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Oral Antiviral Therapies for Achieving Sustained Viral Suppression in Adults with Chronic Hepatitis B: A Systematic Review on Efficacy and Associated Outcomes

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Abstract **- Chronic Hepatitis B be easily managed through antiviral therapies that significantly reduce viral load, thereby decreasing liver inflammation and slowing the progression of liver fibrosis and cirrhosis of a patient. However, their clinical efficacy and safety has yet to be thoroughly determined. Different treatment varies widely in terms of effectiveness and safety concerns, with each treatment's extremity. Moreover, they often elicit different responses across patients due to factors influencing their efficiency such as their age, liver health and immune health status. In this systematic review, we will investigate the different oral antiviral therapies for achieving sustained viral suppression in adults with their efficacy and their corresponding outcomes. 12 various studies were collected using relevant databases like PubMed, Web of Science and Scorpus across Asia and had been analyzed and reviewed. This study evaluated four antiviral drugs including entecavir (ETV), tenofovir (TDF), lamivudine (3TC), and telbivudine (LdT) with treatment variations varied from 1 to 5 years aiming to assess the patients' varying degrees of efficacy such as ALT levels and HBeAg status after receiving the treatment. When comparing the therapeutic medicines, Tenofovir was determined to be effective in reducing viral load (3.4 ± 1.4 log10 IU/mL) and ALT levels (46.9 ± 49.8 U/L) in patients with mild to moderate liver inflammation.**

On the other hand, lamivudine exhibits moderate ALT levels (74.4± 94.7 U/L) and viral loads (6.88 ± 0.62 log10 IU/mL), making this treatment suitable for those experiencing moderate inflammation and requiring effective viral suppression and telbivudine displayed a notable ability to induce both HBeAg seroconversion of 46.4% and HBsAg loss of 31.1%. Overall, Entecavir consistently exhibited superior performance with 99. 4% in viral suppression and 94.5% liver function improvement.

Keywords:- *Viral Suppression, Hbeag-Positive, Hbeag-Negative, Seroconversion, Amino Transaminase Level (ALT)*

I. INTRODUCTION

Liver infection known as the Chronic Hepatitis B caused by the hepatitis B virus remains a major global health problem affecting millions of people. In 2022, the estimated case of chronic hepatitis b was 254 million individuals, including the 61 million people infected in South-East Asia Region, and additional of 1.2 million cases of new infections occur annually (WHO, 2024). Though the development of antiviral therapies has increased significantly, safe and efficient treatments that produce long-lasting viral suppression and other enhanced long-term outcomes are still critically needed. A sustained viral suppression will help protect the liver from further damage and reduce the risk of further getting more serious health problems.

Chronic hepatitis b is an infection with no cure, but with the help of antiviral medications it will help control the infection. The most frequently used treatment for chronic hepatitis is known as nucleoside analogues (Nas). Its function is to prevent the virus from multiplying, though they have a minimal effect on reducing the presence of hepatitis B surface antigen (HBsAg) (Buti et al., 2021). There are currently five oral nucleoside analogue that are approved for the treatment of chronic hepatitis b are generally safe and well-tolerated by the patients (Kayaaslan & Guner 2017).

This systematic review aims to review the efficacy and associated outcomes of oral antiviral therapies for achieving sustained viral suppression in adults infected with chronic hepatitis B. This review will focus on the effectiveness of entecavir, tenofovir, lamivudine, and telbivudine treatment on patients infected with chronic hepatitis b, examining studies from 2014 up to date.

II. METHODOLOGY

A. Data Gathering

In order to collect data for this systematic review, a thorough and organized method is used. Using a thorough search technique, pertinent databases like PubMed, Web of Science, and Scopus were found. To guarantee the selection of relevant studies, specific inclusion must be made while setting exclusion criteria. Potential studies were also retrieved using topic-related keywords and search queries. Following that, the search results are filtered in two steps: full-text review comes after title and abstract review. Relevant data, such as research design, demographic characteristics, interventions, outcomes, and results, were methodically gathered from the chosen studies using data extraction forms. After then, this data is arranged and combined to offer a thorough comprehension of the subject being examined, guaranteeing the process's transparency and reproducibility.

B. Data Sources

To improve the quality of the review procedure, the researchers verified the reliability of the chosen references using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. To find relevant published articles, research papers, and scientific reports for this review, a range of search engines and databases were used, including ScienceDirect, Google Scholar, ResearchGate, and the Directory of Open Access Journals.

C. Search Strategy

Search phrases such as viral suppression, HBeAg-positive, HBeAg-negative, seroconversion, amino transaminase level (ALT) was frequently used. The first 12 relevant publications were considered, with an emphasis on open-access sources. Also, to find pertinent material, grey literature sources including government and non-government papers, websites of international organizations, news items, and policy documents were examined.

D. Exclusion and Inclusion Criteria

The following criteria were used to categorize all pertinent articles that were part of this review: (1) studies that focused on adults diagnosed with chronic hepatitis B (HBV), (2) studies must include both HBeAg-positive and HBeAg-negative patients, (3) studies must evaluate oral antiviral monotherapy (single drug), (4) eligible study designs include cohort studies and comparative observational studies that report on antiviral efficacy and outcomes, (5) only studies published from 2014 to present, and (6) studies must be conducted in Asia.

Studies were excluded if they (1) involve patients with co-infections and liver transplant recipients, or those with other chronic liver diseases; (2) investigate combination therapies, non-oral therapies, or non-antiviral treatments; (3) were case reports, review articles, editorials, and non-comparative studies; (4) were published before 2014; and (5) conduct outside of Asia or studies not specifying the geographic region.

E. Framework of the Study

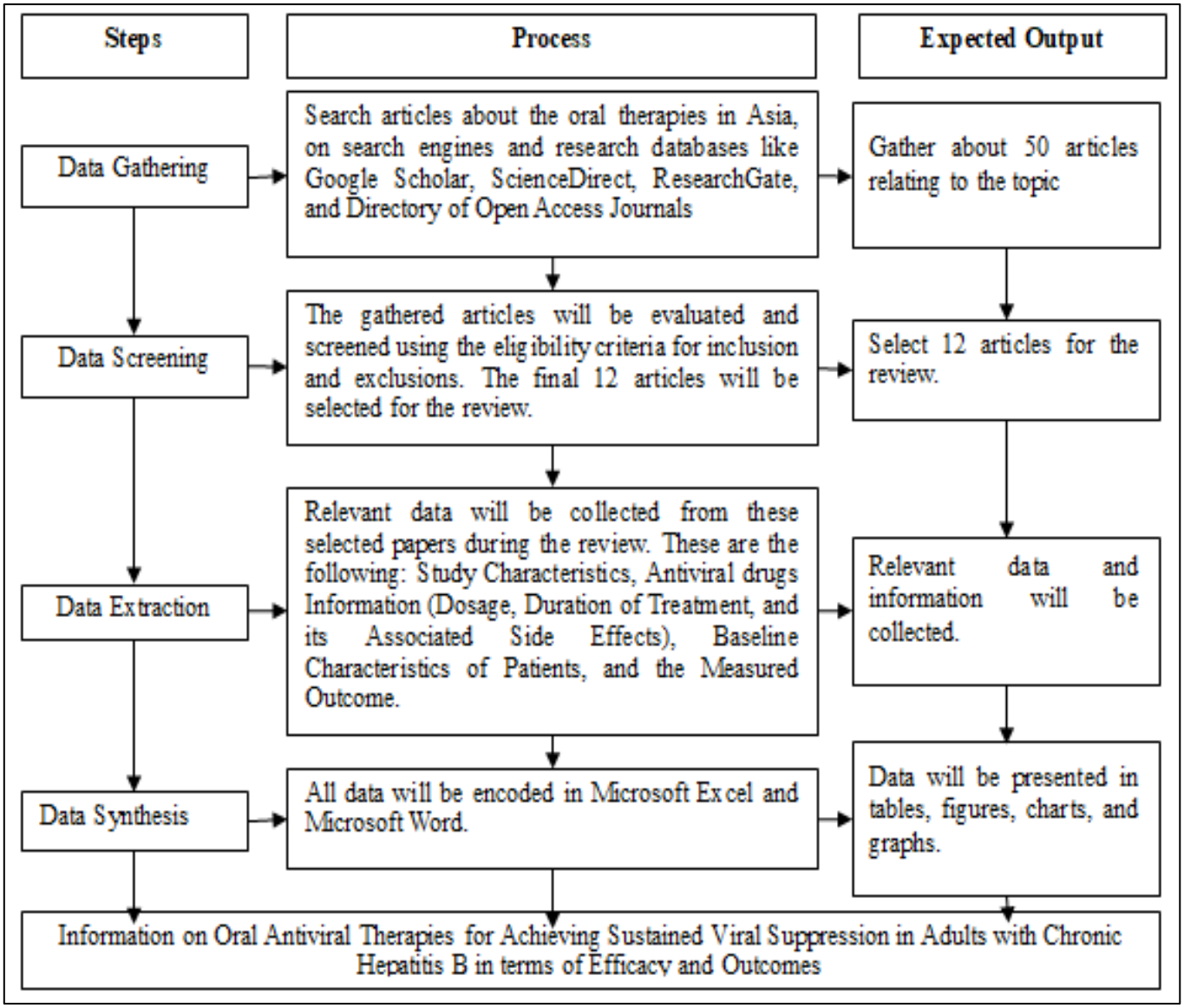

Fig 1 Research Paradigm

F. Data Extraction and Statistical Analysis

The study used Microsoft Word to display the results, adding visual organizers for clarity, and Microsoft Excel to arrange the gathered references. Using keywords, the researcher coded the data, grouped related codes to generate themes, and then checked and updated the codes for accuracy. The study characteristics, antiviral drugs information (dosage, duration of treatment, and its associated side effects), baseline characteristics of patients, and the measured outcome were among the topics that were found. From the combination of search phrases from four databases, a total of 50 studies were first found (7 from ScienceDirect, 35 from Google Scholar, 4 from ResearchGate, and 4 from Directory of Open Access Journals). To make sure that only studies that satisfied the predetermined criteria were included in the review, a total of 12 studies out of 50 papers were chosen using the eligibility criteria. By ensuring that the chosen papers were of excellent quality and pertinent to the study issue, this phase helped to reduce bias. After that, a systematic process of data extraction was used to extract and synthesize pertinent information from each chosen study. Patterns and trends in the efficacy of various oral antiviral therapies were then found by applying the proper statistical techniques to the retrieved data. Additionally, the statistical analysis may have involved comparisons between the different antiviral drugs regarding their efficacy in achieving outcomes like Viral Suppression, Liver Function Improvement, HBeAg Seroconversion, and HBsAg Loss at different time points. This comprehensive statistical analysis allowed for a robust evaluation of the effectiveness of the antiviral drugs under consideration and provided valuable insights into their performance over the course of the study

III. DATA AND RESULTS

A. Study Characteristics

TABLE 1. STUDY CHARACTERISTICS

Study ID	Author (s)	Year of Publication	Study Design	Sample Size	Geographic Location	Inclusion Criteria	Exclusion Criteria
S1	Sriprayoon, T., Mahidol, C., et. al	2016	Randomized Controlled Trial	200 patients	Thailand	• Compensated chro-nic hepatitis B patients • Aged 20-65 years • HBeAg-positive or HBeAg-negative	• Co-infection with hepatitis C virus and/or HIV • Decompensated cirr-hosis
S2	Xie, Y., Ma, H., Feng, B., and Wei, L.	2017	Retrospective Cohort Study	233 patients	China	• HepB surface antigen persisted for at least 6 months before the initial treatment	• Suffered from cirrhosis before ETV treatment • Underwent liver transplantation before ETV treatment • Patients who were not followed up regularly.
S3	Cho, J., Sohn, W., Sinn, D., Gwak, G., Paik, Y., Choi, M. S., Koh, K. C., Paik, S. W., Yoo, B. C., and Lee, J. H.	2016	Retrospective Observational Study	1,009 patients	South Korea	• Chronically infec-ted with HBV • Confirmed HBsAg-positive for at least 6 months • Sufficient clinical data available for analysis.	• Coinfection with hepatitis C virus or HIV patients with entecavir treatment less than 24 weeks • Patients younger than 18 years old.
S4	Liang, X., Xie, Q., Shang, J., Tang, H., Xu, M., Meng, Q., Zhang, J., Gao, P., Sheng, J., Wang, H., Jia, J., Wang, G., Wu, S., Ping, J., & Hou, J.	2021	Single-arm, Open-label, Multicenter Study	213 patients	China	• Only adult males and females within the age range of 18 to 65 years who have tested HBsAg positive for more than six months	• Diagnosed with hepatocellular carcinoma or those having clinical signs of decompensated liver disease or documented coinfection with hepatitis A, C, delta, E virus, or HIV
S5	Zhou, J., Liu, Y., Lian, J., Pan, L., Yang, J., & Huang, J.	2017	Prospective Study	33 patients	China	• CHB HBeAg-positive and negative patients • 18–65 years old and	• Presence of hepatitis C virus infection • Presence of AIDS or other immunodeficiency diseases and autoimmune diseases, alcoholism

S6	Lim, Y., Lee, Y. S., Gwak, G., Byun, K. S., Kim, Y. J., Choi, J., An, J., Lee, H. C., Yoo, B. C., & Kwon, S. Y.	2017	Combined Extension Trial	192 patients	South Korea	• Patients with chronic hepatitis B • Patients between 20 and 75 years old.	• Had prior exposure to TDF for more than 1 week, evidence of decompensated liver disease • Any coinfection with hepatitis C, hepatitis D, or human immune-deficiency virus.
S7	Yue-Meng, W., Li, Y., Wu, H., Yang, J., Xu, Y., Yang, L., & Yang, J.	2016	Retrospective-Prospective Study	45 patients	China	• All patients had detectable HBV DNA above 103 - copies/mL and positive hepatitis B surface antigen (HBsAg) for over 6 months	• Antibodies against hepatitis C virus (anti-HCV), hepatitis D virus (anti-HDV) or human immunodeficiency virus (anti-HIV)
S8	Liang, X., Cheng, J., Sun, Y., Chen, X., Li, T., Wang, H., Jiang, J., Chen, X., Long, H., Tang, H., Yu, Y., Sheng, J., Chen, S., Niu, J., Ren, H., Shi, J., Dou, X., Wan, M., Jiang, J., . . . Hou, J.	2014	Randomized, Open-label, Controlled, Multicenter Study	366 patients	China	• 18–65 years old with detectable hepatitis B surface antigen • HBeAg-positive, and HBeAg-negative	• Had a history of virological breakthrough • Other forms of liver disease; evidence of hepatic decompensation.
S9	Srivastava, M., Singh, N., Dixit, V. K., Nath, G., & Jain, A. K.	2016	Prospective Study	35 patients	India	• Patients with persistent elevation of alanine amino transaminase (ALT) level • HBeAg-positive and HBeAg-negative cases with or without decompensation	• Patients with co-infection with hepatitis C virus (HCV), hepatitis E virus (HEV), hepatitis A virus (HAV) or HIV, presence of sepsis or hepatorenal syndrome, and active alcohol abuse
S10	Wang, C-C., Lin, C-L., Hsieh, T-Y., Tseng, K-C., Peng, C-Y., Su, T-H., Yang, S-S., Hsu, Y-C., Chen, T-M., & Kao, J-H.	2015	An open-label, prospective and retrospective, and multicenter study	116 patients	Taiwan	• Males or females aged more than 18 years • Clinical history compatible with compensated CHB, • Positivity of serum hepatitis B surface antigen (HBsAg)	• Pregnant or nursing female; coinfection with hepatitis C virus (HCV), hepatitis D virus (HDV), or human immunodeficiency virus (HIV)

S11	Tsai, M., Chen, C., Hung, C., Lee, C., Chiu, K., Wang, J., Lu, S., Tseng, P., Chang, K., Yen, Y., & Hu, T.	2014	Retrospective Single-centre match–Control study.	115 patients	Taiwan	• Seropositivity for HBV surface antigen pulse decompensated liver disease	• Had any evidence of autoimmune hepatitis or markers of hepatitis C, hepatitis D and human immunodeficiency virus, or patients received chemotherapy or immunosuppressant agents, and significant intake of alcohol
S12	Sun, J., Xie, Q., Tan, D., Ning, Q., Niu, J., Bai, X., Fan, R., Chen, S., Cheng, J., Yu, Y., Wang, H., Xu, M., Shi, G., Wan, M., Chen, X., Tang, H., Sheng, J., Dou, X., Shi, J., . . . Hou, J.	2014	Multicenter, Open-label, andomized, Controlled Study	599 patients	China	• Patients aged 18-65 years • HBsAg-positive and HBeAb-negative	• Had other forms of liver disease and evidence of hepatic decompensation, pancreatitis • Coinfection with hepatitis C, hepatitis D, or the human immunodeficiency virus

HBsAg-positive, Hepatitis B surface antigen; HBeAb, Hepatitis B e-antibody; HBV, Hepatitis B Virus; CHB, Chronic Hepatitis B; ALT, Alanine amino transaminase; TDF, Tenofovir disoproxil fumarate; ETV, Entecavir; AIDS, Acquired immunodeficiency syndrome.

Table 1 provides a comprehensive overview of twelve (12) studies investigating the characteristics of chronic hepatitis B (CHB) patients and their treatment approaches. These studies, conducted in diverse geographic locations (Thailand, China, South Korea, India, and Taiwan), utilized a range of study designs including randomized controlled trials, retrospective cohort studies, and prospective studies. This diverse range of study designs offers insights into the heterogeneity of CHB patient populations and the effectiveness of various antiviral treatments. The inclusion criteria typically focused on patients with confirmed chronic hepatitis B, defined by persistent hepatitis B surface antigen (HBsAg) positivity for at least six months, and elevated HBV DNA levels. Exclusion criteria were generally aimed at minimizing confounding factors, such as co-infections with other viruses, decompensated liver disease, and pre-existing hepatocellular carcinoma (HCC). The table 1 also indicates the sample sizes of the studies, ranging from 35 to 599 patients, providing an indication of the statistical significance of each study.

The studies evaluated a variety of antiviral drugs, including entecavir (ETV), tenofovir disoproxil fumarate (TDF), lamivudine (3TC), and telbivudine (LdT). The duration of treatment varied across studies, ranging from 3 to 5 years. The reported side effects associated with the antiviral drugs are crucial for assessing their safety profiles. While some studies reported minimal side effects, others documented instances of allergic reactions, virological breakthrough, and even the development of hepatocellular carcinoma. It is important to acknowledge that the studies presented in this table may possess limitations in terms of participant sample size, research methodology, and the extent to which their findings can be applied to larger groups.

B. Evaluation of Antiviral Drugs

TABLE 2. ANTIVIRAL DRUGS EVALUATED

Drug Name	Dosage	Duration of Treatments	Side Effects	Study ID
Entecavir	0.5 mg/day	3 to 4 years	Two patients experienced grade 2 allergic reactions; No patients developed persistent hypophosphatemia or required dose adjustments; Four patients developed small HCC	S1
	0.5 mg/day	5 years	Two patients in the ETV group experienced ALT flares; ETV group experienced transient hypophosphatemia; Two patients in the ETV group developed HCC after more than 6 months of treatment.	S2
	0.5 mg/day	5 years	No serious adverse events were reported during the treatment period.	S3
Tenofovir	300 mg/day	2.76 years	Hepatocellular carcinoma was the most reported SAE. Transient hypophosphatemia; Elevated blood creatine phosphokinase.	S4
	300 mg/day	1 year	There were no clinically significant side effects such as exacerbation of symptoms or death occurred during the follow-up period	S5
	300 mg/day	1 year	None of the serious adverse events was judged to be related to the study medication. HCC was diagnosed in 3 patients in the TDFTDF.	S6
Lamivudine	100 mg/day	2 years	There were no significant side effects associated with LAM treatment.	S7
	100 mg/ day	2 years	Most adverse events were not related to study drug as assessed by clinical investigators	S8
	100 mg/day	2 years	Genotypic mutations were demonstrated at 24 months of therapy. Fifteen patients on LAM therapy revealed mutation.	S9
Telbivudine	600 mg/day	2 years	The adverse events included muscle-related complaints such as pain or weakness in six patients, dizziness in one, insomnia in one, and dysgeusia in one. No severe adverse events were observed during the study period.	S10
	600 mg/day	2 years	Twenty-seven patients developed the telbivudine-resistant mutation of M204I at different times during the study period	S11
	600 mg/day	2 years	Two in the Mono group (hepatitis flare, myopathy, myalgia, cardiac enzymes increased; One event (peripheral neuropathy) improved.	S12

HCC, Hypocellular carcinoma; ETV, Entecavir; ALT, Alanine amino transaminase; SAE, Serious adverse effect; TDFTDF, Tenofovir; LAM, Lamivudine

Table 2 shows the different dosage intakes of Entecavir, Tenofovir, Lamivudine, and Telbivudine in the span of 1 to 5 years of treatment. This table assesses the antiviral efficacy and safety of the four drugs.

➢ *Entecavir.*

A substantial majority of patients (91.39%) experienced no adverse side effects, indicating that the drug is highly tolerable over both short- and long-term treatment durations. However, 4.33% of patients developed hepatocellular carcinoma (HCC), with cases occurring after 12–36 months of treatment or more than six months of treatment in different study groups. This highlights a potential, albeit low, risk of cancer development during prolonged Entecavir use. Virological breakthrough (VBT) occurred in 1% of patients, where the virus became detectable despite continued treatment. Some cases of VBT were associated with Entecavir-resistant mutations, such as rtL180M, rtT184A, and rtM204V. Additionally, 0.33% of patients experienced transient hypophosphatemia, a condition of low phosphate levels in the blood, which resolved without causing persistent complications. Another 0.33% experienced ALT flares, indicating temporary spikes in liver enzyme levels, one of which was linked to drug resistance. Allergic reactions, also affecting 0.33% of patients, were mild (grade 2) and resolved within two weeks with topical steroids and antihistamines.

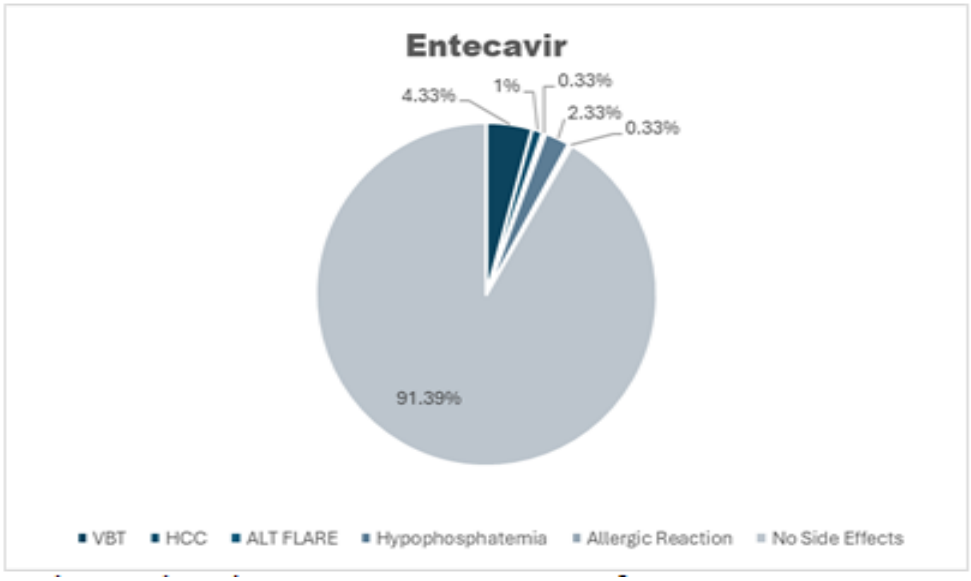

Fig. 2. Side Effects of Entecavir. VBT, Viral Breakthrough; HCC, Hepatocellular Carcinoma; ALT, Alanine amino transaminase

➢ *Tenofovir.*

A significant majority (80.43%) of patients experienced no adverse side effects, highlighting the drug's high tolerability. However, 4.37% of patients developed transient hypophosphatemia, a temporary condition characterized by low phosphate levels in the blood. Additionally, 2.80% of patients experienced elevated phosphokinase levels, which may indicate muscle-related side effects or metabolic disturbances. A small fraction of patients (0.77%) developed infections during the treatment, while 0.63% were diagnosed with hepatocellular carcinoma (HCC),

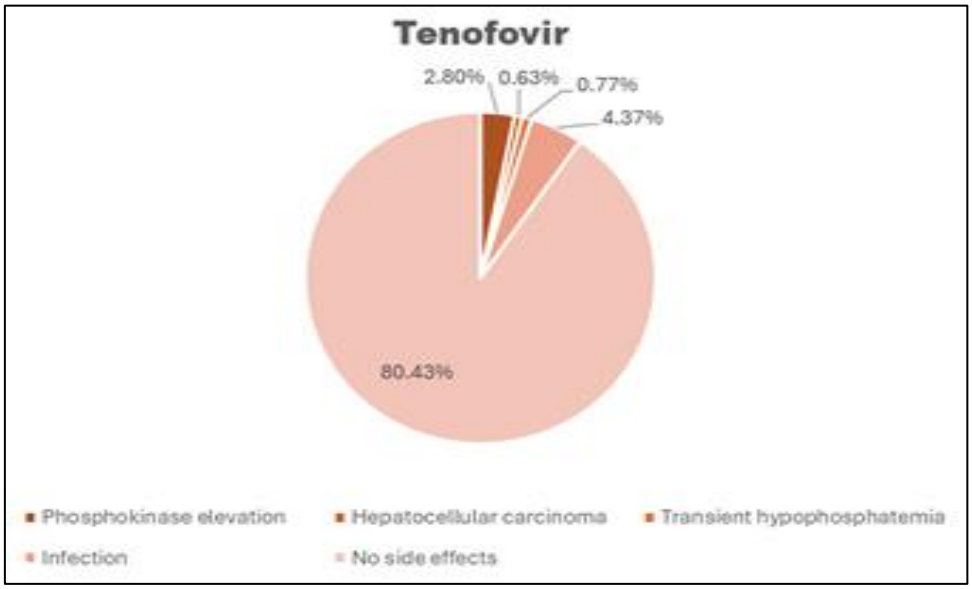

Fig. 3. Side Effects of Tenofovir

➢ *Lamivudine.*

Lamivudine is generally well-tolerated, with a low incidence of serious adverse events. However, long-term use can lead to the development of genotypic mutations in some individuals. Approximately 17.67% of cases experienced serious adverse events related to genotypic mutations. Furthermore, 53% of patients on Lamivudine therapy for 2 years developed mutations. While these mutations may not immediately impact the drug's effectiveness, they could potentially lead to treatment failure over time.

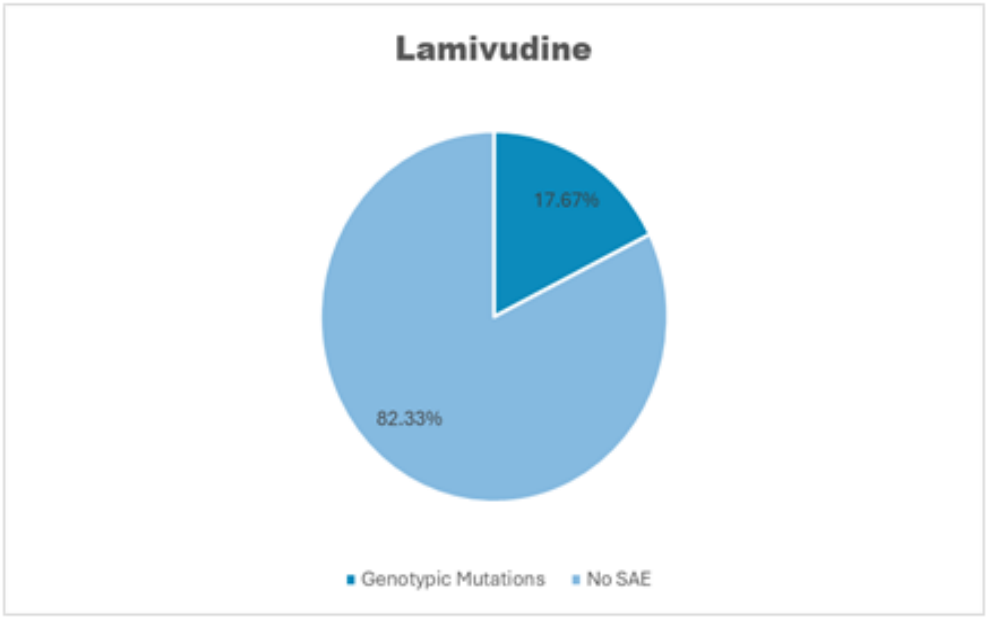

Fig. 4. Side Effects of Lamivudine. SAE, Serious Adverse Effects

➢ *Telbivudine.*

The most common outcome is the absence of adverse events, accounting for 89.22% of cases. A smaller percentage of patients experienced resistant-mutation (8.30%) or a hepatitis flare (1.89%). Less common side effects included dizziness, insomnia, dysgeusia (distorted taste), and muscle pain, each affecting less than 1% of patients. Overall, the chart suggests that Telbivudine is generally well-tolerated, with a majority of patients experiencing no side effects.

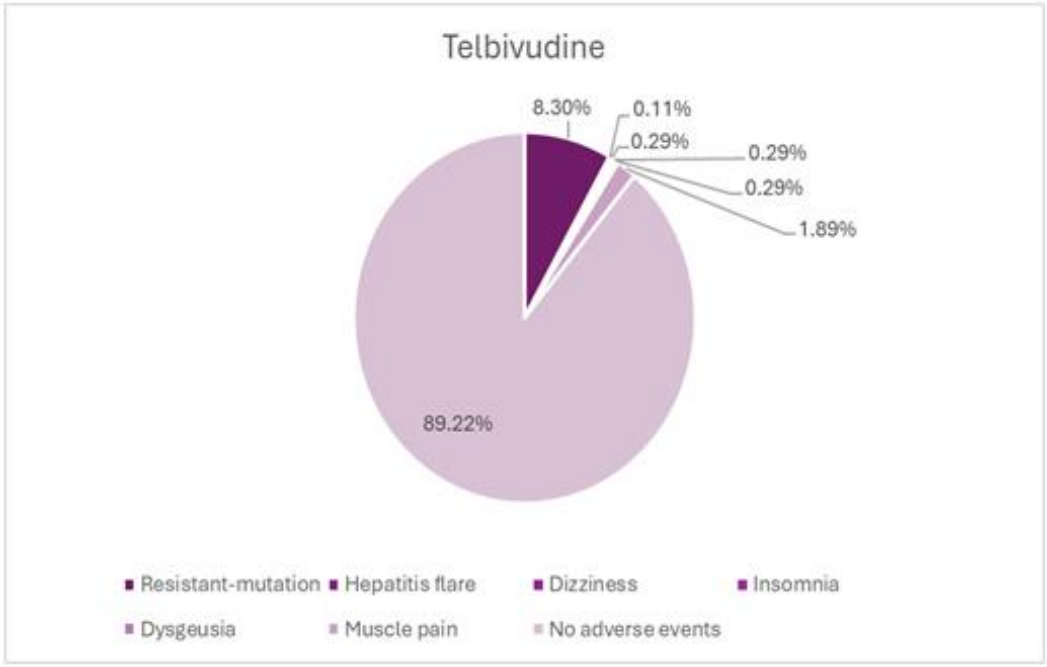

Fig. 5. Side Effects of Telbivudine.

C. *Patients Baseline Characteristics*

TABLE 3. BASELINE CHARACTERISTICS OF PATIENTS

	Entecavir			Tenofovir			Lamivudine			Telbivudine		
	S1	**S2**	**S3**	**S**	**S**	**S**	**S7**	**S8**	**S9**	**S10**	**S11**	**S12**
ALT (U/L)	68.1 ± 64.1	155± 168	154.7 ± 292.3	46.9 ± 49.8	26.00 ± 20.00	32 ± 12	74.4 ± 94.7	3.6± 2.8	84.9 ± 49	261 ± 289	226.8 ± 371.6	4.3 ± 3.8
AST (U/L)	---	---	112.8 ± 183.9	---	---	---	82.6 ± 81.0	---	---	---	---	---
HBeAg-positive Patients (log10 IU/mL)	7.1 ± 1.5	7.0 ± 1.1	6.47 ± 1.40	3.4 ± 1.4	2.00 ± 2	3.57 ± 2.16	6.81 ± 0.59	4.1± 0.8	5.6 ± 1.3	2.327 ± 0.359	2.2 ± 0.84	4.3 ± 0.6
HBeAg-negative Patients (log10 IU/mL)	4.9 ± 1.3	6.0 ± 1.0	6.47 ± 1.40	12.6 ± 2.91	3.48 ± 2.59	3.57 ± 4.62	6.88 ± 0.62	4.2± 0.8	5.8 ± 1.4	2.176 ± 0.305	6.4 ± 3.97	2.7 ± 0.9

Values are presented as the mean ± standard deviation. ALT, Alanine amino transaminase; AST, Aspartate Aminotransferase; HBeAg, Hepatitis B e-antigen.

Table 3 presents the comparative analysis of liver enzyme levels (ALT and AST) with the positive and negative HBeAg status, allowing for the assessment of treatment effects and potential differences categorized by their treatment group (Entecavir, Tenofovir, Lamivudine, and Telbivudine).

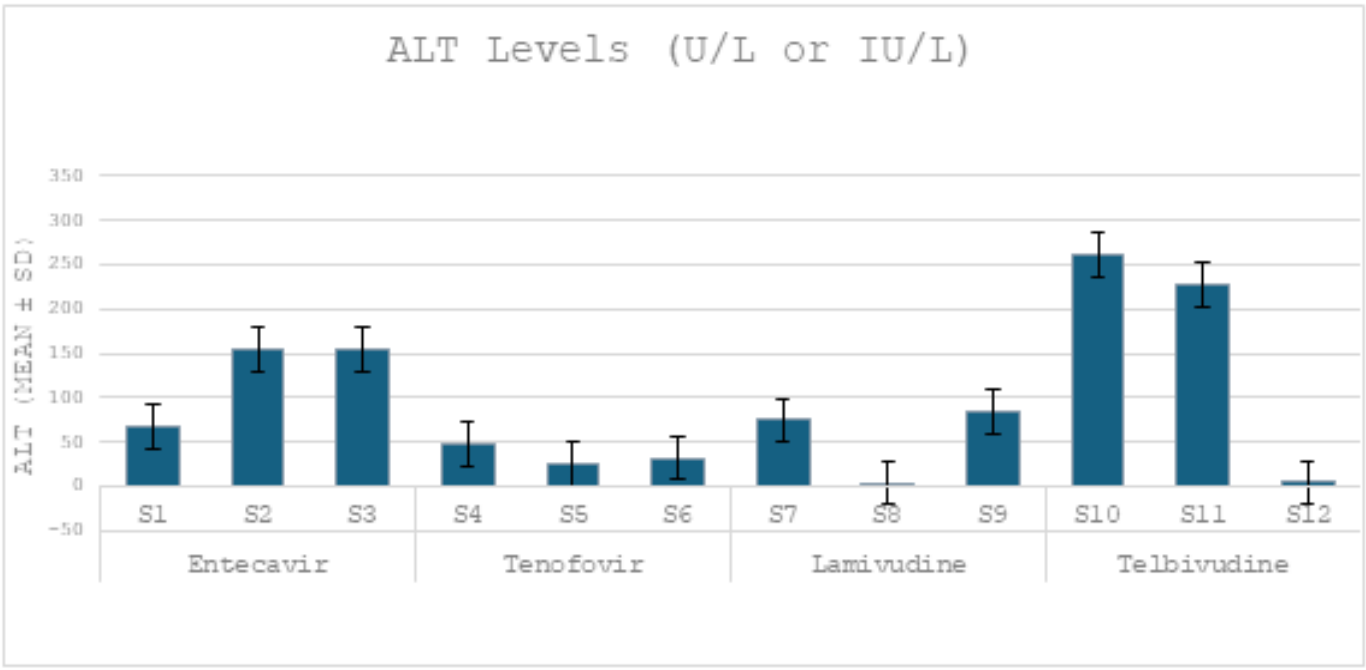

Fig. 6 . ALT Levels Measurement Treated with Specific Oral Therapies (See Discussion)

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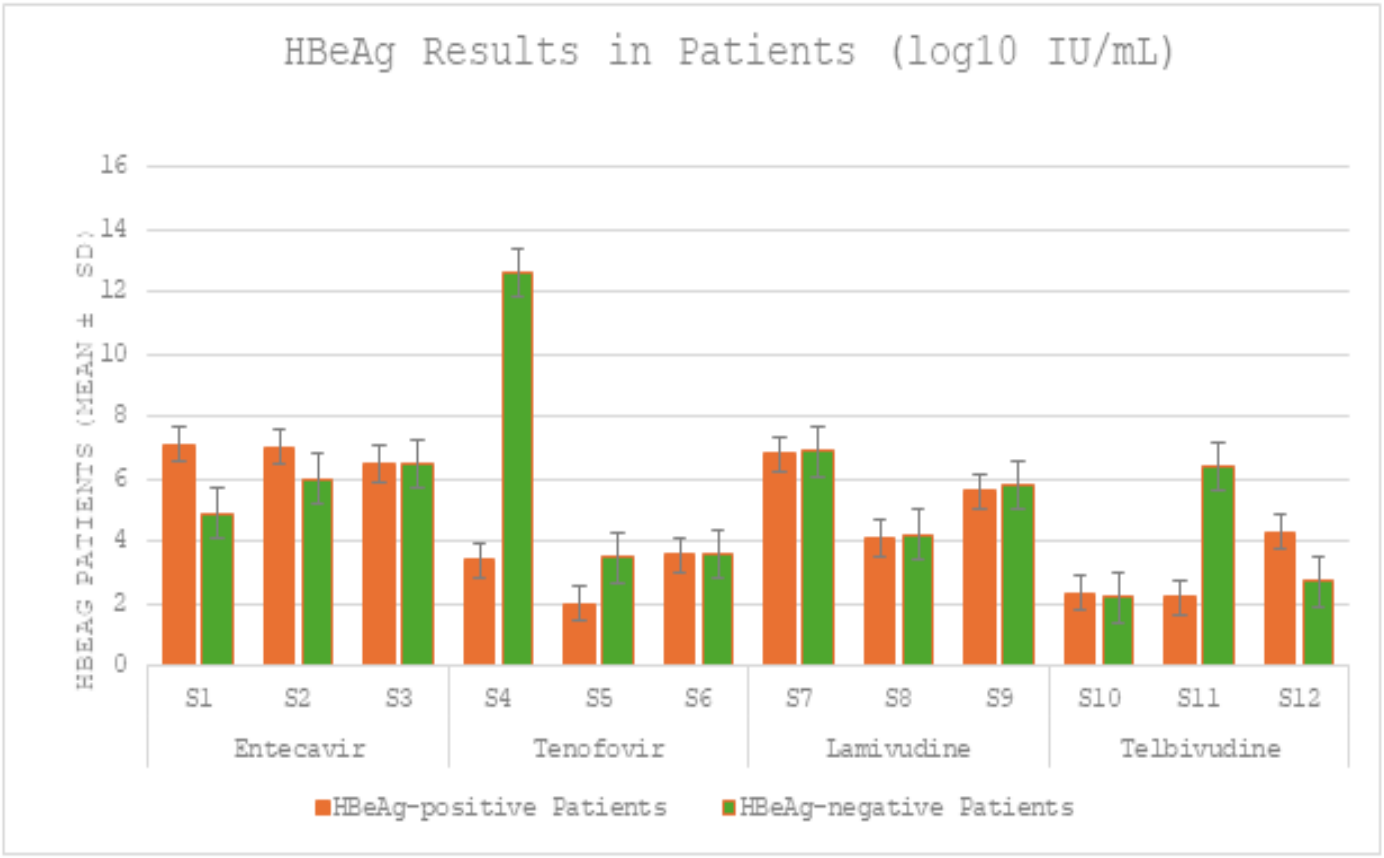

Fig. 7 . HBeAg-Positive and Negaive Results in Patients Treated with Specific Oral Therapies (See Discussion)

D. Patients Baseline Characteristics

Table 4. Efficacy of Four Oral Antiviral Therapy across Four Vital Outcome/Factor

Outcome	***Entecavir***			***Tenofovir***			***Lamivudine***			***Telbivudine***		
	S1	**S2**	**S3**	**S4**	**S5**	**S6**	**S6**	**S8**	**S9**	**S10**	**S11**	**S12**
Viral Suppression	91	94.4	99.4	77	91	93.8	65.3	73.1	84.9	96.6	96.5	61.2
Liver Function Improvement	88.5	89.4	99.5	68.3	86	66.3	63.1	63.6	81.2	85.3	85.2	79.2
HBeAg Seroconversion	27.4	28.2	40.2	4.7	12	4.1	0	40.4	28	29.8	46.4	22.1
HBsAg Loss	1	0	1.6	15.3	16	21	17	26	4.2	18.2	21.7	31.1

Values are presented as percentage. HBeAg, Hepatitis B e-Antigen; HBsAg, Hepatitis B surface antigen

Table 4 compares the efficacy of four substances (Entecavir, Tenofovir, Lamivudine, and Telbivudine) across four outcomes (Viral Suppression, Liver Function Improvement, HBeAg Seroconversion, and HBsAg Loss) from the relevant studies. The table provides a comprehensive overview of how these substances perform in relation to the specified outcomes.

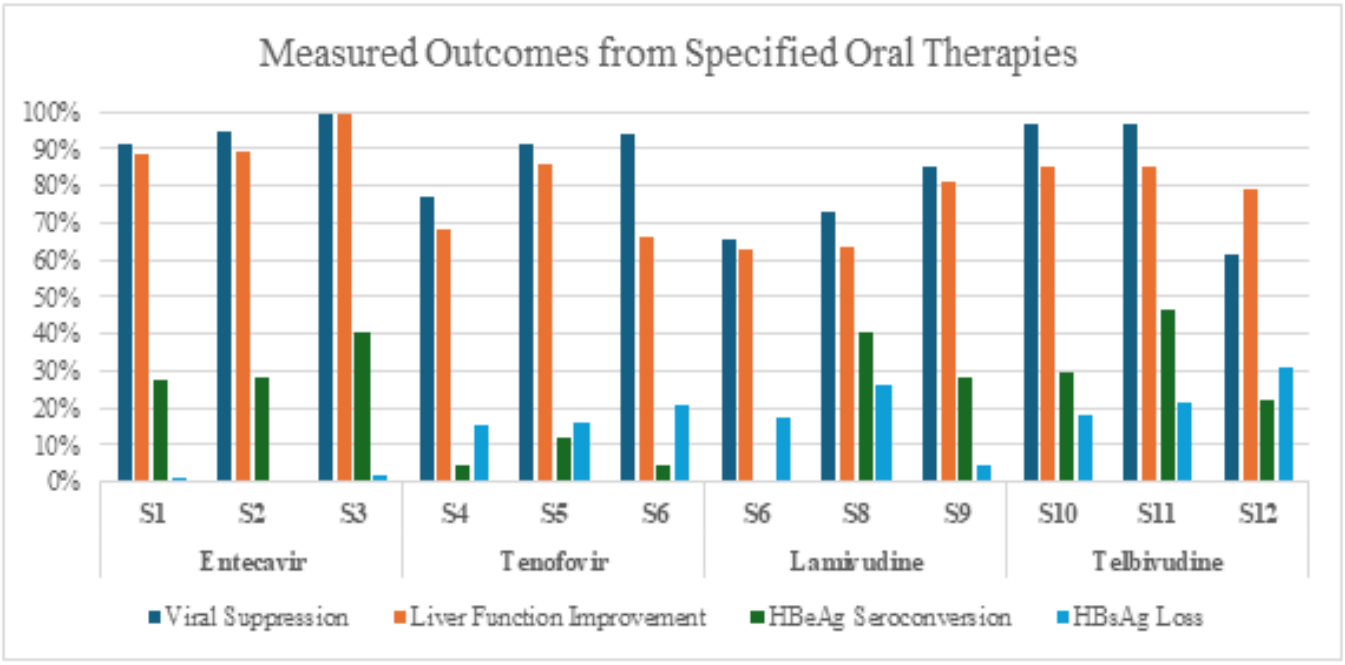

Fig. 7 . Measured Outcomes from Specified Oral Therapies (See page for Discussion)

IV. DISCUSSION

A. Antiviral Drugs Evaluated

➢ *Entecavir.*

Three studies on the effect of entecavir have been evaluated with a dose of 0.5 mg/day over a period of three to five years. In study 1, the incidence of adverse effects was low. Two patients developed mild hypersensitivity responses but improved within two weeks with the help of topical steroids and antihistamines. However, four patients were diagnosed with small hepatocellular carcinoma after twelve to thirty-six months of entecavir therapy. In study 2, viral breakthrough was observed in 13% of patients on entecavir therapy and one patient was found to be resistant to entecavir. Two patients then had ALT flares, one of whom also had developed entecavir resistance. 6.5% of subjects had transient hypophosphatemia and two cases of hepatocellular carcinoma were reported following an excess of 6 months of entecavir therapy. Then in study 3, some patients discontinued treatment but not due the treatment. Entecavir was well tolerated with no severe adverse events reported. To sum up the three studies, the 0.5 mg/day dosed entecavir therapy for a period of 3 to 5 years shows the positive results of the drug. However, in study 1 and 2, patients developed hepatocellular carcinoma following treatment suggesting a possible long-term complication of the treatment.

➢ *Tenofovir.*

Three separate studies ranging in durations between one year and just below three years have been conducted to evaluate the antiviral efficacy and safety of Tenofovir disoproxil fumarate (TDF) given in a dose of 300mg per day. Study 1 was conducted for a total of 2.76 years during which 58.7% of patients experienced adverse events (AEs). Among the most common AEs observed include raised blood creatine phosphokinase levels and upper respiratory tract infections. The study had also reported cases of transient hypophosphatemia and elevated creatine phosphokinase levels in one patient who stopped TDF therapy due to adverse events indicating good tolerance in other patients on longer therapy. Under Study 2, covering a period of one year, the antiviral activity was very satisfactory, given that all the 33 patients achieved sustained viral response without any breakthroughs. Such adverse events as dosages related severe adverse effects, poisoning, or death were not documented during TDF monotherapy. This shows TDF was effective and safe even with shorter times with minimal toxicity on the renal system. Study 3, which also spanned a year, did not consider any of the reported serious adverse events in relation to TDF. To sum up, Tenofovir at a dosage of 300 mg daily shows uniform antiviral activity with tolerable side effects over short and prolonged treatment periods. Serious adverse events such as HCC and deaths were uncommon and mostly unrelated to TDF, which further demonstrates its safety. These data support the use of TDF, an efficacious and safe long-term suppressive antiviral therapy for the majority of patients, with infrequent, mild side effects, and a low risk of significant renal and hepatic toxicity.

➢ *Lamivudine.*

The three studies assessed for the efficacy of Lamivudine have a dosage of 100 mg/day all in 2 years. In study 1, out of 45 patients included none of it showed significant side effects on lamivudine treatment. And in study 2, most of the adverse events the patients experienced were not related to lamivudine treatment. While in study 3, in the same duration of treatment and dosage as the first two studies, study 3 shows a genetic mutation in 53% of patients on lamivudine therapy. 14 patients with genetic mutations were with viral breakthrough and 1 was without any viral breakthrough. These data of genetic mutations which is

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developing a drug resistant indicates a small percentage of efficacy of lamivudine

- *Telbivudine.*

Three studies on Telbivudine treatment have been assessed over a 2-year period with the same dosage of 600 mg/day. In study 1, side effects experienced dizziness, trouble sleeping, and change in taste, while the other experienced muscle-related complaints. Out of the 116 patients, 7.8% indicates that with a low rate of adverse events, telbivudine is generally well tolerated.

In study 2, the efficacy of telbivudine was compared to entecavir. The M204I mutation has led to twenty-seven patients developing resistance to telbivudine at different times. Then in study 3, importantly, out of the 7 patients, 6 of it has been resolved and the other 1 has improved peripheral neuropathy. In summary, telbivudine treatment of 600mg/day in 2 years showed its efficacy in different studies. A small percentage of people who experienced adverse events in study 1 indicated that telbivudine is generally tolerated. Also, the serious adverse events experienced in study 3 have been resolved and improved. While on study 2, it indicates that telbivudine is effective, yet entecavir is more effective to it.

B. Baseline Characteristics of Patients

Table 3 showed that HBeAg-positive patients treated with Tenofovir demonstrate notably lower baseline ALT levels (46.9 ± 49.8 U/L) and a decreased viral load (3.4 ± 1.4 log10 IU/mL). This suggests that Tenofovir may be more appropriate for patients experiencing mild to moderate liver inflammation and lower rates of viral replication. Although beneficial for certain patients, Tenofovir is often not the first choice for those with high viral loads or severe liver disease because of its considerable resistance issues. Patients who are HBeAg-positive and receiving Entecavir therapy show moderate ALT levels (68.1 ± 64.1 U/L) and relatively high viral loads (7.1 ± 1.5 log10 IU/mL), indicating that Entecavir is suitable for those experiencing active viral replication with moderate liver inflammation.

In contrast, Entecavir and Telbivudine had elevated ALT levels, with mean values of 155 ± 168 IU/L and 154.7 ± 292.3 U/L, respectively. These higher ALT levels indicate that individuals taking these medications may have had more considerable liver inflammation at baseline, implying that they were utilized in cases of more active liver disease or severe liver involvement. HBeAg-positive individuals generally show active viral replication, leading to elevated ALT levels, and the choice of Entecavir and Telbivudine in such situations might stem from their potent antiviral effectiveness in quickly reducing viral load and controlling inflammation. Nevertheless, although Entecavir has a minimal resistance profile, Telbivudine presents a greater risk of resistance development, which restricts its long-term usefulness, even though it is initially effective in high-ALT situations.

Patients treated with Entecavir who are HBeAg-negative also exhibit elevated ALT levels (154.7 ± 292.3 U/L) but face an increased risk of developing drug resistance. This resistance constraint suggests that Entecavir could be effective at first in lowering viral load and controlling inflammation, although it is typically not recommended for long-term treatment unless used with other medications. Notably, HBeAg-negative patients treated with Tenofovir show reduced ALT levels (46.9 ± 49.8 U/L) alongside the highest viral load (12.6 ± 2.91 log10 IU/mL), suggesting that Tenofovir may be effective in scenarios with elevated viral replication while maintaining controlled ALT levels. This reduced ALT level may indicate milder liver inflammation or an immune-tolerant phase of disease in these HBeAg-negative patients, but the elevated viral load still requires treatment to avert additional liver harm.

HBeAg-negative individuals show varying treatment implications based on their ALT levels and viral loads. In patients receiving Entecavir, ALT levels are still high (155 ± 168 IU/L), indicating that Entecavir works well in situations of considerable liver inflammation, even in the absence of HBeAg, which may suggest ongoing immune activity or advancing disease. The elevated baseline viral load in HBeAg-negative Entecavir patients (6.0 ± 1.0 log10 IU/mL) corresponds to its potent antiviral efficacy, rendering Entecavir appropriate for individuals with severe liver inflammation, irrespective of HBeAg status.

On the other hand, patients treated with Lamivudine exhibit moderate ALT levels (74.4± 94.7 U/L) and viral loads (6.88 ± 0.62 log10 IU/mL), making this treatment suitable for those experiencing moderate inflammation and requiring effective, long-term viral suppression because of its low resistance characteristics. This intermediate ALT indicates that Lamivudine is appropriate for patients who do not show significant liver inflammation but still need ongoing control of viral replication.

C. Outcomes Measured

Viral suppression is a fundamental goal in chronic hepatitis B treatment, which minimizes the risk of liver disease development. As per the data shown in the table, Entecavir is remarkably effective with the highest rates of viral suppression reaching up to 99.4%, which proves its efficiency in suppression of viral reproduction. Tenofovir also has high ranges of viral suppression between 77%-93.8%, hence making it an effective drug as well. On the opposite side though, Lamivudine shows relatively lower rates of viral suppression, ranging rightfully from 65.3% to 84.9%, and thus revealing that it might be less efficient in controlling the virus completely relative to Entecavir and Tenofovir. Telbivudine has some fluctuations in terms of viral suppression with figures ranging between 61.2%-96.5%, showing it can be useful although the results vary more across the studies.

Improved liver function has been linked to fewer disease consequences and higher overall patient health, making it another important metric. Entecavir yet again exhibits superior performance in this regard, with the rates of liver function improvement ranging from 88.5% to 99.5%, thus confirming its position as a healthy treatment in improving liver conditions for people with chronic Hepatitis B. Tenofovir in this case has a low improvement in liver function, improvement rates range between 63.1% and 68.3% and Lamivudine has a similar range of 63.6% to 81.2%. Telbivudine (S10-S12) shows, however, good improvement rates of liver function, between 79.2% and 85.3%, still generally lower than Entecavir, however. These results suggest that although Entecavir appears to offer the greatest degree of improvement in liver function, Lamivudine and Telbivudine have their advantages too, while Tenofovir is somewhat less potent in this regard.

HBeAg seroconversion (conversion to a less infectious state) is a significant milestone in hepatitis B treatment because it indicates a shift to a less active form of the virus, potentially lowering the risk of transmission. The rates of seroconversion achieved with entecavir are modest, within the figures of 27.4% and 40.2%, which indicates that the drug can serve this purpose but may not be the best option available. On the other hand, only a tiny percentage of subjects treated with tenofovir developed seroconversion; this reached up to 4.7%, which would imply that it is not very effective when it comes to achieving this particular goal. In the case of lamivudine, it has been shown that quite significant levels of seroconversion are possible, amounting up to 40.4%. This illustrates the effectiveness of this drug when it comes to seroconverting patients. A performance acceptable for this purpose is also demonstrated by telbivudine, where seroconversion rates are as high as 46.4%, therefore making it suitable for patients in whom seroconversion is a treatment objective.

In addition, HBsAg loss is regarded an important predictor of viral clearance, as it may signify a more definitive reduction in the virus. Entecavir is noted to have very low rates of HBsAg loss, reported to span between 0% and 1.6%. This indicates that this drug may not be the optimal agent in pursuit of this result. In the opposite case, Tenofovir has reported much higher rates of HBsAg loss of 15.3% and 21% thereby confirming its efficacy in this regard. Lamivudine also has varying HBsAg loss rates with the maximum loss being 26%, thus exhibiting some degree of effectiveness but not as balanced. Telbivudine, however, achieves the highest HBsAg loss rates among the four drugs, with results up to 31.1%, making it a promising option for patients aiming for a more definitive viral clearance.

To sum up, the information presented in this table demonstrates the advantages and disadvantages of every antiviral treatment. Entecavir is an excellent option for managing hepatitis B and improving liver health because of its high efficacy in suppressing viruses and improving liver function. Although tenofovir is less successful at HBeAg seroconversion, it also performs exceptionally well at viral suppression and has significant potential for HBsAg reduction. The effectiveness of Lamivudine and Telbivudine varies; although Telbivudine shows high rates of both HBeAg seroconversion and HBsAg loss, Lamivudine showed strength in seroconversion and moderate viral suppression. This detailed information enables physicians to customize treatment plans according to the clinical objectives of each patient, weighing the available medicines against the desire for viral suppression, liver improvement, seroconversion, or HBsAg loss.

V. CONCLUSION

This systematic review examined the efficacy and associated outcomes of four oral antiviral therapies (entecavir, tenofovir, lamivudine, and telbivudine) for achieving sustained viral suppression in adults with chronic hepatitis B. The review analyzed twelve studies conducted in Asia, revealing that all four drugs demonstrated varying degrees of efficacy in achieving viral suppression, improving liver function, and inducing HBeAg seroconversion and HBsAg loss. Entecavir consistently exhibited superior performance in viral suppression and liver function improvement, while tenofovir demonstrated higher HBsAg loss rates. Lamivudine showed moderate efficacy in viral suppression and HBeAg seroconversion, and telbivudine displayed a notable ability to induce both HBeAg seroconversion and HBsAg loss. However, it's important to note that telbivudine also exhibited a higher risk of developing drug resistance. The findings suggest that the choice of antiviral therapy should be tailored to the individual patient's clinical characteristics and treatment goals, considering factors such as viral load, liver function, and the desired outcome. Further research is needed to investigate the long-term efficacy and safety of these therapies, particularly in relation to drug resistance and potential adverse effects.

REFERENCES

[1]. Buti, M. (MD), Riveiro-Barciela, M. (MD,PhD), & Esteban, R. (MD) (2021). Treatment of Chronic Hepatitis B Virus with Oral Anti-Viral Therapy. *Clinics in Liver Disease*. 1089-3261/21. https://doi.org/10.1016/j.cld.2021.06.003

[2]. Cho, J., Sohn, W., Sinn, D., Gwak, G., Paik, Y., Choi, M. S., Koh, K. C., Paik, S. W., Yoo, B. C., & Lee, J. H. (2016). Long-term real-world entecavir therapy in treatment-naïve hepatitis B patients: base-line hepatitis B virus DNA and hepatitis B surface antigen levels predict virologic response. The Korean Journal of Internal Medicine, 32(4), 636–646. https://doi.org/10.3904/kjim.2016.096

[3]. Kayaaslan B., & Guner R. (2017) Adverse effects of oral antiviral therapy in chronic hepatitis B. *World J Hepatol* 2017; 9(5): 227-241 https://dx.doi.org/10.4254/wjh.v9.i5.227

[4]. Liang, X., Cheng, J., Sun, Y., Chen, X., Li, T., Wang, H., Jiang, J., Chen, X., Long, H., Tang, H., Yu, Y., Sheng, J., Chen, S., Niu, J., Ren, H., Shi, J., Dou, X., Wan, M., Jiang, J., . . . Hou, J. (2014). Randomized, three-arm study to optimize lamivudine efficacy in hepatitis B e antigen-positive chronic hepatitis B patients. *Journal of Gastroenterology and Hepatology*, *30*(4), 748–755. https://doi.org/10.1111/jgh.12835

[5]. Liang, X., Xie, Q., Shang, J., Tang, H., Xu, M., Meng, Q., Zhang, J., Gao, P., Sheng, J., Wang, H., Jia, J., Wang, G., Wu, S., Ping, J., & Hou, J. (2021). Tenofovir disoproxil fumarate for multiple nucleos(t)ide analogues treatment failure hepatitis B: Is monotherapy enough? *Journal of Gastroenterology and Hepatology*, *37*(3), 471–479. https://doi.org/10.1111/jgh.15757

[6]. Lim, Y., Lee, Y. S., Gwak, G., Byun, K. S., Kim, Y. J., Choi, J., An, J., Lee, H. C., Yoo, B. C., & Kwon, S. Y. (2017). Monotherapy with tenofovir disoproxil fumarate for multiple drug-resistant chronic hepatitis B: 3-year trial. *Hepatology*, *66*(3), 772–783. https://doi.org/10.1002/hep.29187

[7]. Sriprayoon, T., Mahidol, C., Ungtrakul, T., Chun-on, P., Soonklang, K., Pongpun, W., Laohapand, C., Dechma, J., Pothijaroen, C., Auewarakul, C., & Tanwandee, T. (2016). Efficacy and safety of entecavir versus tenofovir treatment in chronic hepatitis B patients: A randomized controlled trial. Hepatology Research, 47(3). https://doi.org/10.1111/hepr.12743

[8]. Srivastava, M., Singh, N., Dixit, V. K., Nath, G., & Jain, A. K. (2016d). Comparative evaluation of long-term monotherapies & combination therapies in patients with chronic hepatitis B: A pilot study. *The Indian Journal of Medical Research*, *144*(3), 424. https://doi.org/10.4103/0971-5916.198674

[9]. Sun, J., Xie, Q., Tan, D., Ning, Q., Niu, J., Bai, X., Fan, R., Chen, S., Cheng, J., Yu, Y., Wang, H., Xu, M., Shi, G., Wan, M., Chen, X., Tang, H., Sheng, J., Dou, X., Shi, J., . . . Hou, J. (2014). The 104-week efficacy and safety of telbivudine-based optimization strategy in chronic hepatitis B patients: A randomized, controlled study. *Hepatology*, *59*(4), 1283–1292. https://doi.org/10.1002/hep.26885

[10]. Tsai, M., Chen, C., Hung, C., Lee, C., Chiu, K., Wang, J., Lu, S., Tseng, P., Chang, K., Yen, Y., & Hu, T. (2013). A comparison of efficacy and safety of 2-year telbivudine and entecavir treatment in patients with chronic hepatitis B: a match–control study. *Clinical Microbiology and Infection*, *20*(2), O90–O100. https://doi.org/10.1111/1469-0691.12220

[11]. Wang, C., Lin, C., Hsieh, T., Tseng, K., Peng, C., Su, T., Yang, S., Hsu, Y., Chen, T., & Kao, J. (2015). Efficacy and resistance to telbivudine treatment in chronic hepatitis B patients with favorable predictors: a multicenter study in Taiwan. *Hepatology International*, *10*(2), 294–301. https://doi.org/10.1007/s12072-015-9662-9

[12]. Xie, Y., Ma, H., Feng, B., & Wei, L. (2017). Efficacy of Real-world Entecavir Therapy in Treatment-naïve Chronic Hepatitis B Patients. Chinese Medical Journal, 130(18), 2190–2197. https://doi.org/10.4103/0366-6999.213969

[13]. Yue-Meng, W., Li, Y., Wu, H., Yang, J., Xu, Y., Yang, L., & Yang, J. (2016b). Telbivudine versus lamivudine and entecavir for treatment-naïve decompensated hepatitis B virus-related cirrhosis. *Clinical and Experimental Medicine*, *17*(2), 233–241. https://doi.org/10.1007/s10238-016-0420-7

[14]. Zhou, J., Liu, Y., Lian, J., Pan, L., Yang, J., & Huang, J. (2017). Efficacy and Safety of Tenofovir Disoproxil Treatment for Chronic Hepatitis B Patients with Genotypic Resistance to Other Nucleoside Analogues. *Chinese Medical Journal*, *130*(8), 914–919. https://doi.org/10.4103/0366-6999.204107