Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/q6896466

SAFETY AND EFFICACY OF TENOFOVIR DISOPROXIL FUMARATE VERSUS TENOFOVIR ALAFENAMIDE IN THE TREATMENT OF CHRONIC HEPATITIS B: A HOSPITAL-BASED OBSERVATIONAL STUDY

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Abstract

Background:
While vaccination has lowered the rate of new infections, HBV still results in large number of new cases annually, particularly in the low and middle income countries. Both tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) are prodrugs of tenofovir approved for the treatment of chronic hepatitis B. The primary and secondary objective of the study was to compare the efficacy of TAF versus TDF and safety of the study drugs with respect to their impact on kidneys and bones, respectively.

Method:
A total of 104 patients with CHB were divided equally into two groups; group A received Tab. TDF 300mg once daily for 48wks and group B received Tab. TAF 25mg once daily for 48 weeks. All the cases were monitored 12-weekly up till 48 weeks. Efficacy was assessed in terms of virological, serological and biochemical responses. Safety was evaluated by assessing serum creatinine, serum urea and bone mineral density and any adverse drug reactions.

Results:
HBV-DNA levels and HBeAg status were comparable between the two groups at each follow-up. At 48 weeks, the average ALT levels and serum creatinine levels were significantly lower with TAF than TDF ($p < 0.05$). Bone mineral density tests performed on the hip and spine at 48 weeks revealed that the average BMD with TAF was significantly higher than TDF.

Conclusion: TAF is equally efficacious to the conventionally used TDF while additionally being significantly safer for kidneys and bones.

Keywords: ALT, bone mineral density, HBV-DNA, HBeAg, India

Introduction

Chronic hepatitis B (CHB) caused by the highly infectious hepatitis B virus (HBV) is a leading cause of liver cirrhosis, liver failure and hepatocellular carcinoma contributing to substantial mortality and morbidity globally. While vaccination has lowered the rate of new infections, HBV still results in large number of new cases annually, particularly in the low and middle income countries. The World Health Organisation (WHO) reported that in 2022, India had the second-highest number of hepatitis B cases, only behind China.[1] With a 2% to 4% prevalence rate of hepatitis in the general population, India is classified as an intermediate endemic region for HBV.[2]

The national guidelines for diagnosis and management of viral hepatitis (2018) recommend Tenofovir disoproxil fumarate (TDF), Entecavir and Tenofovir alafenamide fumarate (TAF) for the treatment of CHB in adults.[3] TDF was approved and has been used for treating CHB since 2008; however, its long-term use has been associated with kidney injury and reduction in the bone mineral density in certain individuals.[4] TAF, a novel lower dose prodrug was approved for the treatment of CHB in 2016.[5] Both TAF and TDF are phosphoramidate ester prodrugs of tenofovir (TFV) and share a common intracellular active metabolite, tenofovir diphosphate (TFV-DP). Numerous studies comparing TDF and TAF have been done on HIV patients; comparatively fewer studies have been done with CHB patients. Consequently, the number of studies comparing the two in the Indian population with CHB are limited. With this background, the current investigation was undertaken to evaluate the effectiveness of TDF versus TAF in patients with CHB in our setting, a tertiary care hospital in eastern India.

Materials and method

This two-year prospective, observational, hospital-based study was conducted in the Department of Pharmacology in collaboration with Department of Hepatology of S.C.B Medical College and Hospital, Cuttack from March 2020 to February 2022 with the aim to assess the safety and efficacy of TDF and TAF in patients suffering from CHB. The primary objective of the study was to compare the efficacy of TAF versus TDF in terms of HBV-DNA suppression, HBeAg negativisation, and ALT normalization. The secondary objective was to assess the safety of the study drugs with respect to their impact on kidneys and bones. Ethical approval was acquired from the Institutional Ethics Committee (ECR/84/Inst/OR/2013/IEC No. 869/14.10.2019) prior to the start of the study. Written informed consent was obtained from all the participants. The study was in line with the principles of Declaration of Helsinki. Confidentiality was maintained throughout the study.

Patients suffering from CHB attending or admitted in the Department of Hepatology, S.C.B Medical College and Hospital were screened and those who met the inclusion and exclusion criteria were included in the study. A case of CHB was defined as persistent HBV infection (presence of detectable hepatitis B surface antigen i.e. HBsAg in the blood or serum for atleast six months) with or without associated active viral replication and evidence of hepatocellular injury and inflammation.[6] Adult patients with positive HBsAg and altered serum ALT (alanine aminotransferases) levels (> 60 U/L in males or > 38 U/L in females) were included in the study regardless of the hepatitis e antigen (HBeAg) status and treatment status; both treatment-naive (defined as < 12 weeks of oral antiviral treatment with any nucleoside or nucleotide analogue) and treatment-experienced (defined as ≥ 12 weeks of previous treatment with any nucleoside or nucleotide analogue) patients were included in the study. Individuals with previous history or current evidence of clinical hepatic decompensation, hepatocellular carcinoma, co-infection with hepatitis C virus, HIV, or hepatitis D virus, treatment with interferon within six months, receiving concurrent therapy with corticosteroids or other

nephrotoxic drugs, pre-existing renal/ bone disease, aspartate aminotransferase levels greater than ten times the upper limit of normal or those with known hypersensitivity were excluded from the study.
A total of 104 participants were divided into two groups; group A (TDF group, n = 52) received Tab. Tenofovir Disoproxil Fumarate 300mg once daily for 48wks and group B (TAF group, n = 52) received Tab. Tenofovir Alafenamide 25mg once daily for 48 weeks (Figure 1). Data regarding demographic profile, brief medical history, clinical examination and relevant laboratory findings were noted at baseline. Contact details were recorded for further follow up. All the cases were monitored 12-weekly up till 48 weeks (1 year). Efficacy was assessed in terms of virological, serological and biochemical responses. Virological response was defined as complete viral suppression, shown by serum HBV DNA levels < 29 IU at week 48. Serological response was defined as HBeAg loss with or without its seroconversion (development of anti-HBe antibodies) in HBeAg positive cases. Biochemical response was defined as ALT normalization (decline in ALT levels to less than the upper limit of normal) in patients with pre-treatment elevated ALT levels. Safety was evaluated by assessing serum creatinine, serum urea and bone mineral density (BMD). Adverse drug reaction (ADR) was monitored and any symptom, sign, abnormal clinical or laboratory finding occurring during the therapy was considered as a drug related adverse event. The causality and severity of the ADRs following anti-viral therapy was assessed by utilising the WHO-UMC causality assessment scale and modified Hartwig and Siegel severity assessment scale, respectively.
After collection and compilation of data, statistical analysis was done in Dept. of Pharmacology, SCB Medical College and Hospital, Cuttack using the Statistical Program for Social Sciences (SPSSv.20.0). Categorical data were expressed as frequency and percentage while numerical data were expressed as mean ± standard deviation. Suitable parametric and non-parametric tests were used (mentioned below each table) and p < 0.05 was deemed statistically significant.

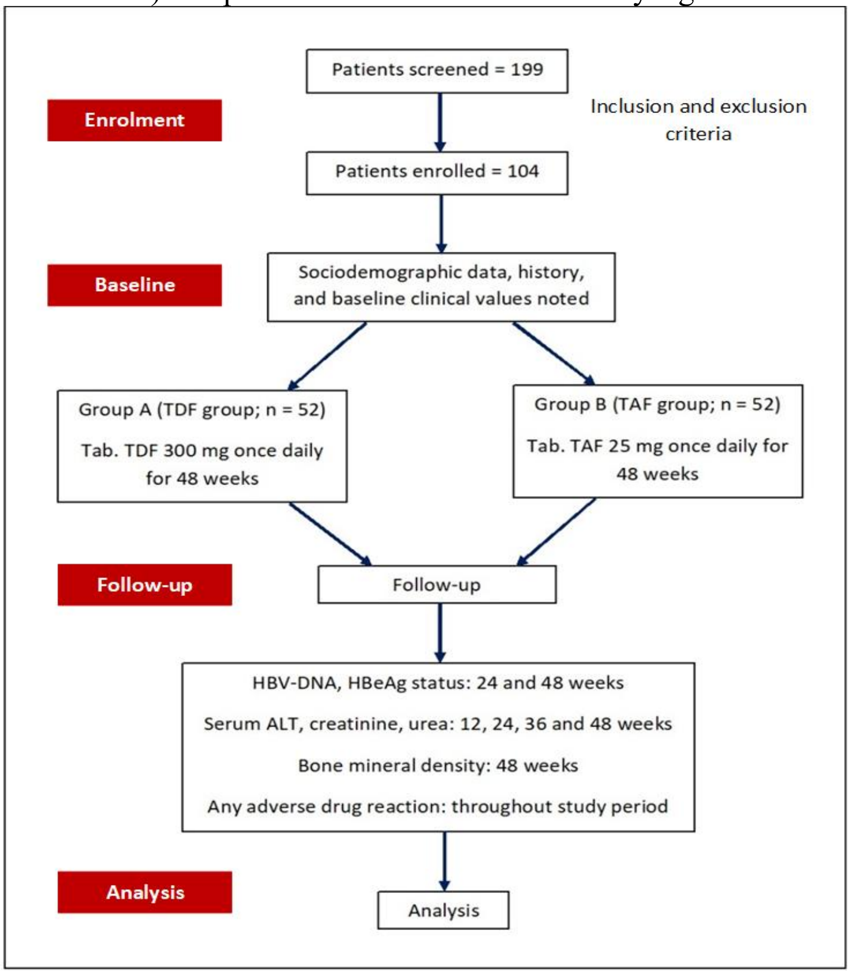

Figure 1. STROBE flow diagram

Results

The baseline sociodemographic and study parameters are displayed in table 1. In both the study groups, majority of the participants comprised of male young adults. The mean age of the participants was higher in TAF group in comparison to TDF group (43 versus 33 years). The most common risk factor associated with CHB in our study was sexually transmitted infection. The virological, serological, biochemical and safety parameters were comparable between the two groups at baseline ($p > 0.05$).

	TDF group (n=52)	TAF group (n=52)	p-value
Gender distribution			
Male	28 (54)	37 (71)	0.07*
Female	24 (46)	15 (29)	
Other	-	-	
Age distribution (years)			
18 – 39	30 (57.7)	22 (42.3)	
40 – 59	19 (36.5)	19 (36.5)	0.05*
> 60	3 (5.8)	11 (21.2)	
Risk factors			
H/o STI	13 (25)	10 (19)	
H/o hospitalisation	8 (15)	9 (17.5)	
Family history	7 (13.5)	9 (17.5)	
H/o IDU	5 (10)	6 (11.5)	0.88*
H/o BT	2 (3.5)	4 (7.5)	
No definite history	17 (33)	14 (27)	
HBV-DNA status			
Detectable	52 (100)	52 (100)	-
Undetectable	0	0	
HBeAg status			
Positive	24 (46)	27 (52)	0.55*
Negative	28 (54)	25 (48)	
Serum ALT (IU/ml)	108.12 ± 38.3	100.19 ± 27.8	0.23#
Serum creatinine (mg/dL)	0.91 ± 0.16	0.91 ± 0.17	0.95#
Serum urea (mg/dL)	24.9 ± 6.5	25.2 ± 6.3	0.94#
Bone mineral density (g/cm^2)			
Hip	-0.47 ± 0.41	-0.46 ± 0.41	0.17#
Spine	-0.49 ± 0.32	-0.51 ± 0.33	0.81#

Table 1. Study parameters at baseline, STI = sexually transmitted infection, IDU = injection drug use, BT = blood transfusion; p value < 0.05 is significant (*chi-square test, #unpaired T-test)

Table 2 presents a comparative analysis of TDF and TAF in terms of viral suppression, HBeAg status and serum ALT levels at different follow-up intervals. The degree of complete viral suppression was comparable between the two groups at 24 weeks ($p = 0.68$) and 48 weeks (0.64). Similarly, at 24 weeks ($p = 0.56$) and 48 weeks ($p = 0.69$), the HBeAg status was comparable between the two treatment groups. Serum ALT levels showed a consistent downward trend from baseline to 48 weeks. Up until 36 weeks, there was no significant difference in the serum ALT levels between the two groups ($p > 0.05$); at 48 weeks, however, the average ALT levels were lower with TAF than TDF ($p = 0.015$).

	TDF group (n=52)	TAF group (n=52)	p-value
Complete viral suppression			
Baseline	0	0	-
At 24 weeks	20 (38.5)	18 (34.5)	0.68*
At 48 weeks	41 (79)	39 (75)	0.64*
HBeAg positive cases			
Baseline	24 (46)	27 (52)	0.55*
At 24 weeks	23 (44.2)	26 (50)	0.56*
At 48 weeks	21 (40.4)	23 (44.2)	0.69*
Serum ALT levels (IU/ml)			
Baseline	108.12 ± 38.3	100.19 ± 27.8	0.23#
At 12 weeks	84.52±26.4	82.15±18.5	0.60#
At 24 weeks	68.69±20.08	67.52±14.2	0.73#
At 36 weeks	53.46±18.7	48.77±13.04	0.14#
At 48 weeks	40.33±16.88	33.75±8.5	**0.015#**

Table 2. Intergroup efficacy assessment; p value < 0.05 is significant (*chi-square test, #unpaired T-test)

Table 3 displays the safety assessment of the study drugs. There was no significant difference in the serum creatinine levels between the two groups until 36 weeks; at 48 weeks the average creatinine levels were significantly lower with TAF ($p = 0.007$). Conversely, the average urea levels were comparable between the two groups throughout the study period ($p > 0.05$ at every follow-up interval). Bone mineral density tests performed on the hip and spine at 48 weeks revealed that the average BMD in patients on TAF was significantly higher than those on TDF (hip BMD: -1.13±0.28 versus -1.88 ± 0.30, p = 0.0004; spine BMD: -1.17 ± 0.30 versus -2.21 ± 0.19, p = 0.0008). While the overall number of ADRs was similar in both the groups, the incidence of diarrhea was significantly higher with TDF ($p = 0.007$).

	TDF group (n=52)	TAF group (n=52)	p-value
Serum creatinine (mg/dL)			
Baseline	0.91 ± 0.16	0.91 ± 0.17	0.95#
At 12 weeks	0.953±0.14	0.913±0.17	0.20#
At 24 weeks	0.901±0.14	0.901±0.14	1#
At 36 weeks	0.892±0.13	0.882±0.16	0.74#
At 48 weeks	0.946±0.19	0.851±0.15	**0.007#**
Serum urea (mg/dL)			
Baseline	24.9 ± 6.5	25.2 ± 6.3	0.94#
At 12 weeks	25.2 ± 5.7	25.1 ± 5.5	0.84#
At 24 weeks	24.9 ± 6.2	24.6 ± 5.4	0.78#
At 36 weeks	24.3 ± 5.7	25.1 ± 6.4	0.49#
At 48 weeks	24.8 ± 5.8	25 ± 6.9	0.88#
Bone mineral density (g/cm^2)			
a. Hip			
Baseline	-0.47±0.41	-0.46±0.41	0.17#
At 48 weeks	-1.88±0.30	-1.13±0.28	**0.0004#**
Mean change from baseline	-1.41	-0.67	-
b. Spine			
Baseline	-0.49±0.32	-0.51±0.33	0.81#
At 48 weeks	-2.21±0.19	-1.17±0.30	**0.0008#**

Mean change from baseline	-1.72	-0.66	-
Adverse drug reactions			
Diarrhoea	8 (15.4)	0	**0.007***
URTI	4 (7.7)	8 (15.4)	0.21*
Headache	5 (9.6)	6 (11.5)	0.75*
Nausea	6 (11.5)	2 (3.8)	0.14*
Cough	0	2 (3.8)	0.3*
Fatigue and weakness	2 (3.8)	1 (1.9)	0.55*
Itching	1 (1.9)	0	0.55*
Total	26 (50)	19 (36.5)	0.16*

Table 3. Intergroup safety assessment, URTI = upper respiratory tract infection; p value < 0.05 is significant (*chi-square test, #unpaired T-test)

Discussion

Among the people living with HBV infection, those with CHB have a higher risk of developing cirrhosis and/or hepatocellular carcinoma contributing to significant morbidity and mortality. By reducing the viral load, rate of viral replication and hepatic inflammation, antiviral therapy can dramatically delay the progression of hepatic damage. In most cases, the oral nucleoside reverse transcriptase inhibitor (NRTI), tenofovir (TDF or TAF) is given indefinitely as discontinuation can result in a viral rebound. Therefore, it is crucial to know the effectiveness and potential long-term adverse effects of these drugs.

In the current study, the mean age of the study participants was 38 years (33 years in TDF group versus 43 years in TAF group). Majority of the patients were young adults aged 18 to 39 years (50%) followed by 40 to 59 years (37%). The findings of our study were consistent with other studies where the average age of the study participants was 37.5 years and 36 years.[7,8] A possible explanation for this could be that many people in this age group remained unvaccinated in their early years of life. In India, Hepatitis B vaccination program was initiated in the year 2002.[9] The adolescents and young adults in our study who were born before the initiation of the universal immunisation program may have acquired the disease in early childhood. Males made up 62.5% of the participants in the study. These findings were consistent with other studies where CHB and related complications were more frequent among males.[10,11] Gender-driven disparities may be as a result of differential immune responses, sexual dimorphism of the liver, androgen-mediated responses to HBV, in addition to its influence on education and exposure to the healthcare services.[12] A complete medical history regarding potential risk factors for HBV transmission was obtained from each patient. A positive history of sexually transmitted infections was found to be the most common risk factor, confirming that the primary ways of HBV spread are through the exchange of infected body fluids, such as saliva, menstrual, vaginal, and seminal fluids and percutaneous exposure to infected blood.

In the current investigation, the efficacy of antiviral therapy was evaluated in terms of HBV-DNA suppression, negativisation of HBeAg and its seroconversion and normalization of ALT. The HBV-DNA and HBeAg concentration was measured at 24 and 48 weeks. A decrease in the viral load signifies optimal response to the antiviral therapy and an increase may indicate emergence of resistant variants. At 48 weeks, complete viral suppression achieved by both the antiviral drugs was comparable (79% with TDF versus 75% with TAF, p = 0.64). The findings of our study were consistent with a similar study by Byun et al. where complete HBV-DNA suppression at 48 weeks was comparable (97.7% with TDF versus 98.9% in TAF, p > 0.99).[13] Similarly, a 3-year study demonstrated that TDF and TAF were comparable in suppressing the HBV-DNA levels at 144 weeks of starting treatment (79% with TDF versus 83% with TAF).[14] These findings suggest that TAF is non-inferior to TDF in efficacy. An HBeAg positive status indicates presence of active HBV replication and high infectivity; HBeAg negativation thus suggests a favourable prognosis. At 48 weeks, the rate of HBeAg negativisation achieved by both the antiviral drugs was comparable (12.5% with TDF versus 15% with TAF, p > 0.05). These findings were consistent with a previous study by

Byrne et al which demonstrated comparable HBeAg loss (12% with TDF versus 14% with TAF, p = 0.47) and HBeAg seroconversion (8% with TDF versus 10% with TAF, p = 0.32).[15] Measurement of serum ALT levels is one of the primary methods to assess hepatobiliary functions and elevated levels signify hepatic damage. At 48weeks of treatment there was a significant difference in the mean ALT values between the two groups (33.75 ± 8.5 with TAF vs. 40.33 ± 16.88 with TDF, p = 0.015). A greater percentage of individuals in the TAF group accounted for normalisation of ALT levels than TDF group (71% versus 63%, p = 0.23). The findings of our study were in line with a study by Chan et al.[16]

Important findings were noted in the renal and bone parameters after 48 weeks of therapy. These distinctions were relevant given that most patients with CHB infection will require lifelong therapy and are particularly crucial for the elderly and those with renal and bone comorbidities. Both the study groups showed changes in serum creatinine levels periodically from the baseline. But at 48 weeks of therapy, the serum creatinine level was significantly lower in the TAF group (0.851 ± 0.15 versus 0.946 ± 0.19, p = 0.007); the mean change in serum creatinine from baseline in TAF group was -0.056 versus +0.037 in the TDF group. In a study comparing the renal effects of TAF and TDF, the later was significantly associated with proximal renal tubulopathy and discontinuance from the study due to renal adverse events (0.04% versus 0.5%, p < 0.001).[17] There was no statistically significant difference observed in serum urea levels between the two study groups throughout the study period. TAF has greater plasma stability, enabling more efficient uptake by hepatocytes at lower plasma concentrations than TDF. Thus, the circulating concentration of TFV is 90% lower with a 25 mg dose of TAF as compared to a 300 mg dose of TDF.[18,19] This difference likely contributes to the better safety profile of TAF. However, the possibility of TAF-associated nephrotoxicity cannot be absolutely ruled out and should be prescribed with caution particularly in patients with underlying renal disease.[20] In our study, no patient in either group experienced a serious renal adverse event resulting in discontinuation of the study drugs. At 48 weeks of therapy, patients receiving TAF had significantly smaller reductions in mean BMD of hip from baseline (-0.67 with TAF versus -1.41 with TDF, p = 0.0004) and spine (-0.66 with TAF versus -1.72 with TDF, p = 0.0008). The findings of our study were in line with previous studies.[21,22] TDF has a direct effect on the bone homeostasis—stimulates osteoclast differentiation and osteoblast inhibition, resulting in increased bone resorption. Additionally, it interferes with the production of calcitriol (the active form of vitamin D) in the kidneys.[23] Thus, switching TDF with TAF has shown to increase BMD, thus reversing the subclinical bone loss.[23–25]

Both TAF and TDF treatment were reported to be well tolerated. Lesser number of ADRs were reported in TAF group (36.5%) compared to TDF group (50%). All the ADRs were mild in nature and did not require discontinuation of the study drugs. There was no death reported during the study period.

A key limitation of our study is that we relied only on serum creatinine and urea to assess kidney function. While these are commonly used and easily accessible markers, they may not fully capture early or subtle changes in renal health—especially those related to tubular function. Ideally, tests such as eGFR (estimated glomerular filtration rate), proteinuria, or specific tubular markers like β2-microglobulin and RBP (retinol-binding protein) would have provided a more complete picture. Unfortunately, due to resource and logistical constraints during the COVID-19 period, we were unable to include these in our study. Furthermore, given the higher cost of TAF compared to TDF, a cost-effectiveness assessment involving a larger sample size would give a clearer insight into the feasibility of replacing the conventionally used TDF with TAF in the management of chronic hepatitis B.

The findings of our investigation reveal that TAF is equally efficacious to the conventionally used TDF while additionally being significantly safer for kidneys and bones than TDF. Thus, TAF may be a good alternative to TDF in the treatment of chronic hepatitis B infection.

Acknowledgements: Nil
Conflict of interest: Nil

Funding source: Nil

References

1. The Hindu. India has second-most hepatitis B , C cases after China : WHO report. 2024 April 10;2022–4. Available from: https://www.thehindu.com/
2. Premkumar M, Kumar Chawla Y. Chronic Hepatitis B: Challenges and Successes in India. Clin Liver Dis. 2021;18(3):111–6.
3. Venkatesh SRKD. Diagnosis & Management of Viral Hepatitis. National Health Mission. 2018;1(1):1–80.
4. Lee BT, Chang M, Lim C, Bae HS, Fong TL. Bone and renal safety profile at 72 weeks after switching to tenofovir alafenamide in chronic hepatitis B patients. JGH Open. 2021;5(2):258–63.
5. Lim YS, Chan HLY, Ahn SH, Seto WK, Ning Q, Agarwal K, et al. Tenofovir alafenamide and tenofovir disoproxil fumarate reduce incidence of hepatocellular carcinoma in patients with chronic hepatitis B. JHEP Reports [Internet]. 2023;5(10):100847. Available from: https://doi.org/10.1016/j.jhepr.2023.100847
6. Nguyen MH, Wong G, Gane E, Kao JH, Dusheiko G. Hepatitis B virus: Advances in prevention, diagnosis, and therapy. Clin Microbiol Rev. 2020;33(2).
7. Chevaliez S, Roudot-Thoraval F, Brouard C, Gordien E, Zoulim F, Brichler S, et al. Clinical and virological features of chronic hepatitis B in the French national surveillance program, 2008–2012: A cross-sectional study. *JHEP Rep*. 2022;4(12):100550. doi:10.1016/j.jhepr.2022.100550.
8. Barbosa JV, Sahli R, Aubert V, Chaouch A, Moradpour D, Fraga M. Demographics and outcomes of hepatitis B and D: A 10-year retrospective analysis in a Swiss tertiary referral center. PLoS One [Internet]. 2021;16(27 April 2021):1–14. Available from: http://dx.doi.org/10.1371/journal.pone.0250347
9. Lahariya C, Subramanya BP, Sosler S. An assessment of hepatitis B vaccine introduction in India: Lessons for roll out and scale up of new vaccines in immunization programs. Indian J Public Health. 2013;57(1):8–14.
10. Liu M, Li L, Zhao J, Ungvari GS, Ng CH, Duan Z, et al. Gender differences in demographic and clinical characteristics in patients with HBV-related liver diseases in China. PeerJ. 2022;10.
11. Hamidu RB, Chalikonda DM, Hann HW. Gender disparity in host responses to hepatitis b-related hepatocellular carcinoma: A case series. Vaccines. 2021;9(8):1–9.
12. Matthews PC, Brown R, Goulder P. Sexual Dimorphism in Chronic Hepatitis B Virus (HBV) Infection: Evidence to Inform Elimination Efforts. Wellcome Open Res. 2022;7(May):1–22.
13. Byun KS, Choi J, Kim JH, Lee YS, Lee HC, Kim YJ, et al. Tenofovir Alafenamide for Drug-Resistant Hepatitis B: A Randomized Trial for Switching From Tenofovir Disoproxil Fumarate. Clin Gastroenterol Hepatol [Internet]. 2022;20(2):427-437.e5. Available from: https://doi.org/10.1016/j.cgh.2021.04.045
14. Hou J, Ning Q, Duan Z, Chen Y, Xie Q, Wang FS, et al. 3-year treatment of tenofovir alafenamide vs. Tenofovir disoproxil fumarate for chronic hbv infection in China. J Clin Transl Hepatol. 2021;9(3):324–34.
15. Byrne R, Carey I, Agarwal K. Tenofovir alafenamide in the treatment of chronic hepatitis B virus infection: rationale and clinical trial evidence. Therap Adv Gastroenterol. 2018;11:1–12.
16. Chan HLY, Buti M, Lim YS, Agarwal K, Marcellin P, Brunetto M, et al. Long-Term Treatment With Tenofovir Alafenamide for Chronic Hepatitis B Results in High Rates of Viral Suppression and Favorable Renal and Bone Safety. Am J Gastroenterol. 2024;119(3):486–96.
17. Gupta SK, Post FA, Arribas JR, Eron JJ, Wohl DA, Clarke AE, et al. Renal safety of tenofovir alafenamide vs. tenofovir disoproxil fumarate: A pooled analysis of 26 clinical trials. Aids. 2019;33(9):1455–65.
18. Sano T, Kawaguchi T, Ide T, Amano K, Kuwahara R, Arinaga-Hino T, et al. Tenofovir alafenamide rescues renal tubules in patients with chronic hepatitis b. Life. 2021;11(3).

19. Johnson KA, Niu X, Glidden D V., Castillo-Mancilla JR, Yager J, Mawhinney S, et al. Lower Urine Tenofovir Concentrations among Individuals Taking Tenofovir Alafenamide Versus Tenofovir Disoproxil Fumarate: Implications for Point-of-Care Testing. Open Forum Infect Dis. 2021;8(7):1–4.
20. Ueaphongsukkit T, Gatechompol S, Avihingsanon A, Surintrspanont J, Iampenkhae K, Avihingsanon Y, et al. Tenofovir alafenamide nephrotoxicity: a case report and literature review. AIDS Res Ther [Internet]. 2021;18(1):1–8. Available from: https://doi.org/10.1186/s12981-021-00380-w
21. Hashwin Singh TS, Jashwin Singh TS, Chin KY. Effects of tenofovir disoproxil fumarate on bone quality beyond bone density—a scoping review of the literature. Pharmaceuticals. 2024;17(2). doi:10.3390/ph17020162.
22. Hill A, Hughes SL, Gotham D, Pozniak AL. Tenofovir alafenamide versus tenofovir disoproxil fumarate: is there a true difference in efficacy and safety? J Virus Erad [Internet]. 2018;4(2):72–9. Available from: https://doi.org/10.1016/S2055-6640(20)30248-X
23. Soldado-Folgado J, Rins-Lozano O, Arrieta-Aldea I, Gonzále-Mena A, Cañas-Ruano E, Knobel H, et al. Changes in bone quality after switching from a TDF to a TAF based ART: A pilot randomized study. Front Endocrinol (Lausanne). 2023;14(March):1–7.
24. Moore AEB, Burns JE, Sally D, Milinkovic A, Krokos G, John J, et al. Bone turnover change after randomized switch from tenofovir disoproxil to tenofovir alafenamide fumarate in men with HIV. Aids. 2024;38(4):521–9.
25. Tseng TN, Chen CH. Editorial: changes in renal function and bone mineral density after switching from tenofovir disoproxil fumarate to tenofovir alafenamide in patients with chronic hepatitis B. Aliment Pharmacol Ther. 2022;56(5):916–7.