ORIGINAL RESEARCH

A Real-World Study on Safety and Efficacy of TAF Treatment in HBV Patients with High Risk of Osteoporosis or Osteopenia in China

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ABSTRACT

Objective • Long-term antiviral treatment is necessary for chronic hepatitis B (CHB) patients, and treatment safety is imperative for these patients. Previous studies showed tenofovir alafenamide (TAF) has shown efficacy non-inferior to that of tenofovir disoproxil fumarate (TDF) with improved renal and bone safety. However, there is still a lack of a rapid and convenient method to identify CHB patients at high risk of osteoporosis before initiating antiviral treatment. The International Osteoporosis Foundation (IOF) recommended a one-minute osteoporosis risk test to identify early high-risk patients. Our aim was to evaluate the feasibility of the one-minute osteoporosis risk test, along with evaluating the effectiveness and safety for virologically suppressed CHB patients switching to TAF.

Methods • In this multicenter, prospective study, patients with chronic HBV infection who had been receiving TDF or Entecavir (ETV) for 48 weeks or more with HBV DNA less than 20 IU/mL for longer than 6 months were screened by one-minute osteoporosis risk test. Patients with a high risk of osteoporosis and then diagnosed with osteopenia or osteoporosis by dual-energy X-ray absorptiometry (DEXA) were enrolled. Safety in bone and bone turnover markers and antiviral efficacy of TAF were assessed respectively at 24 and 48 weeks.

Results • 84.95% (175/206) CHB patients screened by one-minute osteoporosis risk test were at risk of osteoporosis.85.71% (150/175) were diagnosed with osteopenia by DEXA. The analysis included a total of 138 patients, of whom 92(62.3%) were male and 46 (37.7%) were female, with a mean age of 45 years old. HBV DNA was suppressed at 48 weeks at 88% (35/40) in the prior ETV group and 90% (88/98) at 48 weeks group in the prior TDF group. Bone mineral density (BMD) of the lumbar spine (L1-L4) from TDF switching to TAF was improved at 24 weeks (1.03±0.11 vs. 0.97±0.12, P = .001) than baseline. Propeptides of type I procollagen (PINP) and beta-C-terminal telopeptides of type 1 collagen (CTX) in serum at 24 weeks after switching from TDF to TAF declined compared with baseline (50.35±18.90 vs. 63.65±19.17, P = .016 and 0.21±0.13 vs. 0.32±0.10, P = .017). BMD, PINP, and CTX in ETV to TAF group remained stable during treatment.

Conclusion • Attention should be paid to osteoporosis risk during lone-term nucleot(s)ide analogue treatment. One minute test of osteoporosis risk could rapidly identify most CHB patients at risk of osteoporosis. Given its convenience, we recommend using this test for early screening in CHB patients prior to initiating antiviral treatment. Our results further demonstrated that an improvement in bone safety after switching to TAF in virologically suppressed CHB patients with osteoporosis. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Over 250 million people are positive for hepatitis B surface antigen (HBsAg) and are living with chronic HBV,[1] while a chronic HBV infection causes almost 800 000 deaths annually. However, without treatment, CHB infection can cause progressive fibrosis of the liver, which can lead to

cirrhosis, liver decompensation, and hepatocellular carcinoma (HCC).[2] HBV is a preventable disease, so vaccination should be recommended for the entire population. The treatment can inhibit suppression of HBV DNA replication, decrease hepatic necroinflammation, and improve fibrosis, thus preventing the development of cirrhosis, hepatic decompensation, HCC, and ultimately, HBV-related mortality.[2-5] Unfortunately, there is no effective treatment at present that can achieve a virological cure, which means eradication of circular covalently closed DNA (ccc-DNA) in liver cells.[6] Since the loss of hepatitis B surface antigen rarely occurs, long-term suppression using potent nucleos(t)ide analogs (NAs) antivirals remains the mainstay therapy in the treatment of CHB.[7] Given the need for long-term therapy, antiviral agents with a low risk of long-term drug-related toxicities are imperative for the overall health of patients with CHB. High-barrier-to-drug resistance NAs, including ETV, TDF, and TAF, are first-line treatments for CHB in the clinical practice due to multiple contraindications and safety associated with IFN-based regimens.[8,9] TDF is a NAs with a high genetic barrier that is highly effective in achieving suppression with no reported resistance,[10] long-term use of which has been associated with the risk of renal dysfunction and reduction of BMD.[11] TAF a novel prodrug of tenofovir, was developed to have greater plasma stability than TDF, thereby enabling more efficient delivery of the active metabolite to target cells at a substantially lower dose. Furthermore, tenofovir alafenamide (TAF) can reduce renal toxicity while maintaining antiviral efficacy. When TAF is given at a dose of 25 mg to patients with HBV infection, the circulating concentration of tenofovir was about 90% lower than the concentration with the standard 300 mg dose of TDF.[12] ETV is currently used in several patients with CHB because of its antiviral effect and safety. One study's relatively long-term (96 weeks) observation revealed that the effects on serum HBsAg level and renal function were similar between the ETV continuation and TAF switching groups.[13] But another study from Korea showed ETV was associated with a higher risk of kidney function decline than TAF in patients with treatment-naïve CHB.[14]

Hepatic osteodystrophy (HO) has been demonstrated in patients with various types of chronic liver disease. Decreased osteoblastic function, increased bone turnover, and increased bone resorption are related to the pathogenesis of HO.[15] Clinical outcomes of virally suppressed CHB patients with osteoporosis risk who switched from prior ETV or TDF to TAF therapy are limited. This study is to evaluate the effectiveness and safety of virally suppressed CHB patients with osteoporosis risk evaluated by a one-minute risk test switched from prior ETV or TDF to TAF.

METHODS

Patients

A prospective single-arm open-label study was conducted between September 2019 and October 2022 at three Hospitals. Each patient signed informed consent before enrolment and before testing. The specific inclusion and exclusion criteria were as follows: Inclusion criteria: 1) Consecutive adult CHB patients (age ≥18 years) who were treated with any oral antiviral agent (TDF or ETV) for at least 1 year and with virologically suppressed (at least 70% of patients using TDF switched to TAF and ETV patients at least 30% switched to TAF) were invited to participate. 2) Those who require drug intervention for osteoporosis (other than calcium and /or vitamin D) during the study period will be included but evaluated using a sensitivity analysis. Exclusion criteria: 1) Patients who had already undergone drug intervention due to osteoporosis at screenin88g will be excluded from the study. 2) CHB patients with decompensated cirrhosis, co-infected with HIV or HCV or HDV, hepatocellular carcinoma, decompensated cirrhosis, eGFR<15 mL/min/1.73m^2 without hemodialysis, and pregnant were excluded. 3) Patients who received a liver and/or kidney transplant were also excluded. Eligible patients received 25 mg TAF orally once daily administered with food, other than switching from TDF to TAF, and no additional drugs that patients were taking at baseline were altered.

Study design

Hepatitis B e antigen (HBeAg) positive or negative CHB patients treated by ETV or TDF for over 48 weeks, virally suppressed (HBV DNA <20 IU/mL) for longer than 6 months were screened for osteoporosis risk by one-minute osteoporosis risk test. One-minute osteoporosis risk test of the IOF. (Table 1).

Patients at risk of osteoporosis, diagnosed with osteopenia or osteoporosis through DEXA scan, were included in this study. BMD in the lumbar spine (from L1 to L4) and hip was measured. T-score change from the hip and lumbar spine BMD results using the World Health Organization established range (normal, ≥-1.0; osteopenia, ≤ -2.5 to < -1.0; osteoporosis, < -2.5). All scans were conducted on the same machine by the same operator. All patients underwent BMD assessment at screening and then at weeks 24 and 48 of treatment. We aimed to evaluate the feasibility of the one-minute osteoporosis risk test as well as the effectiveness and safety among virologically suppressed CHB patients switching to TAF.

Table 1. Non Modifiable Risk Factors

	Non Modifiable Risk Factors	Answer	
1	Have either of your parents been diagnosed with osteoporosis or broken a bone after a minor fall (a fall from standing height or less)?	Yes	No
2	Did either of your parents have a stooped back (dowager's hump)?	Yes	No
3	Are you 40 years old or older?	Yes	No
4	Have you ever broken a bone after a minor fall, as an adult?	Yes	No
5	Do you fall frequently (more than once in the last year) or do you have a fear of falling because you are frail?	Yes	No
6	After the age of 40, have you lost more than 3 cm in height (just over 1 inch)?	Yes	No
7	Are you underweight (is your Body Mass Index less than 19 kg/m^2)?	Yes	No
8	Have you ever taken corticosteroid tablets (cortisone, prednisone, etc.) for more than three consecutive months?	Yes	No
9	Have you ever been diagnosed with rheumatoid arthritis?	Yes	No
10	Have you been diagnosed with an over-active thyroid, overactive parathyroid glands, type 1 diabetes or a nutritional/gastrointestinal disorder such as Crohn's or celiac disease?	Yes	No

Note: A score of 5 on the one-minute osteoporosis risk test indicates a high risk of osteoporosis; a "yes" response to an item does not imply that the respondent has osteoporosis, but rather that the respondent possesses the corresponding risk factor, and so has a higher risk of osteoporosis.

Measurements

HBeAg and anti-HBe were determined using commercially available enzyme immunoassay kits. Quantitative measurements of HBV-DNA and HBsAg were performed using real-time polymerase chain reaction (COBAS Taqman HBV Test version 2.0; Roche Diagnostics) and chemiluminescent immunoassay (Abbott, Japan), respectively. Laboratory tests were obtained, including plasma creatinine, plasma phosphate), uric acid level, estimated glomerular filtration rate by Cockcroft-Gault equation (eGFR), and urine phosphate. β-CTX and PINP in serum were detected by the electrochemiluminescence method (Roche luminometer). We did not test β-CTX and PINP in urine. All markers were collected from patients following an overnight fast.

Outcome

The primary safety endpoint included changes in BMD values, as demonstrsted by the mean percent change from baseline and shifts from baseline in T-score. Key prespecified secondary safety endpoints included biomarkers of bone turnover, such as CTX associated with bone resorption, and PINP associated with bone formation.

The second efficacy endpoint was the proportion of patients with sustained HBV DNA less than 20 IU/mL at week 48 of treatment with TAF as determined by PCR(COBAS Taqman HBV Test version 2.0; Roche Diagnostics), quantification of HBsAg by chemiluminescent immunoassay (Abbott, Japan), and ALT normalization (defined as ALT above the upper limit of normal at baseline and within the normal range at 48 weeks) as determined by the laboratory with normal range 50U/L in men and 40 U/L in women by Chinese Society of Hepatology.

Statistical analysis

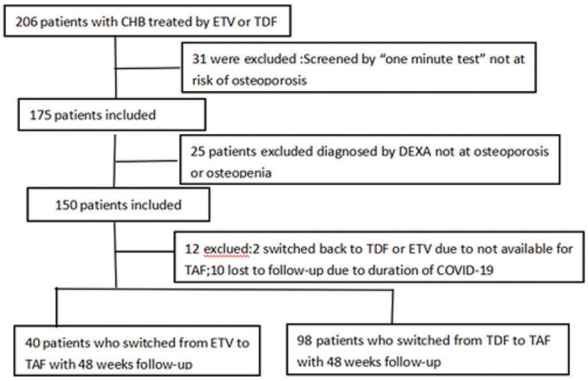
The baseline characteristics and laboratory values were described as either means (standard deviation), or frequencies (percentages). Laboratory values were compared by treatment status (baseline, weeks 24 and 48 of switching). BMD values were also reported as mean percentage changes from baseline. A paired sample *t* test or Wilcoxon signed-rank test were used to compare differences as appropriate. The level of statistical significance was set at $P < .05$. All statistical analysis was performed using the R Statistical Software.

RESULTS

206 CHB patients treated by ETV or TDF for over 48 weeks were screened using "one-minute test." Patients who were excluded from the study are illustrated in Figure 1. 84.95% (175/206) of the patients were identified as having an osteoporosis risk, and among them, 72.81% (150/206) were diagnosed with osteopenia or osteoporosis by DEXA. 85.71% (150/175) of CHB patients at risk of osteoporosis were diagnosed as osteopenia or osteoporosis by DEXA (Figure 1).

At baseline, 92 (62.3%) patients were male, and 46 (37.7%) were female, with a mean age of 45 years old. The age and sex structure of patients between the two groups were similar. Before switching to TAF, there was no difference in the duration between ETV and TDF groups (Table 2).

Figure 1. Study enrollment overview



Virological response

At the outset of the study, all patients had HBV DNA < 20 IU/mL. During 48 weeks of TAF treatment, 88% (35/40) in switching to TAF from the prior ETV group were suppressed. 90% (88/98) at 48 weeks in the TDF to TAF group had HBV DNA < 20 IU/mL. (Table 2).

ALT concentration

ALT concentration was compared at 24 and 48 weeks. The mean concentration in ALT between baseline and week 24 or week 48 did not differ in switching to TAF from the prior ETV or TDF group ($P > .05$); However, in prior TDF switching group there was a tendency for ALT level to decrease, ALT concentration at 24 and 48 weeks numerically decreased by 11.7% and 7% respectively compared with baseline (from baseline 24.44±14.96 to 21.45±10.49, $P > .05$ and from 24.44±14.96 to 24.47±14.53, $P > .05$, perspectively). (Table 2).

Bone safety

PINP and β-CTX were stable between 0, 24, and 48 weeks after switching from ETV to TAF. There was a decline in PINP compared with baseline and at 24 weeks after switching from TDF to TAF (50.35±18.90 vs. 63.65±19.17, $P = .016$), β-CTX was a decline compared with baseline (0.21±0.13 vs. 0.32±0.10 with $P = .017$), level of serum PINP and β-CTX at 48 weeks were not different significantly changed compared with baseline (Table 3).

There was an improvement in BMD at weeks 24 to baseline by measurement at the lumbar spine site after switching TDF to TAF (1.03±0.11 vs. 0.97±0.12, $P = .001$) and maintained stable till 48 weeks (1.03±0.11 to 1.01±0.13, $P > .05$). Changes in BMD at the total hip after switching ETV or TDF to TAF from baseline to 24 and 48 weeks were not significantly different (Table 3).

Renal safety

Results on an item related to renal function are shown in Table 1. In switching to TAF from prior ETV, eGFR, urine beta2-microglobulin and urine phosphorus between 0, 24

Table 2. Demographics, renal parameters and efficacy at weeks 0, 24, 48

	ETV to TAF			TDF to TAF		
	0 W	24 W	48 W	0 W	24 W	48 W
Number	40			98		
Age(year)	47.20±8.93			41.91±9.10		
Sex(%male)	64.7			60.9		
Race(% Asian)	100			100		
ALT(U/L)	24.09±13.00	27.21±19.32	24.45±11.93	24.44±14.96	21.45±10.49	24.47±14.53
Normalized ALT by central laboratory normal range	—	—	4/9(44%)	—	—	1/1(100%)
Albumin(g/L)	45.7±2.22	44.35±2.54	45.38±2.32	44.93±1.95	44.77±2.03	45.68±2.21
Cr(mg/dl)	72.95±16.56	72.90±15.59	75.13±15.24	76.60±16.41	74.35±15.78	74.87±14.80
Serum phosphorus(mg/dl)	0.99±0.13	1.03±0.11	1.07±0.23	0.99±0.11	1.02±0.11	0.95±0.13
TG(mmol/L)	1.26±0.62	1.55±1.16	1.42±0.72	1.30±0.92	1.77±1.18[b]	2.22±1.99
HDLC(mmol/L)	1.31±0.36	1.31±0.34	1.27±0.27	1.10±0.27	1.14±0.33	1.16±0.37
LDL(mmol/L)	2.93±0.86	3.09±0.83	3.01±0.93	2.25±0.53	2.45±0.0.73	2.63±0.74
Urine β2MG(ug/L)	0.35±0.84	0.22±0.33	0.27±0.28	0.49±0.55	0.38±0.43[b]	0.33±0.34[d]
eGFR(mL/min)	102.09±20.59	97.80±14.77	97.21±16.82	100.35±20.24	101.17±14.58	107.52±35.94[c]
Urine phosphorus(mg/dl)	9.64±4.40	8.9±4.4	7.84±1.90	13.49±4.35	9.07±3.19[b]	9.35±3.55[d]
AFP	2.96±1.14	2.72±0.88	2.79±1.25	2.97±1.86	2.61±1.74	2.29±1.21
The proportion of HBV-DNA<20 IU/mL	100	34/40	35/40	100	89/98	88/98

[a]$P < .05$
[b]$P < .01$, compared with baseline
[c]$P < .05$
[d]$P < .02$, compared with baseline

Abbreviations: ALT, alanine aminotransferase; LDL, low density lipoprotein; HDL: high density lipoprotein; TG, Triglyceride; AFP, alpha-fetoprotein; AST: aspartate aminotransferase; Cr, creatine; eGFR, estimated glomerular filtration rate; β2MG, β2-microglobulin.

Table 3. Bone parameters of patients at weeks 0, 24, 48

	ETV to TAF			TDF to TAF		
	0 W	24 W	48 W	0 W	24 W	48 W
Serum bone biomarkers						
PINP(ug/L)	67.07±22.09	55.19±18.89	48.84±17.10	63.65±19.17	50.35±18.90[a]	55.03±16.51
β-CTX(ng/L)	0.32±0.13	0.26±0.10	0.23±0.29	0.32±0.10	0.21±0.13[a]	0.24±0.10
Bone mineral density(g/cm^2)						
Lumbar spine	0.99±0.10	0.98±0.11	1.01±0.12	0.97±0.12	1.03±0.11[b]	1.01±0.13
Lumbar spine T-score	-1.47±0.91	-1.19±0.97	-1.20±1.1	-1.71±0.83	-1.04±0.95[b]	-1.23±0.89
Percent change from week 0(%)	0	1.9	1.8	0	3.9**	3.0
Total hip	0.85±0.14	0.87±0.12	0.90±0.11	0.87±0.11	0.88±0.12	0.89±0.14
Total hip T-score	-1.08±0.76	-1.06±0.75	-1.05±0.78	-1.69±0.62	-1.62±0.57	-1.64±0.61
Percent change from week 0(%)	0	1.8	2.7	0	1.15	2.29
HBsAg (IU/mL)	2856± 3693	2698±4008	2772±3958	4775±5310	4216±4693[b]	5365±6676

[a]$P < .05$
[b]$P < .01$, compared with baseline

Abbreviations: β-CTX, beta-C-terminal telopeptides of type 1 collagen; HBsAg, hepatitis B surface antigen; PINP, Propeptide of type I procollagen.

and 48 weeks were not significantly different which was shown in Table 1. In switching to TAF from prior TDF, eGFR at week 48 increased by 12.1% compared with baseline (107.52±35.94 vs. 100.35±20.24, $P = .016$), level of eGFR was numerically enhanced but not statistically different between 24 weeks and 48 weeks (101.17±14.58 vs. 107.52±35.94, $P = .54$). Urine beta2-microglobulin at 24 and 48 weeks after switching from TDF to TAF both statistically declined compared with baseline (from baseline 0.49±0.55 to 0.38±0.43 ug/mL, $P = .000$ and from 0.49±0.55 to 0.33±0.34 ug/mL, $P = .013$). Urine phosphorus at 24 and 48 weeks after switching from TDF to TAF decreased by 20.9% and 12.3%, respectively, compared with baseline (9.07±3.19 vs. 13.49±4.35, $P = .001$, and 9.35±3.55 vs. 13.49±4.35, $P = .004$). Changes maintained stable from 24 weeks to 48 weeks.

Lipid profile

We observed triglyceride (TC) had a mild increase at 24 weeks after switching from TDF to TAF compared with baseline (from 1.30±0.92 mmol/L to 1.77±1.18 mmol/L, $P = .001$). Other lipid profiles, including high-density lipoprotein (HDL) and low-density lipoprotein (LDL), did not change significantly during treatment both in TDF to TAF and ETV to TAF groups (Table 2).

qHBsAg change

There was no significant difference in serum HBsAg quantification level between baseline and week 24 or week 48 in the prior ETV group ($P > .05$). Serum HBsAg quantification level in the prior TDF group at week 24 decreased compared with baseline ($P < .01$); however, there was no statistical change in HBsAg level at week 48 compared with baseline or week 24 ($P > .05$) (Table 3).

DISCUSSION

A one-minute Osteoporosis Risk Assessment Test (10 questions in its early version) with good sensitivity had been introduced by the IOF. Several published data studied the validation of the early version (10 questions) of the One-minute Test.[16] In our study, we screened 206 CHB patients for a one-minute Osteoporosis Risk Assessment Test, 175 were at risk of osteoporosis. Of 150 CHB patients diagnosed with osteoporosis or osteopenia by DEXA, 100% of patients were screened by a one-minute test tool as the risk of osteoporosis with a high sensitivity of 85.71%. Therefore, osteoporosis is a common complication of chronic liver disease, as the hepatitis B virus can disturb the body's vitamin D and bile salt metabolism, increasing the prevalence of osteoporosis, in line with the findings of another study.[15]And from our study, one-minute test was a convenient method to rapidly identify most of CHB patients with osteoporosis risk.

The bone effects of TDF regimens are probably related to an increase of phosphate tubular turnover but also a modulation in osteoclastic/blastic activity.[17] A prospective open-label trial detected significant changes only 12 weeks after switching from TDF to TAF. The effect of TDF on BMD loss has been especially seen in measurements of the hip compared with the lumbar spine.[18] In our study, we observed an improvement in lumbar spine BMD at 24 weeks, and improvement remained stable until 48 weeks. There still is a conflict of bone effect for ETV. In the Korea study (n=298), the risk of progression in CKD stage ≥ 1 was significantly higher in patients treated with ETV than TAF with a mean 19~22 months follow-up duration.[14] But another study (n=80) displayed that the effects on BMD of switching from ETV to TAF were similar to those continuing ETV with 96 weeks treatment duration.[13] Some researches showed ETV did not cause mitochondrial damage in renal tubular cells, although it was exclusively excreted from the kidney via glomerular filtration and renal tubular secretion.[19] In our

study, BMD and bone turnover markers in the ETV to TAF group remained stable from baseline to 48 weeks of TAF treatment. So, ETV might have less impact on bone-kidney metabolism and still need long-term observation.

On the other hand, discordance of hip and lumbar spine measurements by DEXA can be seen, especially in increasing age and postmenopause.[20] Of the 46 female patients in this study, 25 were perimenopausal. A sustained mild decline of BMD could be observed in perimenopausal patients both in ETV to TAF and TDF to TAF groups. Previous studies have also indicated that CHB virus infection is a critical factor leading to bone mass loss, especially in patients with reduced estrogen levels. Therefore, this might be an important reason for less improvement after switching to TAF in these patients in our study.

Human immunodeficiency virus-infected patients treated with TDF have shown increases in bone turnover markers, suggestive of increases in both osteoblast and osteoclast activity.[21] One analysis observed percentage changes in markers of bone formation and resorption were greater in patients treated with TDF than TAF.[18] In our study, CTX, a resorption marker, compared with the formation markers, notably P1NP, have increased at 24 weeks after switching to TAF compared with screening; the bone turnover markers were stable at 48 weeks compared with baseline. Our findings, therefore, support the notion that reduced systemic exposures to tenofovir may be responsible for the minimal changes in bone turnover and BMD.

In our study, renal function improvement, including β2MG, and urinary phosphorus, could be seen in the TDF to TAF group. The eGFR maintained stable in both the ETV to TAF and TDF to TAF groups during 48 weeks of treatment. The results supported the reversibility of the renal disorder induced by TDF. The decrease in eGFR, increase in urine β2MG, and urinary phosphorus were inhibited by switching TDF to TAF.[17] The favorable pharmacological profile of TAF compared with TDF reduces systemic exposure to the active moiety tenofovir-diphosphate and, consequently, may improve bone and renal safety.[12]

Most of the patients maintained undetectable HBV DNA levels during TAF treatment for viral suppression. In our study, a total of 15 patients with HBV DNA < 20 IU/mL at baseline turned detectable at 48 weeks after switching to TAF. One patient in ETV to TAF group at week 48, whose HBV DNA was 624 IU/mL, continued to drink intermittently during treatment. The other four patients discontinued TAF treatment for several days due to traffic problems in the duration of COVID-19 before the last follow-up date. And in the TDF to TAF group, for the ten patients with HBV DNA detectable but lower than 100 IU/mL, treatment compliance needed to be verified due to the COVID-19 pandemic in China during the study period.

Regarding the change in HBsAg, we observed a decline at week 24 in the TDF to TAF group, while no change was noted in the ETV to TAF group. In two phaseIII studies of TDF and TAF for treatment naïve CHB patients, all groups (TAF alone or TDF switch to TAF) experienced a similar mean decline in qHBsAg over 5 years, and the rate of HBsAg loss and seroconversion remained low in each group (1~3%).[22] Therefore, a long-term follow-up is necessary to observe changes in HBsAg within each group.

Koshm Agarwal et al. showed that treatment with TAF resulted in a similar rate of viral suppression compared with that of TDF. A higher percentage of patients in the TAF group who had elevated ALT levels at baseline achieved ALT normalization than those in the TDF groups at both weeks 48 and 96.[23] In our study, most of the patients had normal ALT levels at baseline and maintained stability, even though a mild decline in normal levels was observed in the TDF to TAF group. For patients with enhanced ALT levels at baseline, most of them had a trend of reduction, and no patient had ALT flair during treatment. 44% (4/9) had ALT normalization after 48 weeks of switching to TAF from TDF. The remaining 5 patients had a numerical decline in ALT level but upper than 40 U/L.

For lipid profile (Normal TC value: < 5.2mmol/L), a retrospective study found that TC decreased in the TDF group and increased in both ETV and TAF groups after 48 weeks of treatment.[24] In two studies of CHB patients treated with TDF with a median 42 months' follow-up also found that TC, TG, LDL-C and HDL-C decreased significantly in the first 6 months, but the changes of lipid indexes were relatively mild from 6 months to 42 months.[25,26] In our study, the TC of patients switching from TDF to TAF experienced an increase significantly at 24 weeks in our study. But as the previous studies' conclusion, this increase was transient. There was no continued increase in TC at 48 weeks compared to 24 weeks, and the TC level at 48 weeks showed no significant difference from the baseline. Both HDL and LDL did not increase after switching to TAF in both prior ETV and TDF groups. No patient initiated low lipid therapy in our study. Therefore, we considered that more attention should be paid to the clinic's influence on the fluctuation of lipids rather than numerical changes.

Our study has several limitations. Firstly, the study lacked control groups, such as those continuing with ETV or TDF, it was a single-arm study conducted exclusively with Asian patients. Secondly, a 48-week duration might be insufficient for a conclusive evaluation of the effectiveness and safety of TAF. A longer follow-up (up to 2 years) is planned to determine whether the short-term improvements we observed in bone and renal parameters will translate to a reduced incidence of bone and renal events over the long term. Future studies can enhance the investigation of TAF efficacy by broadening the study population and prolonging the follow-up period, among other approaches.

In conclusion, osteoporosis risk needs significant attention in CHB patients. A minute test of osteoporosis risk could rapidly identify most CHB patients at risk of osteoporosis. This test is convenient, and we recommend it for early screening in CHB patients before initiating antiviral treatment. Switching to TAF could lead to an improvement

in bone safety among virologically suppressed CHB patients with osteoporosis. Further long-term observational studies with large numbers of CHB patients treated to TAF at risk of osteoporosis are required.

AUTHORS' CONTRIBUTION

Wei Jia: Study design, approval of the final version of the manuscript; Li Hui: Study design, collection, and analysis of data, approval of the final version of the manuscript; Li Chunmei: Analysis of data, writing of the manuscript, approval of the final version of the manuscript; Gong Ming, Zhang Ruyi, Geng Jiawei, Wang Hongyan, Yu Zhijian: Collection, and analysis of data. Wang Zi: Clinical trial process supervision. Liu Xiang: Analysis of data. Chunmei Li and Hui Li contributed equally to this work

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ETHICAL COMPLIANCE

This study was approved by the ethics committee of The Fourth Affiliated Hospital of Kunming Medical University. Signed written informed consents were obtained from the patients and/or guardians.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

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