E, which is more prevalent in West African countries [15] where the prevalence of patients needing antiviral therapy is comparatively low. On the other hand, genotype D, which is more common in Austria [16], where the prevalence was much higher, is linked to higher rates of basal core promoter gene mutations and more progressive liver disease compared to genotype A [17]. This concept is supported by a nearly similar proportion of 15.3% reported in a large cohort in Ethiopia [4] where genotype A is predominantly present like in our setting [18].

Our study revealed a significant gender disparity in our HBV-infected population, with male patients having higher odds of requiring antiviral therapy compared to their female counterparts. These findings align with previous research findings from endemic areas to hepatitis B. Data from the African Multi-Country Research Collaborative Network showed that males make up more than 60% of patients registered in 13 cohorts of hepatitis clinics across 8 African

countries [19]. Furthermore, a community-based cross-sectional study in Zambia, reported that males had 2 - 5 times higher eligibility for antiviral treatment [12] compared to females. These findings support the well-established pattern of HBV exposure susceptibility, associated progression of liver disease and complications exhibiting strong gender predominance [20]. Based on these findings, we strongly recommend that males be prioritized in the future HBV elimination programs in Tanzania, including early screening efforts.

As previously indicated [21], HBV infection usually affects younger age groups in areas with high or intermediate-high endemicity, but a need for antiviral therapy arises later. Similarly, the median age of our population was 36 years, while the mean age of patients who required antiviral therapy was higher at 41 years. These findings support the notion that increasing age is often considered a risk factor for treatment eligibility due to the higher likelihood of liver disease progression in older individuals compared to younger ones. Several factors may contribute to this, including extended duration of HBV infection, weakened immune system associated with aging and the presence of comorbidities [22]. It is worth noting that a significant proportion of elderly patients requiring treatment in our study had comorbidities and more advanced liver disease, as determined by clinical criteria of decompensated liver disease.

Our data further support the presence of healthcare disparities, particularly in regards to hepatitis B services. The majority of patients registered at our hepatitis clinic were referred from healthcare facilities in remote areas outside of Mwanza city. These referred patients have a three-fold higher likelihood of requiring antiviral therapy compared to patients from the city. No other studies were found that describe the association between geographical location and eligibility for HBV therapy. Our findings suggest two important perspectives. Firstly, it is possible that the remote healthcare facilities lack the capacity to properly diagnose and manage HBV cases. This speculation aligns with a recent report from the Tanzanian Ministry of Health [9] that highlights a severe shortage of viral hepatitis centers and a lack of adequately trained healthcare professionals to manage chronic viral hepatitis in the country. It is estimated that only 10% of physicians possess the correct knowledge for managing viral hepatitis. Secondly, it can be speculated that HBV infection rates are higher in these remote areas, and diagnoses often occur late. However, further analysis is necessary to confirm this assumption. Collectively, these findings highlight the potential need to address regional disparities in hepatitis B care and treatment availability in the country.

In this study, we have revealed a significant association between anemia and eligibility for HBV antiviral therapy. Previous researches have already established a clear connection between HBV infection and anemia. Aplastic anemia, for instance, is a commonly observed extra-hepatic manifestation of HBV [23]. Moreover, anemia is frequently diagnosed in patients with HBV-associated cirrhosis and is considered a risk factor for decompensation in these individuals [24]. However, the direct relationship between anemia and eligibility for HBV

antiviral therapy has yet to be determined, and to the best of our knowledge, this association has not been described before. We propose that the correlation we have identified may be due to the fact that most of our eligible patients already had advanced liver disease, which often coincides with anemia. Nevertheless, it is crucial not to underestimate the potential direct association between anemia and eligibility for antiviral therapy, and further evaluation is warranted.

A notably finding from this study is the limited number of eligible patients receiving antiviral treatment for hepatitis B. The WHO, in its strategic plan for eliminating viral hepatitis by 2030, recommends expanding treatment to all eligible patients with the goal of achieving global coverage of 80% by 2030 [1]. Recent data indicates an increase in global coverage from 7.4% in 2015 to 22% in 2019 [25], although there are significant disparities between countries. The European countries and United States have reported coverage rates of over 50% among eligible patients [13] [26]. Similarly, few low-income countries like Uganda [27] and Ethiopia [28], which have implemented effective strategies to combat viral hepatitis, have reported good coverage rates of 51% and 77% respectively. However, there is currently no available data on this subject for many other low-income countries including Tanzania. Considering previous reports on the scarcity of viral hepatitis centers and the unaffordability of Tenofovir chemotherapy for most patients in Tanzania [9], we believe our findings may reflect the overall situation in the country. Therefore, these significant findings underscore the need for prompt implementation of the local National Strategic Plan for the Control of Viral Hepatitis which is available [9] to ensure the successful achievement of the global target for eliminating viral hepatitis.

We must acknowledge several limitations in our study. Firstly, we relied solely on baseline evaluations for HBV surface antigen and ALT levels, without considering their persistence over time. Secondly, there were missing and incomplete data regarding important study parameters such as alcohol misuse and Schistosomiasis, which are recognized as potential confounding factors. Previous findings from our research indicate that patients with HBV/Schistosomiasis coinfection are more prone to severe liver injury and a higher risk of decompasation, compared to those with HBV monoinfection [29]. Therefore, it is imperative to interpret our results cautiously, as treatment eligibility may have been overestimated in individuals with underlying Schistosomiasis infection. Thirdly, we encountered a lack of data on the status of HIV infection for all patients. The WHO recommends simultaneous therapy for both HIV and HBV to HIV/HBV coinfected patients. This could potentially lead to an underestimation of the proportion of individuals eligible for antiviral therapy, especially considering the higher incidence of HIV/HBV coinfection in our environment [30].

5. Conclusion

In conclusion, the present study revealed that a significant number of patients with HBV infection patients who visit the hepatitis clinic are suitable candidates

for antiviral therapy, yet none of them have initiated the treatment. As far as we know, this study is the first to describe the population infected with HBV and assess the treatment requirements in Tanzania. Overall, these findings highlight the necessity of scaling up hepatitis B services in the country. This should involve early diagnosis, timely assessment, and treatment, as well as the proper dissemination of these services.

Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Joint Research and Publication Committee of the Catholic University of Health and Allied Sciences and Bugando Medical Centre (CREC/2405/2022).

Availability of Materials

The data supporting this study's findings are available from the corresponding author upon reasonable request.

Acknowledgements

We would like to acknowledge all staff from the BMC main laboratory and Molecular technology laboratory for their.

Conflicts of Interest

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

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Appendix. Data Collection Sheet

A: Demographic information

1. Hospital registration number: |__|__|__|__|__|__|
2. Code: |__|__|__|
3. Gender Male |__| Female |__|
4. Residence: Mwanza city |__| Mwanza Region |__| Outside Mwanza region |__|
5. Comorbidities: Diabetes Mellitus |__| Hypertension |__| Hepatitis C |__|

B: Laboratory investigations

6. Alanine Transaminase level (U/L) |__|__|__|__|
7. Aspartate Aminotransferase level (U/L) |__|__|__|__|
8. Total Bilirubin level (µmol/L) |__|__|__|
9. Albumin level (g/L) |__|__|__|
10. Alpha-fetoprotein (ng/mL) |__|__|__|
11. Platelets (10^9/L) |__|__|__|
12. Total white blood count |__|__|__|
13. Hemoglobin (g/dl) |__|__|__|
14. INR |__|__|
15. Prothrombin time (sec) |__|__|
16. HBV viral load (IU/mL) |__|__|__|__|__ |__|__|__|__ |

C: Clinical features

17. Pruritis: Yes |__| No |__|
18. Jaundice: Yes |__| No |__|
19. Fatigue: Yes |__| No |__|
20. Palmar erythema: Yes |__| No |__|
21. Edema: Yes |__| No |__|
22. Encephalopathy: Yes |__| No |__|
23. Arthralgia: Yes |__| No |__|
24. Variceal bleeding: Yes |__| No: |__|

D: Ultrasound findings:

25. Ascites: Yes |__| No |__|
26. Hepatomegaly: Yes |__| No |__|
27. Splenomegaly: Yes |__| No |__|