Determine the Efficacy and Side Effects of Tenofovir Alafinamide and Tenofovir Disoproxil Fumarate in Patients with Hepatitis B Infection

Attique Abou Bakr,[1] Azhar Hussain,[2] Amtiaz Ahmad,[3] Shahbaz Ahmed[4]

Abstract

Objective: To determine the efficacy and side effects of tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF) in patients with Hepatitis B infection.

Material and Methods: The study design was Observational study using Non-Probability Purposive Sampling. The study was conducted in the Hepatitis Clinic, Jinnah Hospital, Lahore. The duration was February 01, 2020 – March 09, 2024A total of 114 patients were enrolled and monitored for 144 weeks. Patients were randomized into two groups using a double-blind methodology: A total of 57 patients were assigned to receive TDF (Group A), and an equal number received TAF (Group B). Demographic details, treatment efficacy (defined as HBV DNA < 29 IU/ml), and safety outcomes were recorded.

A total of 114 patients were randomized into two groups: 57 received TDF (Group A) and 57 received TAF (Group B). Patients were monitored for 144 weeks. Outcomes were analyzed using SPSS version 24.0, with t-tests and Chi-square tests ($p < 0.05$)

Results: The mean age was 49.32 ± 22.87 years in Group A and 48.14 ± 23.02 years in Group B (P = 0.89). Treatment efficacy was achieved in 38 (66.7%) cases in Group A and 32 (56.1%) in Group B (P = 0.33). At 144 weeks, 78.1% of Hepatitis B e antigen (HBeAg)-positive and 88.2% of HBeAg-negative patients in Group A had HBV DNA < 29 IU/ml, compared to 82.75% and 92.8% in Group B. Group B showed a significantly lower decline in estimated glomerular filtration rate (eGFR) (≥ 25% at week 144) compared to Group A (8.77% vs. 24.56%; P = 0.042).

Conclusion: TAF demonstrated comparable efficacy to TDF with improved renal and bone safety over 144 weeks.

Keywords: Hepatitis B, Tenofovir alafinamide, Tenofovir disoproxil

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Introduction

Since its discovery in the late 90s, hepatitis B virus (HBV) has infected over 350 million individuals across the globe.[1] Major morbidities of HBV include chronic hepatitis, hepatitis decompensation and liver cancer.[2] Every year, over a million people die due to this virus related complications.[3] Most people infected with hepatitis B are chronic carriers,[4] indicating the infection's continuity, positive HBsAg in blood and the presence of HBV DNA in liver cells. 15–40% of HBV carriers develop liver cancer. The prevalence of chronic HBV disease varies greatly from one part of the world to other. Most of the susceptible people contract the infection via percutaneous or sexual transmission.[5,6]

Tenofovir disoproxil fumarate (TDF) is a popular nucleotide antiretroviral therapy (ART) that can treat

1,3,4. Department of Gastroenterology, Allama Iqbal Medical College, Lahore.

2. Department of Gastroenterology, Services Institute of Medical Sciences, Lahore.

Correspondence:
Dr Azhar Hussain, *Associate Professor of Gastroenterology, Medical unit 4, SIMS, Lahore, Pakistan. E-mail: drazhar163@yahoo.com*

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and prevent transmission of HIV and hepatitis B. Despite its tolerability, TDF has two main drawbacks: reduction in bone mineral density and nephrotoxicity. Compared to TDF, tenofovir alafenamide (TAF), a newer prodrug form, converts into tenofovir diphosphate, which is used in the treatment of HBV and HIV. It has higher intracellular concentrations.[6] Since HBV cannot be eradicated entirely, the goal of the drug treatment is to pace down the disease progression and save lives by interrupting the chain of HBV replication. TDF treatment, in both treatment-experienced and treatment-naive cases, has been shown to be highly effective and has a positive safety profile, with concomitant fibrosis regression, decrease in viral load and no emergence of drug resistance.[7]

The rationale of this research was to evaluate the efficacy and safety profile of TAF and TDF as no data was available in this context in Pakistani Population and both of these drugs were available and prescribed to hepatitis B infected patients in Hepatitis clinic of Jinnah Hospital, Lahore. If the findings of this trial turn out to be substantial, we may be able to use TAF as a first-line medication for treating hepatitis B infection in all of these patients. This may help lower mortality and morbidity from this serious but curable illness.

Material and Methods

After approval from hospital ethical committee (64th/ERB.), this study employed Non-Probability Purposive sampling. A total of 114 patients from the Hepatitis Clinic, Jinnah Hospital, Lahore, were enrolled between February 01, 2020, and February 21, 2021, and followed for 144 weeks until March 09, 2024. The sample size, with a 95% confidence interval and 80% power, was calculated based on expected efficacy rates of 83% for Tenofovir disoproxil fumarate (TDF) and 67% for Tenofovir alafenamide (TAF).

Following formula used to calculate.[8]

$$n = \frac{z_{1-a/2}\sqrt{2\bar{P}(1-\bar{P})} + z_{1-p}\sqrt{P1(1-P_1) + P_2(1-P_2)}}{(P_1 - P_2)^2}$$

$Z_{1-\alpha/2} = 95\% = 1.96$

$Z_{1-\beta/2} = 80\% = 0.80$

$P_1 = 83\% = 0.83$

$P_2 = 67\% = 0.67$

$P = P_1 - P_2$

Patients aged 25-70 years with Chronic HBV (HBV DNA >2000 IU/ml, ALT >40 IU/ml) and non-cirrhotic or compensated cirrhosis were included (Child Pugh score 5 and 6, having APRI score <1.5). Randomization was done using sealed envelopes, assigning fifty-seven (57) patients each to either Group A (TDF 300mg daily) or Group B (TAF 25mg daily). Treatment efficacy was defined as achieving HBV DNA levels <29 IU/mL, HBeAg loss or seroconversion, and HBsAg loss or anti-HBs appearance at 48 and 144 weeks. Safety outcomes included renal function decline (≥ 25% reduction in eGFR from baseline at week 144) and bone safety (changes in lumbar spine bone mineral density and incidence of osteoporosis or osteopenia). HBeAg-positive status indicated detectable serum Hepatitis B e antigen, while HBeAg-negative status indicated undetectable levels. Adverse effects, including nasopharyngitis, fatigue, and changes in renal or hepatic markers, were documented during the study.

Exclusion criteria included other liver disease etiologies, pregnancy, stage IV CKD, decompensated cirrhosis, severe anaemia (Hb <8 mg/dl), and severe side effects. Efficacy was assessed by achieving HBV DNA <15 IU/ml, HBeAg loss/seroconversion, and HBsAg loss/Anti-HBs appearance at weeks 48 and 144.

During study, 2 patients of Group A and 1 patient of Group B having HBeAg+ disease were excluded due to loss of Follow up; and 1 patient of Group A and 2 patients of Group B having HBeAg- disease were excluded from study for the same reason. Intention to treat Analysis and Perprotocal Analysis were formed.

Based on the Chronic Liver Disease Questionnaire (CLDQ), we have created our own survey. The CLDQ is a validated questionnaire that is specific to CLD and can be used to assess quality of life in this population. The chron bach's alpha value of this questionnaire, which has been pretested in international research, is 0.8. It covers a total of 29 elements, including anxiety, emotional function, systemic symptoms, activity, lack of energy, and digestive problems. A 7-point scale, ranging from "always" to "never," was generated from the CLDQ findings, covering the range of potential CLDQ answers.[9]

SPSS version 24.0 was used for data analysis. Qualitative variables were evaluated using percentages and frequencies, and treatment outcomes were compared using the Chi-square test. Quantitative data were analyzed using

mean, standard deviation, and Independent Student t-test, The independent sample t-test was used to compare means between the two groups as they were randomized and independent, with continuous data assumed to follow a normal distribution with a p-value of <0.05 considered statistically significant.

Results

In Group A, the mean age was 49.32 ±22.87 years, while in Group B, it was 48.14 ± 23.02 years (P=0.89) as shown in Table 1. Table 2 (a) and (b), show efficacy at 48 and 144 weeks. At 48 weeks, in Group A, primary end point was achieved in 38(66.6%) cases and in 32 (56.1%) cases in Group B (p-value=0.25). And the overall efficacy of both groups was seen in 70 patients (61.4%). In group A ,78.1% HBeAg positive and 88.2% of HBeAg negative patients had HBV DNA <15IU/ml at 144week while in group B,82.75% HBeAg positive and 92.8% HBeAg negative patients had this response at 144 weeks. So the efficacy was marginally comparable in both groups. In Intention to Treat Analysis, 62.5% (20/32) HBeAg+ patients and 72%(18/25) HBeAg- patients in Group A got primary end point at 48 weeks while 78.1%(25/32) HBeAg+ patients and 88% (22/25) HBeAg-patients got primary end point at 144 weeks. In Group B, as per Intention to Treat Analysis, 55.1% (16/29) HBeAg+ patients and 57.1%(16/28)HBeAg-patients got primary end point at 48 weeks while 82.7% (24/29) HBeAg+ patients and 89.28% (25/28) HBeAg-patients got primary end point at 144weeks. As per Per protocal Analysis, 66.6%(20/30)HBeAg+ patients and 75%(18/24)HBeAg- patients in Group A got primary end point at 48 weeks while 83.3%(25/30) HBeAg+ patients and 91.6%(22/24)HBeAg-patients got primary end point at 144weeks. In Group B, as per Protocal Analysis, 57.1%(16/28)HBeAg+ patients and 61.5% (16/26) HBeAg- patients got primary end point at 48 weeks while 85.7%(24/28) HBeAg+ patients and 96.1% (25/26) HBeAg-patients got primary end point at 144weeks. By week 144, the eGFRCG of patients treated with TAF had fallen by 4.6 ±11.42 , while in TDF group it had decreased by 9.34 ±15.04 (p = 0.06) as shown in

Table 3: *Baseline Demographic and Clinical Characteristics of the Study Population, Stratified by Treatment Groups (TDF vs. TAF)*

Variable		Group A (TDF,n=57)	Group B (TAF,n=57)	P value
Age (years) mean ± SD		49.32 ±22.87	48.14 ± 23.02	0.89
Male (n [%])		41 (71.9%)	36 (63.2%)	0.42
Mean BMI (kg/m2 [SD])		23.74 ± 2.12	23.18 ± 2.14	0.16
Mean HBV DNA (log10 IU/mL [SD])		5.39 ± 0.93	5.31± 1.07	0.65
ALT		70.38 ± 17.77	71.24± 17.27	0.79
HBeAg status	Positive	32	29	
	Negative	25	28	0.70
History of cirrhosis	Non cirrhotic	46(80.7)	42 (73.7)	
	Child A	11(20.3)	15 (26.3)	0.36
Mean eGFR by Cockcroft-Gault		110.28 ±7.36	111.91 ±9.97	0.32
High Cholesterol levels		4	3	1.0
Heart disease		6	4	0.74
High Blood pressure		18	13	0.4
Diabetes mellitus		20	18	0.84
Lumbar spine BMD clinical status	Normal (T score ≥ −1.0)	31 (54.38%)	37 (64.91%)	
	Osteopenia / Osteoporosis	26(45.62%)	19 (33.34%)	033
	Status not determined	0	1 (1.75)	
Previous nucleos(t)ide use (n [%])	Any drug	21(36.84)	20(35.08)	
	Previous lamivudine (n [%])	9 (15.78)	10(17.54)	0.88
	Prior entecavir, n (%)	12(21.05)	10 (19)	

Note: p-values were calculated using the Independent Sample t-test for continuous variables and Chi-square test for categorical variables. All values represent pre-treatment baseline characteristics. A p-value <0.05 was considered statistically significant. Abbreviations: BMI – Body Mass Index; eGFR – estimated Glomerular Filtration Rate; ALT – Alanine Aminotransferase; AST – Aspartate Aminotransferase; HBeAg – Hepatitis B e Antigen.

Table 2: *Comparison of Treatment Efficacy Indicators Between TDF (Group A) and TAF (Group B) at 48 and 144 Weeks*

Treatment efficacy at 48 weeks							
Response indicators	**HBeAg-positive patients**		**HBeAg-negative patients**		**Group A (n %) =57)**	**Group B (n %=57)**	**P value**
	Group A (n% = 32)	**Group B (n%= 29)**	**Group A (n% = 25)**	**Group B (n% = 28)**			
(HBV DNA <15 IU/mL)	20(62.5%)	16(55.17%)	18(72%)	16(57.14%)	38(66.6%)	32(56.1%)	0.8
Loss of HBeAg	6(18.75%)	5(17.24%)	-	-	6	5	
Seroconversion of HBeAg	2(6.25%)	2(6.8%)	-	-	2	2	1
Loss of HBsAg loss	0	0	0	0	0	0	
Seroconversion of HBsAg	0	0	0	0	0	0	
ALT normalization by 2018 AASLD criteria	19(59.37%)	18(62.06%)	15(60%)	14(50%)	34	32	0.9
Treatment efficacy at 144 weeks							
Response Indicators	**HBeAg-positive patients**		**HBeAg-negative patients**				**P value**
	Group A (n%= 32)	**Group B (n% = 29)**	**Group A (n% = 25)**	**Group B (n% = 28)**			
HBV DNA <15 IU/mL	25 (78.1%)	24(82.75%)	22 (88.2%)	25 (92.8%)			0.79
Loss of HBeAg	9(28.1)	7(24.1)	–	–			0.78
Seroconversion of HBeAg	6(18.75)	6(20.6)	–	–			1.0
Loss of HBsAg	0	1(6.8)	0	1(3.5)			0.24
Seroconversion of HBsAg	0	1(3.4)	0	0			1.0
ALT normalization by 2018 AASLD criteria	21 (65.6)	23(79.3)	18(72)	22(78.57)			0.53

Abbreviations: AASLD – American Association for the Study of Liver Diseases; ALT – Alanine Aminotransferase; HBeAg – Hepatitis B e Antigen; HBsAg – Hepatitis B surface Antigen.

Table 3 . Furthermore, a lesser proportion of TAF-treated patients developed deterioration in their CKD stage. When the indicators of proximal tubular function (proteinuria, low molecular weight rather than albumin) were examined, substantial differences were discovered that favored TAF therapy. Table 3(b) presented the bifurcation of side effects in these groups. Figure 1 presents the graphical presentation (box and whisker graph) of age in years. Figure 2 presents the graphical representation of descriptive statistics of sex in all patients (male versus female). In addition, Figure 3 presents the descriptive statistics of overall side effects in both groups.

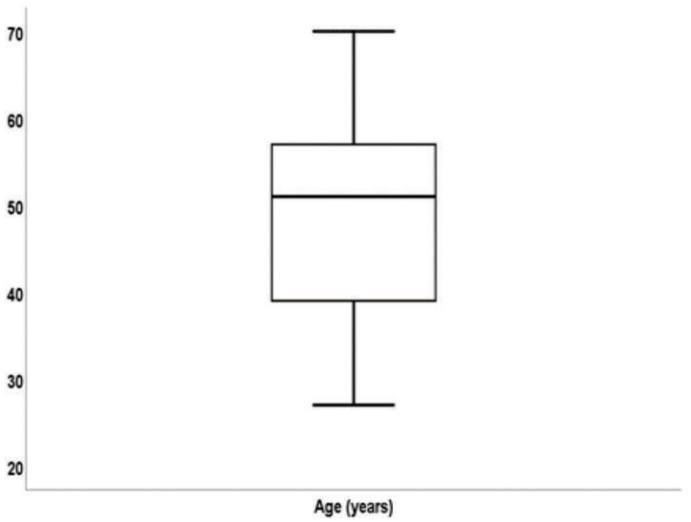

Figure 1: *Combined Graphical Representation of Baseline Descriptive Statistics, Including Gender and Age Distribution*

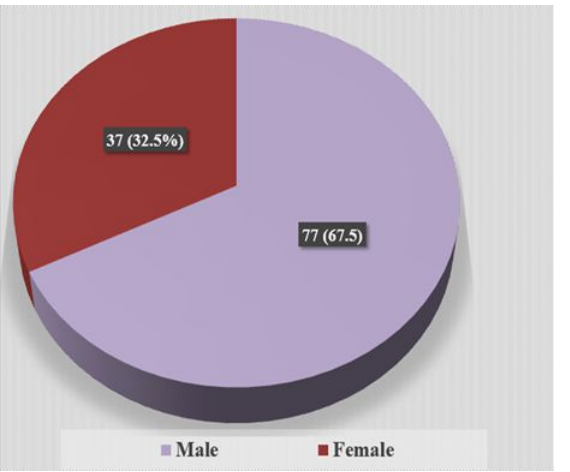

Figure 2: *Graphical presentation of descriptive statistics of sex*

Table 3: *Renal Parameters and Side effects in both treatment Groups*

Renal Parameters in both treatment Groups			
Renal Parameters	**Group A**	**Group B**	**P value**
Mean Serum Creatinine (mg/dL) ± SD			
Baseline	0.94 ±0.14	0.94 ±0.12	0.93
At 144weeks	1.03 ±0.21	0.98 ±0.13	0.13
Change at week 144	0.11 ±0.19	0.03 ±0.1	0.006
Mean eGFRCG (mL/min			
Baseline	110.19 ±7.21	112.03 ±9.7	0.25
At 144 weeks	100.88 ±15.10	107.56 ±13.89	0.016
Change at week 144	-9.34 ±15.04	-4.6 ±11.42	0.06
≥25% decrease from baseline in eGFRCG (n/n)	14/57 (24.56%)	5/57 (8.77%)	0.042
Shifts in CKD stage: baseline at week 144			
Worsening			
Stage 1 to 2	1/9 (11.1%)	1/11 (9%)	>0.9
Stage 2 to 3	0/6 (0%)	0/4 (0)	
Mean Urinary Proximal Tubular Markers (µg/g): Baseline and Week 144 Changes			
Proteinuria (low molecular weight)			
Baseline	93 ± 16.59	91 ±16.5	<0.001
At 144weeks	120 ±16.5	83 ± 16.59	
% change at week 144	27	–8	
Side effects in both treatment groups.			
Side effects	**Group A (n%=57)**	**Group B (n%=57)**	**P-value**
Naso-pharyngitis	12(21.05)	21(36.84)	0.11
Cough	5(8.7)	8(14.0)	0.37
Oropharyngeal Pain	6(10.5)	4(7.0)	0.74
Diarrhea	7(12.2)	6(10.5)	1.0
Abdominal pain/distension	6(10.5)	4(7.0)	0.49
Headache	7(12.2)	10(17.5)	0.6
Fatigue	6(10.5)	6(10.5)	1.0
Peripheral Neuropathy	6(10.5)	8(14.0)	0.77
UTI	7(12.2)	6(10.5)	1.0
Hepatic steotosis	6(10.5)	5(8.7)	1.0
Elevated Serum Amylas	6(10.5)	1(1.7)	0.11
Elevated PTH	6(10.5)	3(5.2)	0.49
Osteoporosis	6(10.5)	1(1.7)	0.11
Weight loss>5kg	7(12.2)	2(3.4)	0.16
Elevated ALT	8(14.0)	7(12.2)	1.0
Elevated AST	4(7.0)	2(3.4)	0.67
Increased ALT/AST	5(8.7)	9(15.7)	0.39
Increased CK	4(7.0)	4(7.0)	1.0
Increased LDH	0(0)	4(7.0)	0.11
Anemia	5(8.7)	1(1.7)	0.2
Urine Glucose(dips stick 4+)	1(1.7)	3(5.2)	0.61
Occult blood	12(21.0)	10(17.5)	0.81
Urine Erythrocytes	17(29.8)	12(21.0)	0.39
Proteinuria	9(15.7)	5(8.7)	0.39
Nausea	7(12.2)	2(3.4)	012

Abbreviations: eGFR – estimated Glomerular Filtration Rate; ALT – Alanine Aminotransferase; AST – Aspartate Aminotransferase; UTI – Urinary Tract Infection, PTH: Parathyroid hormone

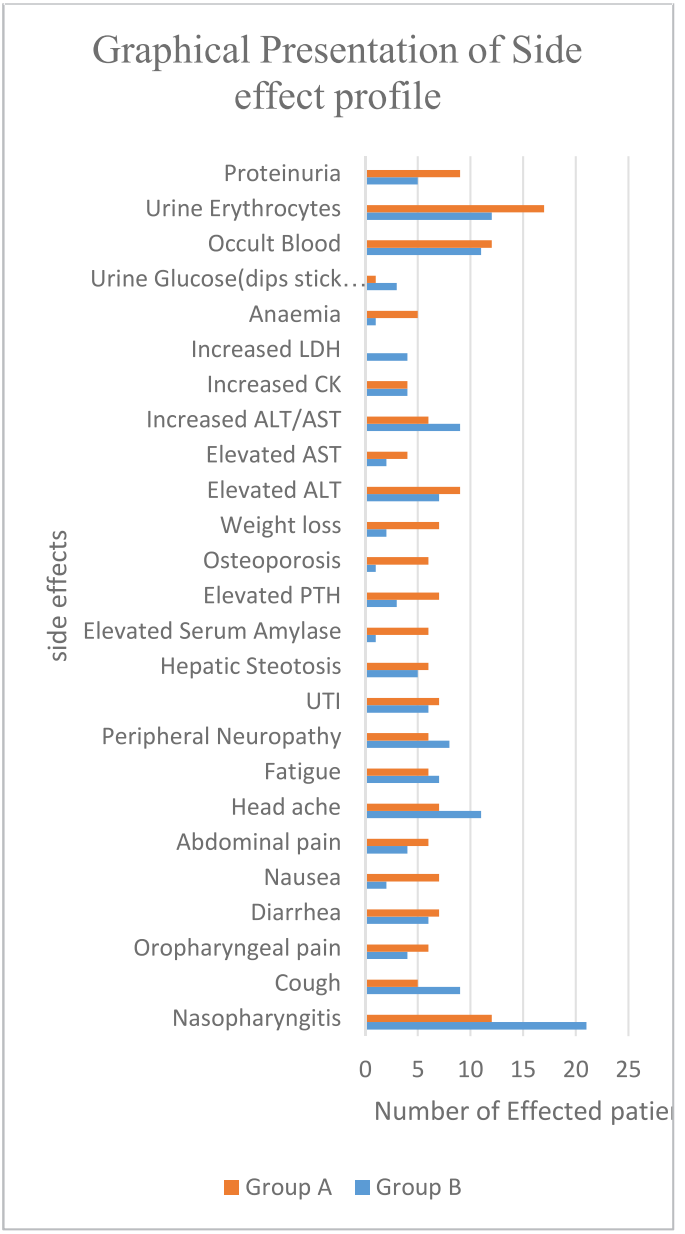

Figure 3: *Graphical presentation of descriptive statistics of side effects*

Discussion

This study concludes that there is no significant difference in efficacy between TDF and TAF, but TAF is safer regarding bone and renal parameters. Although the results were observed at 48 and 144 weeks, further research is needed to assess the long-term benefits of TAF over TDF. No statistically significant differences in treatment outcomes were found for subgroups defined by age, gender, baseline HBV DNA level, or prior antiviral medication history. Neither group developed resistance during the 144-week treatment.[10] While most patients in Group A showed normalized ALT levels,

unexpected outcomes require further exploration.[11] TDF is known to reduce cholesterol levels in HIV patients,[12-14] though its clinical significance is unclear. TAF is considered "lipid neutral" compared to TDF,[15,16] with higher LDL levels observed in TAF patients by week 48.[17,18] However, these differences were not clinically significant.

Safety outcomes in this study were consistent with existing literature.[19-20] The low proportion of patients at higher risk for TDF-associated renal and bone complications (e.g., those over 60 or with significant disease history) warrants further study.[21-22] Patients included had HBV DNA >2000 IU/mL and elevated ALT levels, making it unclear if those with viral suppression who switch from TDF to TAF would have similar safety or antiviral benefits.[23-24] Agarwal et al.[25] found similar viral suppression rates at week 48 for HBeAg-positive patients on TAF and TDF, with TAF showing better ALT normalization. By week 144, both drugs achieved comparable viral suppression, with slightly higher rates in TAF patients. ALT normalization was also higher in the TAF group, particularly among HBeAg-positive patients. HBeAg loss and anti-HBeAg seroconversion rates were compar-able between groups, though HBsAg loss and serocon-version were more frequent in the TDF group.[26]

Conclusion

In this study, Tenofovir alafenamide (TAF) demonstrated comparable efficacy to Tenofovir disoproxil fumarate (TDF) in suppressing HBV DNA levels at 48 and 144 weeks. However, TAF exhibited significantly better renal and bone safety profiles, with a lower incidence of renal function decline and fewer bone-related side effects. These findings suggest that TAF may be a preferable first-line therapy for chronic hepatitis B patients, particularly those at risk of renal or bone complications. Further large-scale and long-term studies are warranted to confirm these results and explore the broader applicability of TAF in diverse patient populations.

Conflict of Interest None

Funding Source None

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Authors Contribution

AAB: Conceptualization of Project
AAB, AA, SA: Data Collection
AAB, AH: Literature Search

AH, AA: Statistical Analysis

AAB: Drafting, Revision
AH, SA: Writing of Manuscript