RATE OF COMPLETE VIROLOGIC RESPONSE AT 12 MONTH AND ASSOCIATED FACTORS AMONG CHRONIC HEPATITIS B PATIENTS TREATED WITH TDF IN TASH FROM 2019-2023

A Thesis Proposal Submitted to the Department of Internal Medicine Addis Ababa University in Partial Fulfilment of the Requirements for the Specialization Degree in Internal Medicine

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DECLARATION

I, Dr TigistGeresu, do hereby declare that this research thesis is a result of the works of my own making, except where due is made in a review of previous literature in the content and by my knowledge, has never been submitted for any prior academic award odds ratio (OR) qualification in this Institution.

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The undersigned have examined the proposal entitled "The rate of CVR (complete virologic response; undetectable viral load) and associated factors among chronic hepatitis B patients following at GI clinic Tikur Anbessa Specialized Hospital: Across-sectional study (2019-2023)" presented by Dr.Tigist Geresu with registration number GSR/2099/13 a candidate for the internal medicine residency program and hereby certify that it is worthy of acceptance.

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Abbreviations and Acronyms

ADV–aAdefovirdipivoxil

ALT–Alanine Aminotransferase

AOR–Adjusted Odds Ratio

APRI–Aspartate Aminotransferase to platelet Ratio Index

AST–Aspartate Aminotransferase level

cccDNA–covalently closed circular Deoxyribonucleic Acid

CHB–Chronic hepatitis B

CI–Confidence Interval

CVR–Complete Virological Response

DNA–Deoxyribonucleic acid

ETV–Entecavir

GI–Gastroenterology

HBeAg–hepatitis B e antigen

HBsAg–Hepatitis B surface Antigen

HBV–Hepatitis B virus

HCC–Hepatocellular Carcinoma

HIV–Human Immunodeficiency Virus

HVL–High baseline Viral Ievels

IFN–standard interferon

LAM–Lamivudine

NA–Nucleoside Analogues

PegIFN–Pegylated Interferon alpha

SPSS–Statistical Package for the Social Sciences

SVR–Sustained Virologic Response

TAF–Tenofoviralafenamide

TASH–TikurAnbessa Specialized Hospital

TBV–Telbivudine

TDF–TenofovirDisoproxil Fumarate

ULN–Upper Limit of Normal

WHO–World Health Organization

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Abstract

Background: Chronic hepatitis B is a significant public health problem in sub-Saharan Africa, including Ethiopia. Despite the availability of antiviral therapies, achieving complete virological response could be challenged by several factors, including limited healthcare access, co-infections, and poor treatment adherence.

Objective: To assess the rate of complete virological response and the associated factors among chronic hepatitis B patients followed at the Gastrointestinal follow-up clinic of Tikur Anbesa Specialized Hospital.

Method: This retrospective cross-sectional study included patients receiving treatment for chronic hepatitis B at the Gastrointestinal follow-up clinic of Tikur Anbesa Specialized Hospital from 2019 to 2023. Data were collected through chart reviews by trained professionals, focusing on demographics, clinical characteristics, and risk factors like alcohol use, smoking, and treatment adherence. The data were entered into SPSS after verification for quality and completeness. Descriptive statistics summarized the data, while multivariable binary logistic regression identified predictors of complete virological response. Variables with a p-value < 0.05 in the regression analysis were considered statistically significant.

Results: The study included 182 chronic hepatitis B patients, with 66.5% male and 50% aged 18–39 years. The overall complete virological response rate was 72.5% (95%CI,65.4%,78.9%).From 2019 to 2023, the response rates fluctuated between 62.1% and 90.2%. Among HBeAg-positive patients, the complete virological response rate was 67.6%. Multivariable analysis identified high baseline viral load (>20,000 IU/mL; AOR = 5.7, 95% CI: 1.13–18.13, p = 0.001), alcohol use (AOR = 4.43; 95% CI: 1.46–13.46, p = 0.01), smoking (AOR = 7.31; 95% CI: 1.74–30.77, p = 0.01), herbal medication use (AOR = 5.49; 95% CI: 1.51–19.99, p = 0.01), and non-adherence (AOR = 16.9; 95% CI: 10.55–122.16, p = 0.001) as independent predictors of delayed response.

Conclusion and recommendation: While Ethiopia achieved notable complete virological response rates, delayed response persists due to high viral loads, substance use, and non-adherence. Strengthening early diagnosis, adherence support, and culturally tailored behavioral interventions are critical to meeting WHO's 2030 HBV elimination targets in resource-limited settings.

1. Introduction

1.1. Background

Hepatitis is inflammation of the liver. It has multiple causes, such as heavy alcohol use, autoimmune disorders, drugs, and toxins. However, the most common cause is viral hepatitis. Several hepatitis viruses are of public health importance. Among these hepatitis A, hepatitis B and hepatitis C viruses are the most common worldwide. In addition, hepatitis D and E viruses are worthy of mention, although they are encountered infrequently(1).

Based on the duration of infection, hepatitis can further be classified into acute and chronic hepatitis. Chronic hepatitis B (CHB) is a spectrum of disease characterized bythe persistence of detectable hepatitis B surface antigen (HBsAg) in blood serum for more than 6 months(2).

HBV infection remains a global health concern, with approximately one-third of the world's population showing serological evidence of past or present infection. Among these, more than 300 million individuals are chronic carriers of HBsAg. The clinical spectrum and natural progression of chronic HBV infection are variable, ranging from an inactive carrier state with minimal liver impact to progressive CHB. CHB may further advance to cirrhosis and, ultimately, to Hepatocellular Carcinoma (HCC), which is the 4thleading cause of cancer-related death in the world(3, 4).

Africa has the second-highest number of individuals with chronic HBV infection globally, with an estimated 6.1% of the adult population affected(6). Within the continent, Sub-Saharan countries make a large contribution with 60 million people live with HBV. Approximately 1 in 15 people is affected in this region (7). It is estimated that 95% of individuals in sub-Saharan Africa with chronic HBV infection are unaware of their condition, which prevents them from accessing clinical care, treatment, and interventions aimed at reducing further transmission. (8)

In Ethiopia, a 2004 study conducted in the Gondar region reported an HBsAg prevalence of 8.2% among blood donors. A study from Jimma, involving over 6,000 adult blood donors, found HBsAg prevalence rates of 2.1%(9). A recent study conducted in Dessie shows that among a total of 1080 adults included in the study, the prevalence of HBV infection was found to be 27.4% from two hospitals in the area. (10)

CHB may be classified as hepatitis B e antigen (HBeAg)-positive or HBeAg-negative CHB. The HBeAg-positive form is typically associated with higher rates of viral replication and increased infectivity. The HBeAg-negative form of the disease has been increasing in

prevalence over the globe as a result of the aging of the HBV-infected population and the predominance of specific HBV genotypes. (5,11,12)

Chronic hepatitis B (CHB) remains a global public burden associated with cirrhosis and HCC. The level of circulating HBV DNA is strongly correlated with progression to cirrhosis and HCC in CHB infection. Therefore, early eradication of HBV, suppressing viral replication through effective oral nucleos(t)ide analogs (NAs) is a key strategy against the progression of CHB infection.(46, 47)

Morbidity and mortality in CHB patients are directly related to the continuity of viral infection and further evolution to cirrhosis and HCC. Studies show that untreated patients with CHB have an 8% to 20% five-year cumulative risk of developing cirrhosis. Furthermore, from those who have compensated cirrhosis the five-year cumulative risk for untreated patients to progress to hepatic decompensation is approximately 20%.(3–5,13–15) In addition, untreated patients with decompensated cirrhosis have only a 14% to 35% probability of five-year survival.(3–5,13,14)

In patients with HBeAg-positive chronic hepatitis B, either spontaneous or treatment-induced clearance of HBeAg, followed by seroconversion to anti-HBe, is often associated with a prolonged period of low-level viral replication, commonly referred to as a sustained virologic response (SVR). It was also implicated that in patients treated with nucleos(t)ide analogs, low baseline HBV DNA but not viral genotype is positively associated with virologic response. During treatment, the best predictor of response is HBV DNA kinetics. Early viral suppression is associated with favorable virologic response and reduced risk for subsequent resistance mutations. (16)

Meanwhile, for patients who are HBeAg-negative, the primary goal of antiviral treatment is to achieve both a virologic response, undetectable odds ratio (OR) suppressed HBV DNA, and a biochemical response, normalization of aminotransferase levels(16).

Studies conducted in high-income countries indicate that antiviral treatment for CHB lowers the risk of disease progression. Long-term antiviral therapy has been shown to halt and even reverse liver fibrosis, as well as prevent the development of HCC. (17,18).

1.2. Significance of the study

The variability in the course of chronic HBV infection presents significant challenges for clinical management, as it necessitates a tailored approach to patient care. Research shows that disease progression and efficacy of antiviral therapy are influenced by factors such as viral load, co-infections, host genetic factors, and environmental or lifestyle influences like alcohol misuse and obesity(3–5,41–44).Through this study, we will explore these factors, especially focusing on viral load and how it affects virological response.

Virological response rate as it is mentioned in the literature has important prognostic factors for patients with CHB. This study will determine the rate of virologic response and associated factors in patients treated in one of the biggest referral hospitals in the country.

We believe that this study will add value in improving patient care and creating a tailored approach to treatment in sub-Saharan Africa.

2. Literature review

The persistence of covalently closed circular DNA (cDNA) in hepatocytes is a key factor in chronic hepatitis B (CHB) infection (4). HBsAg acts as an indicator of the transcriptional activity of cDNA (19,20).

The World Health Organization (WHO) recommends initiating antiviral treatment in patients with chronic hepatitis B (CHB) based on several clinical criteria. Treatment should be started in individuals with evidence of significant liver fibrosis, indicated by an APRI score greater than 0.5 or a transient elastography (FibroScan) value exceeding 7 kPa. It is also recommended for those with established cirrhosis, regardless of ALT levels or HBV DNA concentration. Antiviral therapy is indicated in patients with HBV DNA levels above 2000 IU/mL in combination with an ALT level above the upper limit of normal (30 U/L for men and boys, and 19 U/L for women and girls). In addition, the presence of coinfections—such as HIV, hepatitis D, or hepatitis C—warrants treatment initiation. Other factors supporting the need for therapy include a family history of hepatocellular carcinoma or cirrhosis, the presence of immunosuppression, comorbidities like diabetes or metabolic liver disease, and extrahepatic manifestations such as glomerulonephritis or vasculitis, regardless of fibrosis stage or viral load(21)

The same WHO guideline shows that the effectiveness of antiviral treatment for CHB across different baseline HBV DNA strata is different in preventing serious clinical outcomes such as HCC, cirrhosis, and liver-related death. (21)

For example patients with lower HBV DNA (<2000 IU/mL) treatment was protective of adverse clinical outcomes with a relative risk of 0.72 (95% CI: 0.43–1.20).; it is required to treat 210 patients to prevent one case of HCC, 119 to prevent cirrhosis, and 1190 to prevent liver-related death. In individuals with intermediate HBV DNA strata (2000–20,000 IU/mL) treatment was associated with a reduced risk of adverse liver outcomes with a relative risk of hepatocellular carcinoma(HCC). This translates to a number needed to treat 59 to prevent one case of HCC, 21 to prevent cirrhosis, and182 to prevent one liver-related death. In comparison, patients with higher HBV DNA (20,000–200,000 IU/mL) experienced greater benefit from treatment, to prevent HCC. In this group, the numbers needed to treat were 14 for HCC prevention, 7 for cirrhosis, and 12 for liver-related death, indicating more pronounced clinical efficacy at higher viral load.

In summary, the data suggest that as HBV DNA levels increase, the effectiveness of treatment in reducing the risk of severe outcomes also improves, emphasizing targeted antiviral therapy in managing chronic hepatitis B to enhance long-term patient outcomes.

In a large-scale, long-term follow-up study involving a population-based cohort of Taiwanese adults with chronic HBV infection (the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer HBV [REVEALHBV] study), elevated serum HBV DNA levels were identified as the most significant single risk factor for the progression to cirrhosis. (22) While a study of 2,682 decompensated CHB patients in Korea estimated that the 5-year mortality was 32.6% and the cumulative 5-year incidence of HCC was 24.1%. (23)adding to the need for treatment to prevent the severe outcomes of CHB.

Furthermore, because multiple treatment options have limited effectiveness in achieving lasting outcomes and antiviral resistance may develop during long-term therapy, it is crucial to monitor for SVR both during and after treatment. (24)

A study in Ethiopia conducted in 2015 among 291 patients who started treatment estimated 5-year HCC-free survival rate to be 99.0% in patients without cirrhosis at baseline. In comparison, the rate was 88.8% in those with compensated cirrhosis, and dropped significantly to 54.2% in patients with decompensated cirrhosis. (25)

In both the above studies (done in Ethiopia and Korea), the authors found that both mortality and HCC incidence were significantly reduced after the initial 1–2 years of antiviral therapy. In addition, the annual HCC incidence appeared to be quite similar (around 2%) in patients with compensated and decompensated cirrhosis after 2 years of therapy. (23,25)

There is limited information on the factors that predict response to treatment for chronic hepatitis B. This is partly due to the variety of treatment options available. Before the last decade, the only approved medications in the European Union and other regions were standard interferon (IFN) and lamivudine (LAM).(16)

The ideal treatment goal is to achieve a "functional cure," characterized by the clearance of HBsAg, sustained virological response, loss of HBeAg, normalization of alanine aminotransferase (ALT) levels, and improvement in liver tissue damage. (3,20,26)

Currently, drug management for HBV virus infection falls into two main classifications: nucleoside analogs (NAs) and pegylated interferon alpha (PegIFN). (3,27) The NAs that have

been approved in Europe for HBV treatment include LAM, adefovirdipivoxil (ADV), entecavir (ETV), telbivudine (TBV), tenofovirdisoproxil fumarate (TDF) and tenofoviralafenamide (TAF). (28) These are further categorized as those associated with low barriers against HBV resistance (LAM, ADV, TBV) hence leading to resistance to treatment, and those with high barriers to HBV resistance (ETV, TDF, TAF). Current WHO guidelines do not recommend the use of the lower barrier-to-resistance drugs and strongly recommend the use of those with high barriers to HBV-resistance drugs (namely ETV and TDF) for the adult treatment of CHB. (21)

The goal of this approach is to achieve long-term immunological control through a finite course of treatment. This strategy can significantly reduce HBsAg levels, moving closer to the ideal outcome of functional cure in patients with chronic hepatitis B (CHB). However, responses to these agents vary widely among patients, making careful patient selection essential. Additionally, their use is often associated with notable safety concerns(28,29)

Tenofovirdisoproxil fumarate (TDF) an oral prodrug of tenofovir and an acyclic nucleoside phosphonate analog of adenosine 5'-monophosphate, has an excellent safety profile and high potency in adults who are HBV infected(30,31)

In a Korean study that defined a CVR as a decrease in serum HBV DNA to an undetectable level ($\leq$20 IU/mL by real-time PCR assay) results show that treatment with TDF resulted in CVR at week 24 of treatment in 47.1% of patients and by week 48 in 71.5%of the patients(32)

Analysis of the same study showed that baseline serum HBV DNA levels of the total patients (HR, 0.830; 95% CI 0.888 to 0.911) and HBeAg negativity (HR, 1.685; 95% CI 1.096 to 2.590) were significantly associated with achieving CVR. Meanwhile, age, gender, baseline ALT, and liver cirrhosis did not show any association with a CVR. (32)

Earlier clinical trials also show that lower baseline HBV DNA levels were predictive of HBeAg loss or seroconversion and viral suppression in patients receiving antiviral therapy. (33)(34)

Another Korean study shows that patients with undetectable serum HBV DNA at 24 weeks (early viral suppression) had significantly higher virological response than those with HBV DNA > 2000 IU/ml, as was shown in LAM resistance patients taking Adefovirdipivoxil (ADV). (35)

Similar studies have shown that HBV viral kinetics has persistently been shown to predict the sustained virologic response in patients taking earlier less potent antivirals used in the early days of CHB treatment. Even though there are less frequent data on highly potent nucleotide analogs like TDF. (36–38)

A review of the efficacy of hepatitis B treatment, based on results from clinical trials (phase III), states that 21%–76% of HBeAg-positive CHB patients show an undetectable level of HBV DNA, and 41%–77% of them had a normalized level of ALT after 1 year of treatment with nucleotide analogs. Even more the same trials for HBeAg-Negative CHB patients taking TDF show that 93% of the subjects had undetectable levels of HBV DNA within 1year of therapy. (39)

A study that compares the efficacy of TDF with ADV, concluded that TDF monotherapy is effective in patients with high baseline viral levels (HVL), defined in the study as HBV DNA levels $\geq 10^9$ copies/ml, with 98.3% of HVL and 99.2% of non-HVL patients achieving virologic response (VR), defined by HBV DNA<400 copies/ml, by week 240 of treatment. (40)

In a five-year cohort study done at St. Paul's Hospital Millennium Medical College, a referral hospital in Addis Ababa, Ethiopia, results show that out of the 108 patients treated with TDF that had HBV viral load results available at 4 years of treatment, 94 % had suppressed viremia whereas 4% had treatment failure (viral load > 1000 IU/mL). (25)

There is limited data in Sub-Saharan Africa and Ethiopia about the rate of CVR as it significantly affects patient outcomes. Nevertheless, 5-year studies of treatment and VR show similar results as high and medium countries.

2.1 Conceptual framework

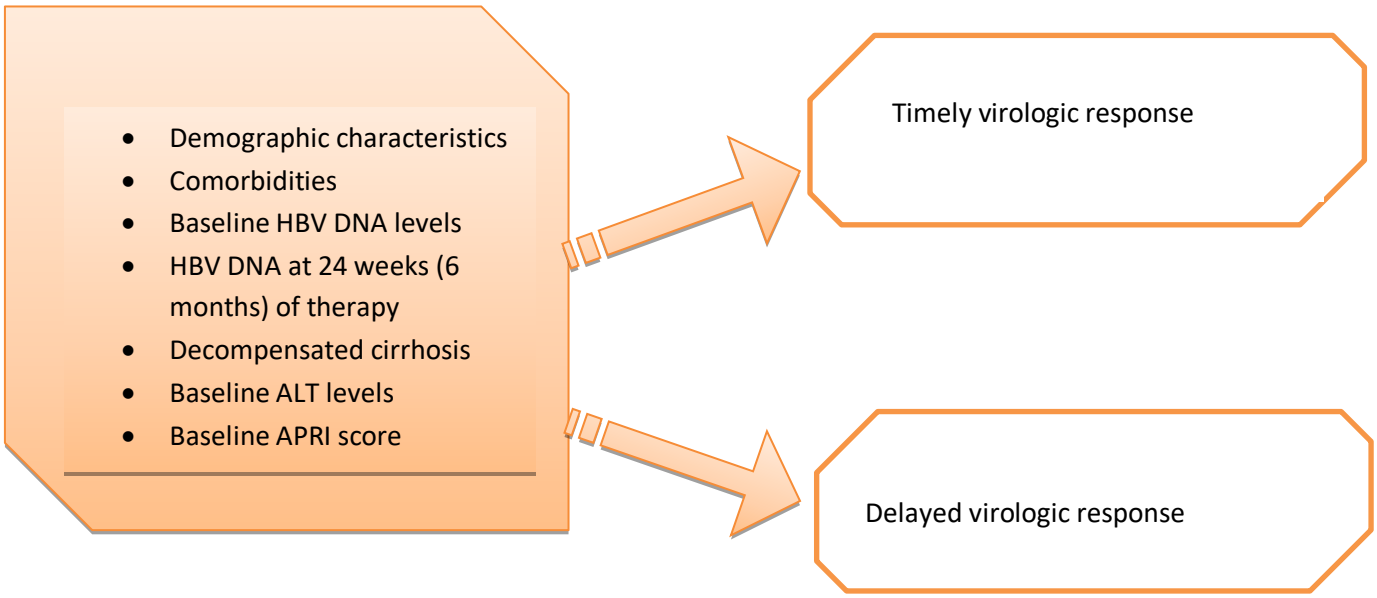

Figure 1; Conceptual framework on rate of (complete virology response; undetectable viral load) and associated factors among chronic hepatitis B patients, how independent factors affect the dependent factors

2.1. Objective

2.1.1. General objectives

To assess the rate of CVR at 12 months and its associated factors among chronic hepatitis B patients followed at the GI clinic at Tikur-Anbessa Specialized Hospital (TASH)-Addis Ababa, Ethiopia, 2019-2023.

2.1.2. Specific objective

To assess the rate of CVR at 12 months among chronic hepatitis B patients followed at GI clinic TASH; Addis Ababa, Ethiopia, 2019-2023.

To analyse factors associated with timely and delayed VR among chronic hepatitis B patients followed at TASH's GI clinic.

3. Methodology

3.1. Study design, study place, and study period

This study used a retrospective cross-sectional study design. The study was done at (TASH) Gastroenterology follow-up clinic from the year 2019 to 2023GC.

3.2. Source population

The source population is all adult patients who had to follow up for chronic hepatitis B in the TASH GI clinic during the study period.

3.3. Study population

The study population is all CHB patients who have viral load determination at least once after 6 months of TDF treatment.

3.4. Sample size

- A single population proportion formula

  S = (Z) ² p (1-p) / M2, will be used to estimate the sample size

- Where:

  S–sample size

  Z- Z score Which is 1.96 using a CI of 95%

  P-estimated proportion of success (assumed to be 85% at 1year=0.85)

  M- margin of error which is 0.05

  S = (1.96)²(0.85) (1-0.85)/ (0.05)2 = 195

Sample Size Adjustment for Anticipated Incomplete Data (10%)

$$N = \frac{n}{1-p} = \frac{195}{1-0.1} = 216$$

3.5. Inclusion and exclusion criteria

Inclusion criteria

- age 18 years and above;
- all adult patients diagnosed with CHB on treatment (for at least 6 months);
- patients who have viral load determined at least once after 6 months of TDF treatment.

Exclusion criteria

- age <18 (children and adolescents);

- pregnancy;
- those who have co-infection with hepatitis C virus (HCV), hepatitis D infection (HDV), human immunodeficiency virus (HIV)
- those patients with no viral load determinations

3.6. Study variables

Dependent variables

- **Viral response**

Independent variables

- demographic data;
- Comorbidities;
- other risk factors (alcohol, drugs, smoking);
- baseline HBV DNA level;
- HBV DNA at 24 weeks (6 months) of therapy;
- presence of decompensated cirrhosis at the initiation of therapy;
- baseline ALT levels;
- baseline APRI score
- previous NA treatment (NA-experienced patient)

3.7. Data collection technique

The study included all patients diagnosed with chronic hepatitis B (CHB) who were treated with tenofovir disoproxil fumarate (TDF) and had a viral load determination performed at least 6 months after initiating treatment. This cohort was identified through electronic medical records from the gastrointestinal (GI) clinic at TASH and also some missing data's were collected during patient visits to GI clinic and using direct phone calls to the patients. Both primary and Secondary data were extracted and recorded using the Kobo Toolbox, an efficient data collection tool that enables systematic abstraction of relevant patient information, including demographics, clinical parameters, and biological outcomes. The viral load at 12 months on -treatment was the primary outcome variable used for assessing the effectiveness of antiviral therapy.

3.8. Data quality control

To ensure the integrity and accuracy of the data, several quality control measures were implemented throughout the data collection process. First, data cleaning techniques were

applied to identify discrepancies, inconsistencies missing information within the data set, which were then addressed to maintain data reliability.

Additionally, the data collectors underwent comprehensive training sessions on proper medical record abstraction procedures to ensure consistency in data entry and minimize human error. Continuous supervision and oversight by clinical researchers were also established, ensuring adherence to protocol and timely resolution of any data-related issues.

3.9. Data processing

After data collection, the data was manually cleaned and coded. Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) software version 27. Descriptive statistics, including frequencies, means, standard deviations, and measures of central tendency, were calculated to summarize the data. Results were compiled and presented through tables, graphs, and written summaries. Factors associated with the delayed VR after antiviral treatment were analyzed using logistic regression. Variables with a p-value < 0.20 in the bivariable analysis were considered for inclusion in the multivariable regression model. The final model aimed to identify independent predictors of delayed VR, adjusting for potential confounders. Statistical significance was declared at a 95% confidence interval (CI) for the OR and a p-value less than 0.05.

3.10. Operational definitions

- **Chronic hepatitis B (CHB)**–persistence of HBsAg for 6 months or more.
- **Complete Virologic response**–defined as undetectable HBV DNA by a sensitive PCR assay (≤20 IU/mL by real-time PCR assay).
- **Timely responders**–defined as undetectable HBV DNA by a sensitive PCR assay after 12 monthsof TDF therapy.
- **Delayed responders**–decrease in HBV DNA levels but detectable HBV DNA after 12 monthsof TDF therapy.
- **APRI score–A** non-invasive test with validated cut-offs that correlate with specific histological stages including grades of fibrosis and cirrhosis. (21)

  APRI = [(AST / ULN) x 100] / Platelet count

  Where:

  - **AST:** Aspartate aminotransferase level
  - **ULN:** Upper limit of normal range for AST
  - **Platelet count:** Number of platelets per microliter of blood

- **significant fibrosis**–APRI score (high cut-off) >0.5;
- **Cirrhosis**–APRI score (low cut-off) >1;
- **Decompensated cirrhosis**–Decompensated cirrhosis is defined as an acute deterioration in liver function in a patient with cirrhosis and is characterized by the presence of one of the following jaundice, ascites, hepatic encephalopathy, hepatorenal syndrome, or variceal hemorrhage (46,47)

3.11. Ethical consideration

The study was conducted after obtaining ethical clearance from the Department of Internal Medicine Research and Ethics Committee and IRB of the College of Health Sciences, Addis Ababa University. Access to the information collected was limited to the principal investigator and confidentiality will be maintained throughout the project.

3.12. Result dissemination

Upon completion of data analysis and interpretation, the findings of this research will be disseminated through publication to contribute to the scientific body of knowledge. Both electronic and printed copies of the thesis will be made available to the Department of Internal Medicine, School of Medicine, College of Health Sciences at Addis Ababa University, as well as other relevant stakeholders.

4. Results

4.1. Socio-demographic characteristics

Out of 216 eligible adult patients with chronic hepatitis B, a total of 182 individuals participated in the study yielding a response rate of 84.3%. These participants had been on antiviral therapy for at least five years, between 2019 and 2023. The distribution of patients by year of treatment initiation was as follows: 47 in 2019, 29 in 2020, 27 in 2021, 26 in 2022, and 53 in 2023.

The age distribution was evenly split, with 50% of participants aged 18–39 years and the remaining 50% aged above 40. A majority of participants were male (66.5%) and married (67.0%). Regarding educational attainment, nearly half (49.5%) had attained a diploma or higher education, while 28.0% had no formal education. In terms of monthly income, 53.3% of participants earned between 5,000 and 15,000 Ethiopian Birr (whereas 33.0% earned less than 5,000 ETB. Geographically, 59.9% resided in Addis Ababa, while 40.1% were from outside the capital. The major risky behaviors observed were alcohol use (26.9%) and herbal medication use (16.5%).

Table 1: Socio-demographic Characteristics of Adult Patients with chronic Hepatitis B virus (CHBV) Infection in a tertiary Hospital in Addis Ababa, Ethiopia (n = 182)

Variables		Count	Percentage
Age groups (year)			
	18 to 39	91	50.0%
	≥40	91	50.0%
Sex			
	Male	121	66.5%
	Female	61	33.5%
Marital status			
	Married	122	67.0%
	Single	54	29.7%
	Widowed	6	3.3%
Educations			
	No formal education	51	28.0
	Complete grade 12	41	22.5
	Diploma and above	90	49.5
Monthly income			
	less than 5000	60	33.0
	5000-15,000	97	53.3
	Above 15,000	25	13.7
Residency			

	Addis Ababa	109	59.9
	Outside Addis Ababa	73	40.1
Risky behavior			
	Alcohol history	49	26.9
	Smoking history	24	13.2
	Use Herbal Medications	30	16.5

4.2. Treatment Indications, Comorbidities, and Baseline Investigations

The major findings from this study highlight several important clinical characteristics and treatment patterns among HBV patients. A significant proportion of patients (66.5%) initiated treatment due to the presence of significant fibrosis or cirrhosis, while 9.9% were treated for persistently elevated liver enzymes. The majority of patients (57.7%) had a baseline viral load exceeding 20,000 IU/mL, indicating a high level of viral replication. Hepatitis E antigen status was undetermined or undocumented in 57.7% of cases (table 2).

Regarding liver function, most patients (64.8%) had ALT levels within normal limits, and 50.5% had AST levels within the normal range. A substantial proportion of patients (65.4%) had a platelet count below 150,000, which may suggest liver-related complications. The majority of patients (61.0%) had an APRI score between 0.5 and 1.5, indicating moderate liver fibrosis(table 2).

Abdominal ultrasound findings were suggestive of cirrhosis were noted in 50.0% of patients. Comorbidities such as hypertension (7.7%), diabetes (5.5%), and MASLD (5.5%) were present in a small proportion of patients. Notably, 74.7% of patients reported consistent adherence to their prescribed medications, reflecting a high adherence rate. Only five (2.7%) patients had creatinine levels above the normal value and four (2.1%) patients had a history of exposure to TDF antiviral medication.

Table 2Clinical Characteristics, Baseline Investigations, and Comorbidities of HBV Patients on Antiviral in a Tertiary Hospital in Addis Ababa, Ethiopia (n = 182)

Variables		Count	Percent
Indication for treatment			
	Significant fibrosis/cirrhosis/	121	66.5
	Persistently elevated liver enzyme	18	9.9
	Immunosuppressive treatment(malignancy)	11	6.0
	Unknown or not documented	32	17.6
Baseline Viral load			
	<2000	38	20.9

	2000-20000	39	21.4
	≥20,000	105	57.7
Hepatitis e antigen status			
	Positive	34	18.7
	Negative	43	23.6
	Undetermined/nondocumented/	105	57.7
Baseline ALT			
	Less than UNL	118	64.8
	Between 2 to 5 times UNL	54	29.7
	Above 5times UNL	10	5.5
Baseline AST			
	Less than UNL	92	50.5
	Between 2 to 5 times UNL	86	47.3
	Above 5times UNL	4	2.2
Baseline Platelet			
	less than150000	119	65.4
	Above 150000	63	34.6
Baseline APRI score			
	APRI < 0.5	37	20.3
	APRI ≥ 0.5 and < 1.5	111	61.0
	APRI ≥ 1.5	34	18.7
A**bdominal Us at bassline**			
	Suggest cirrhosis	91	50.0
	Ascites and other complications	33	18.1
C**omorbidities**			
	Diabetes	10	5.5
	Hypertension	17	7.7
	MASLD	10	5.5
Adherence			
	Always took medication	136	74.7
	Sometimes forget taking	40	22.0
	Often forget to take(>15days)	6	3.3

4.3. HBV CVR on Treatment

In a cohort of 182 CHBV patients on antiviral treatment, 72.5%(95%CI,65.4%,78.9%) achieved sustained viral suppression(undetectable) after 12 months of therapy. Additionally, a significant majority of patients, 94.0% (171) experienced normalization of alkaline phosphatase (ALT) levels. From 2019 to 2022, the viral response rates remained relatively stable, fluctuating between 62.1% and 70.2%. However, in 2023, there was a significant increase in the viral response rate, reaching 90.6%. This sharp rise in 2023 suggests an improvement in the treatment response compared to previous years (figure 1). Approximately

two-thirds of HBeAg-positive patients (67.64%, 23/34), had CVR to antiviral therapy (within one year of treatment.

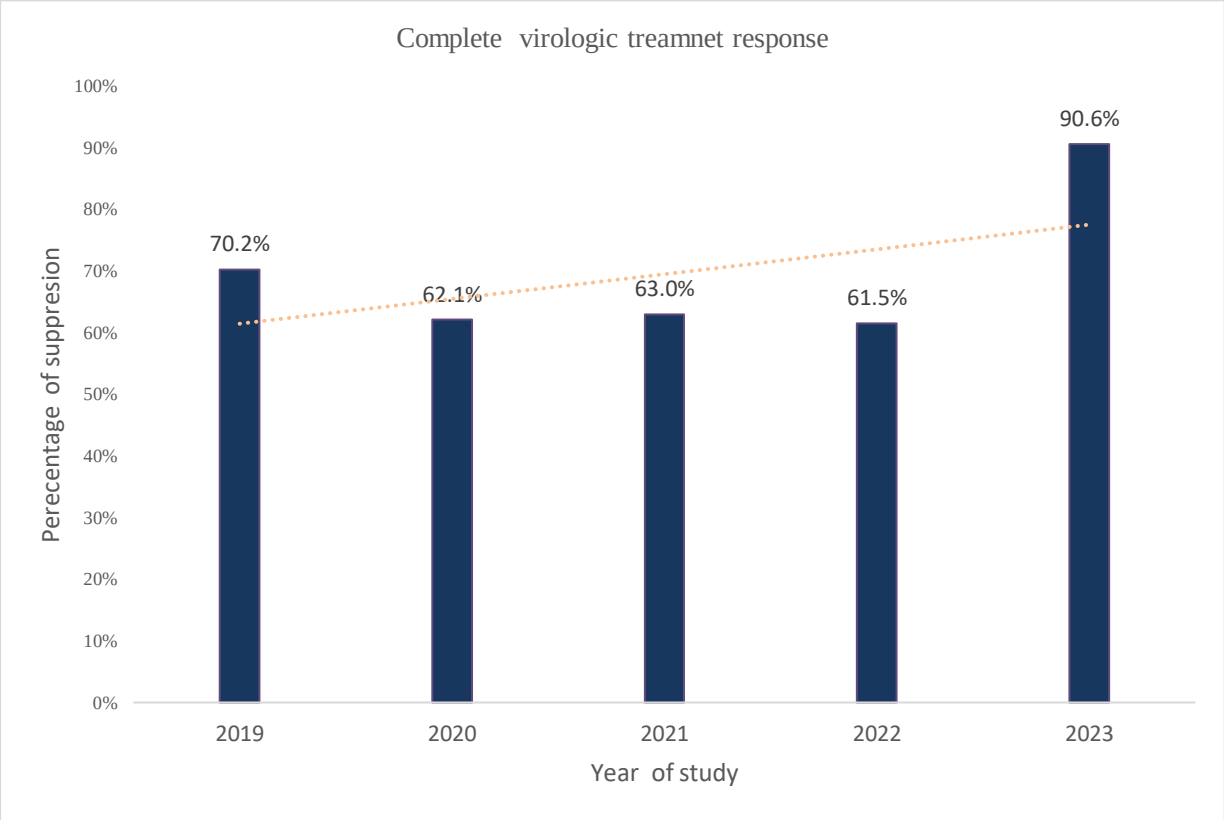

Figure 2: Pattern of complete viral treatment response over the five years

4.4. Factors for Delayed VR in HBV Patients on Treatment

In the univariate logistic regression analysis, variables with a p-value < 0.20 were selected for the multivariable logistic regression model. These included elevated baseline viral load (>20,000, p = 0.02), baseline ALT (2–5× UNL: p = 0.01; >5× UNL: p = 0.03), elevated baseline AST (2–5× UNL, p = 0.001), APRI score ≥ 0.5 (p = 0.001), alcohol use (p = 0.001), smoking (p = 0.001), herbal medication use (p = 0.001), abdominal ultrasound suggestive of cirrhosis (p = 0.003), presence of ascites or upper gastrointestinal bleeding (p = 0.004), and medication non-adherence (p = 0.001).

In the multivariable logistic regression analysis, five factors were found to be significantly associated with delayed VR. Specifically, alcohol use was associated with more than a four-fold increase in the odds of delayed response (AOR = 4.43; 95% CI: 1.46–13.46; p = 0.01). Similarly, smoking was linked to a greater than seven-fold increase in risk (AOR = 7.31; 95% CI: 1.74–30.77; p = 0.01). Compared to a viral load of <2000, individuals with a baseline viral load greater than 20,000 have 5.7 times higher odds of experiencing a delayed viral response in

CHBV patients on treatment (AOR = 5.7, 95% CI: 1.13, 18.13, p = 0.001).Herbal medication use was also significantly associated with delayed VR, with an adjusted OR of 5.49 (95% CI: 1.51–19.99; p = 0.01). The most notable finding was the strong association between medication non-adherence and delayed virologic response. Patients who were non-adherent to their medication had nearly 17 times higher odds of experiencing delayed response compared to adherent patients AOR = 16.9; 95% CI: 10.55–122.16; p = 0.001).

Table 3:Multivariable Logistic Regression Analysis of Factors Associated with Delayed VR in HBV Patients

Variables	COR (95%CI)	P-value	AOR (95%CI)	P value
Bassline Viral load				
<2000	1		**1**	
2000-20000	2.55(0.61,10.72)	0.20	1.94(0.41,8.43)	0.56
>20,000	7.17(2.07,24.88)	0.002	5.7 (1.13, 18.13)	0.001
Baseline ALT				
Less than UNL			1	
2 to 5 times UNL	3.24(1.59,6.59)	0.01	0.94(0.22.3.91)	0.93
Above 5times UNL	4.36(1.16,16.38)	0.03	1.14(0.05,26.57)	0.93
Baseline AST				
Less than UNL	1		1	
2 to 5 times UNL	3.19(1.58,6.46)	0.001	3.60(0.88,14.58)	0.07
Above 5times UNL	5.13(0.67,39.34)	0.115	8.28(0.06,151.77)	0.40
APRIL score	2.91(1.66,5.08)	0.001	0.75(0.21,2.70)	0.661
Alcoholic history				
Yes	8.92(4.23,18.80)	0.001	4.43(1.46,13.46)	**0.01**
No	1		1	
Smoking history				
Yes	5.86(2.36,14.52)	0.001	7.31(1.74,30.77)	**0.01**
No	1		1	
Herbal medication				
Yes	6.74(2.90, 15.63)	0.001	5.49(1.51,19.99)	**0.01**
No	1		1	
AUS suggest cirrhosis				
Yes	2.79(1.41,5.56)	0.003	1.15(0.36,3.58)	0.81
No			1	
Ascites or UGIB				
Yes	3.18(1.46,6.96)	0.004	0.91(0.23,3.74)	0.89
No	1		1	
Loss of medication				
Yes	31.37(12.84,76.59)	0.001	16.9(10.55,122.16	**0.001**
No	1		1	

5. Discussion

This study aimed to evaluate the treatment response rate and the factors associated with delayed VR in adult patients with chronic HBV infection after 12 months of antiviral treatment. The complete treatment response rate after 12 months of therapy was 72.5%. From 2019 to 2023, the response rates remained relatively stable, fluctuating between 62.1% and 90.6%, with 70.2% recorded in 2019.Approximately two-thirds (67.64%) of the HBeAg-positive patients achieved CVR at 12 months of antiviral therapy.In the multivariable logistic regression analysis, baseline viral load, alcohol use, smoking, herbal medication use, and medication non-adherence were significantly associated with delayed VR, increasing the odds of delayed response in these patients.

Our study reported an overall CVR rate of 72.5% over 5 years, which aligns closely with global benchmarks, such as the 71.5% CVR at 48 weeks observed in a Korean cohort (32) and the 80% CVR at 1 year reported in an Ethiopian pilot program (45). A striking feature of our study is the 5-year trend in CVR, which improved from 61.2% in earlier years to 90.6% by 2023. The 2023 peak (90.6%) not only surpasses the Ethiopian pilot's 1-year results but also approaches the 93% suppression rate seen in HBeAg-negative patients globally (39), illustrating the cumulative benefits of long-term TDF use. Changes in yearly rates show the effect of early problems, like poor patient follow-up and limited testing, which were gradually improved through flexible solutions. The upward trajectory likely reflects programmatic refinements, including standardized viral load monitoring and incremental healthcare system strengthening.

The 67.65% CVR observed in HBeAg-positive patients in our study over 5 years aligns closely with global benchmarks, including Phase III trials (39), which reported a CVR range of 21–76% in HBeAg-positive patients after 1 year of nucleotide analog therapy (*e.g.*, TDF), positioning our findings within the upper half of this spectrum and suggesting comparable or slightly improved efficacy relative to trial averages. Furthermore, meta-analyses from high-income settings highlight that HBeAg-positive patients typically achieve 60–70% HBV DNA suppression after 1–2 years of TDF therapy(50).Since less than half of the study participants had documented HBeAg status, the calculated virological response was derived solely from this subgroup. Consequently, the reported rate may not represent the response of the entire

study population, and the actual virological response could vary—potentially being either higher or lower than the observed 67.64%. Nonetheless, it is well-established that HBeAg-positive patients tend to have lower virological response rates compared to their HBeAg-negative counterparts. This is primarily due to higher baseline HBV DNA levels and a state of immune tolerance, which may diminish antiviral efficacy and necessitate prolonged therapy to suppress persistent viral replication.

High baseline viral load is a key predictor of delayed VR in chronic hepatitis B (CHB), as shown by global and regional studies. Other studies conducted in Korea (17) and Ethiopia (25) identified poor predictors of the antiviral treatment responses. Additionally, patients with high viral loads may be at greater risk of developing antiviral resistance, further complicating treatment efforts and prolonging the time required to achieve a sustained VR.

Behavioral factors such as alcohol use, smoking, herbal medication use, and treatment non-adherence have been consistently associated with delayed virological response and suboptimal outcomes in chronic hepatitis B (CHB) management. Alcohol consumption has been shown to accelerate liver fibrosis and increase the risk of HCC among individuals with HBV by promoting oxidative stress, impairing immune responses, and synergizing with viral replication. Notably, alcohol intake exceeding 20 grams per day significantly reduces the likelihood of achieving HBV DNA suppression, as demonstrated in cohort studies [51]. While direct evidence linking smoking to delayed virological suppression is limited, smoking contributes to the progression of liver disease. A large longitudinal study involving 1.2 million Korean adults found that smoking increased the risk of HCC by 1.5-fold in HBV-infected individuals and was associated with a reduced likelihood of achieving complete viral suppression during CHB treatment [52]. Non-adherence to antiviral therapy remains a major contributor to treatment failure. Key barriers include cost, forgetfulness, and stigma, with adherence rates below 90% associated with 3-fold higher HBV DNA levels, whereas improved adherence is correlated with better virological suppression [53].

Finally, herbal remedies, commonly used in many cultures without medical supervision, have been linked to hepatotoxicity in HBV-infected patients, further worsening liver function [54]. Importantly, some patients may use traditional medications as alternatives to antiviral therapy and discontinue prescribed treatment, leading to poor virological suppression outcomes.

6. Strengths and limitations

This study benefits from a strong retrospective design, analyzing a real-world cohort of 182 patients over five years, which enhances the clinical relevance of its findings.By considering a comprehensive range of clinical and demographic factors, the study offers a thorough understanding of the variables influencing VR to TDF therapy for chronic hepatitis B. Additionally, the study's longitudinal approach allows for the assessment of long-term treatment outcomes, providing valuable insights into the durability of virologic suppression and potential predictors of treatment failure

Despite its strengths, this study has several limitations. First, its retrospective nature may introduce selection bias, as patients included in the cohort were not randomly assigned, potentially affecting the generalizability of the findings. Second, the study relies on data from a single center, which may limit the applicability of the results to other populations or settings with different clinical practices or patient demographics. Additionally, the study lacks a detailed assessment of potential drug resistance mutations or adherence data, which are critical factors in determining the long-term success of treatment. Furthermore, the cross-sectional design limits the ability to establish causal relationships. While regression analyses can identify associations between clinical and demographic factors and VR, they cannot definitively determine causality due to the snapshot in time provided by a cross-sectional study. Finally, the relatively short follow-up period for some patients may not capture the long-term effects or complications associated with chronic hepatitis B or TDF therapy.

7. Conclusion and recommendations

This study found a significant proportion of patients achieved a VR at 12 months, highlighting the efficacy of tenofovir TDF in the management of chronic hepatitis B. It also provides valuable insights into the factors influencing VR to TDF therapy. These findings contribute to a better understanding of how clinical and behavioral factors influence treatment outcomes, which could guide clinicians in optimizing patient care and treatment strategies.

Based on these findings, it is recommended that clinicians focus on regular monitoring of baseline viral load and liver function, as these factors were identified as significant predictors of treatment efficacy. In addition, addressing behavioral factors such as medication adherence is crucial to improving treatment outcomes, and strategies to enhance adherence, including

patient education and regular follow-ups, should be prioritized. Further research with longer follow-up periods is essential to capture the long-term effects of TDF therapy, including potential drug resistance or other complications related to chronic hepatitis B. Additionally, expanding the study to include multiple centers with diverse patient populations would improve the generalizability of the findings. Finally, future studies should focus on investigating the impact of drug resistance mutations and patient adherence on treatment outcomes to better tailor therapy for chronic hepatitis B patients and improve long-term success.

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9. ANNEX

9.1. Questionnaire

Medical record number (MRN)

PART 1: Socio-demographic characteristics

1.1	**Age**	**A- 18-39**		**B- >=40**
1.2	Sex	A- Male		B- Female
1.3	Marital status	A- Unmarried	B- married	C- widdo
1.4	Educational level	A- no formal education	B- learned up to grade 12	C- Diploma and above
1.5	Residency	A- Addis Ababa		A- Outside of Addis Ababa

Part 2: Clinical Data

2.1	**Year of treatment initiation**		
2.2	Previous treatment with NA	A- Yes	B- No
2.3	Baseline viral load		
			B- >=UNL reference

2.4	Baseline ALT	A- < UNL	range
2.5	Baseline AST	A- < UNL	B- >=UNL reference range
2.6	Baseline Platelet count	A- <150,000	B- >=150,000
2.7	Abdominal U/S suggestive of cirrhosis	A- Yes	B- No
2.8	If yes	A- Compensated	B- Decompensated
2.9	HB viral load at 24wks		
2.10	Viral load at 1 year	A- Undetectable	B- Detectable (report the number)

Part 3: Lifestyle behavioral and other factors

3.1	**Drug adherence(patient report)**	**A- Adherent**	**B- Nonadherent**

3.2	Current/ previous Smoker		A- Yes		B- No
3.3	Alcohol use(current/previous)		A- Yes		B- No
3.4	Physical activity		A- Yes		B- No
3.5	Co-morbidity	A- DM	B- HTN	C- CKD	D- Others
3.6	Herbal medication use(current or previous)		A- Yes		B- No