Comparative risk of osteoporosis and fractures in chronic hepatitis B patients: Tenofovir disoproxil fumarate vs. entecavir in a Korean nationwide cohort

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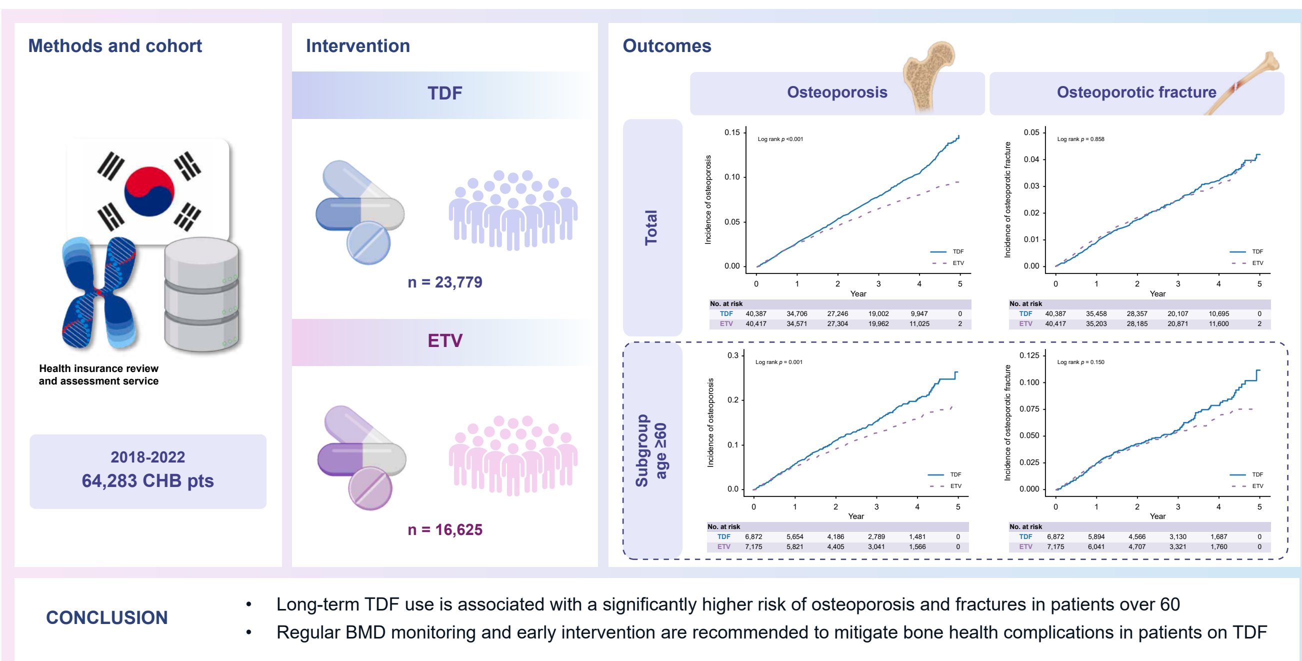
Graphical abstract



Highlights:

- TDF use in patients with CHB is linked to a 30% higher risk of osteoporosis compared to ETV.
- No overall fracture risk difference was found between TDF and ETV in the general CHB cohort.
- In patients aged ≥60, TDF increased both osteoporosis and fracture risk *vs.* ETV.
- Bone health monitoring is crucial for older patients with CHB receiving long-term TDF therapy.

Impact and implications:

Our study highlights the need for careful antiviral selection in patients with chronic hepatitis B aged ≥60 due to the increased risk of osteoporosis and fractures with long-term tenofovir disoproxil fumarate use. We recommend using entecavir or tenofovir alafenamide fumarate as the preferred therapies for patients at high risk of fractures. Early intervention is essential, as fracture incidence tends to rise after 2-3 years of tenofovir disoproxil fumarate therapy, making regular bone mineral density monitoring critical for these patients.

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Comparative risk of osteoporosis and fractures in chronic hepatitis B patients: Tenofovir disoproxil fumarate vs. entecavir in a Korean nationwide cohort

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Background & Aims: The optimal antiviral agent for patients with chronic hepatitis B (CHB) at risk for osteoporosis remains debated. The aim of this study was to compare the incidence of osteoporosis and osteoporotic fractures between patients treated with tenofovir disoproxil fumarate (TDF) and entecavir (ETV) using a nationwide cohort in South Korea.

Method: We analyzed 40,404 patients with CHB treated with either TDF (n = 23,779) or ETV (n = 16,625). The risk of osteoporosis and osteoporotic fractures was evaluated using Cox proportional hazards models, incidence rate ratios (IRRs), and Kaplan–Meier survival analysis. To adjust for baseline differences, inverse probability of treatment weighting was applied.

Result: Over a mean follow-up of 50.8 months, osteoporosis occurred in 1,712 TDF users and 1,094 ET V users. The incidence rate of osteoporosis was significantly higher in the TDF group (IRR 1.30, 95% CI 1.23–1.37; p <0.001). Multivariate Cox regression also confirmed increased osteoporosis risk with TDF (hazard ratio [HR] 1.328, 95% CI 1.258–1.401; p <0.001), while fracture incidence was not significantly different (HR 1.027, 95% CI 0.939–1.122, p = 0.569). In patients aged ≥60 years, the TDF group had a significantly higher risk of both osteoporosis (HR 1.347, 95% CI 1.224–1.484; p <0.001) and fractures (HR 1.213, 95% CI 1.051–1.403; p = 0.009), with divergence in Kaplan-Meier curves evident after 1 and 3 years of treatment, respectively.

Conclusion: Long-term use of TDF is associated with a significantly increased risk of osteoporosis and fractures, especially in patients aged ≥60 years. These findings support the need for proactive bone health surveillance in patients with CHB receiving long-term TDF therapy.

Introduction

Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are widely used as first-line treatments for HBV infection because of their high efficacy, robust genetic barrier, and well-established long-term safety profiles.[1–3] However, long-term use of TDF can lead to side effects, including renal impairment and osteoporosis.[4–6] The mechanisms underlying TDF-induced osteoporosis appear to be multifactorial, including suppression of osteoblast gene expression,[7] the development of hypophosphatemic osteomalacia due to proximal tubular dysfunction,[8] and disruptions in parathyroid hormone and vitamin D metabolism.[9]

When osteoporotic fractures occur during treatment, patients are often switched to ETV or tenofovir alafenamide fumarate (TAF), which are associated with fewer bone-related side effects.[10–12] However, guidance on initial antiviral selection in populations at high risk of fracture, such as the elderly or those with pre-existing osteoporosis, is limited. There are also no established thresholds for switching based on bone mineral density (BMD) or fracture risk before clinical events occur, leaving such decisions at the discretion of clinicians. The AASLD (American Association for the Study of Liver Diseases) guidelines do not indicate a preference between ETV and TDF regarding long-term bone-related side effects.[13] In contrast, the EASL (European Association for the Study of the Liver) guidelines recommend considering a switch to ETV or TAF for patients on TDF who are at risk of developing or already have underlying renal or bone disease, depending on their previous exposure to lamivudine.[14]

Previous studies have evaluated the risk of osteoporosis and fractures associated with TDF using BMD measurements and clinical data, but findings remain inconsistent.[15,16] A small prospective study reported greater BMD loss and higher rates of hip osteopenia in TDF compared to ETV users,[17] while a large retrospective cohort study (n = 41,531) found a significantly higher fracture risk in the TDF group (subdistribution hazard ratio [HR] 1.80, 95% CI 1.11–2.93).[18] In contrast, a recent meta-analysis of 16 studies found no significant

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difference in osteoporosis or osteopenia incidence between the two drugs (risk ratio 1.29, 95% CI 0.93–1.77, p = 0.13).[6] These conflicting findings underscore the need for further research involving larger patient cohorts and extended follow-up periods to better understand the long-term effects of TDF on bone health.

The aim of this study was to determine whether TDF elevates the risk of osteoporosis or osteoporotic fractures compared to ETV. To achieve this, we utilized data from the South Korean Health Insurance Review and Assessment Service (HIRA) database.

Patients and methods

Data source

This retrospective cohort study employed the HIRA database from South Korea, which serves as a comprehensive resource within the country's mandatory, government-run health insurance system. This database provides extensive coverage of patient data nationwide. It includes patient diagnosis codes based on ICD-10, along with prescription information. This study adhered to the Declaration of Helsinki and received approval from the Institutional Review Board of Soonchunhyang University Bucheon Hospital (SCHBC 2023-07-016-001, registered on September 23, 2023).

Study population

Between January 1, 2018, and December 31, 2022, a total of 1,351,240 patients with CHB were screened. Among them, 64,283 patients who had been prescribed either TDF or ETV for more than 3 months after January 1, 2018, and had no antiviral prescriptions in the preceding year were selected for the study. After applying the exclusion criteria, 40,404 patients remained. This excluded 281 patients under the age of 18, 3,871 patients with cross-medication, 15,129 patients diagnosed with osteoporosis or fractures before 2018, and 4,598 patients whose observation period was zero days or could not be calculated due to data inconsistencies. Ultimately, there were 23,779 patients in the TDF group and 16,625 in the ETV group (Fig. 1).

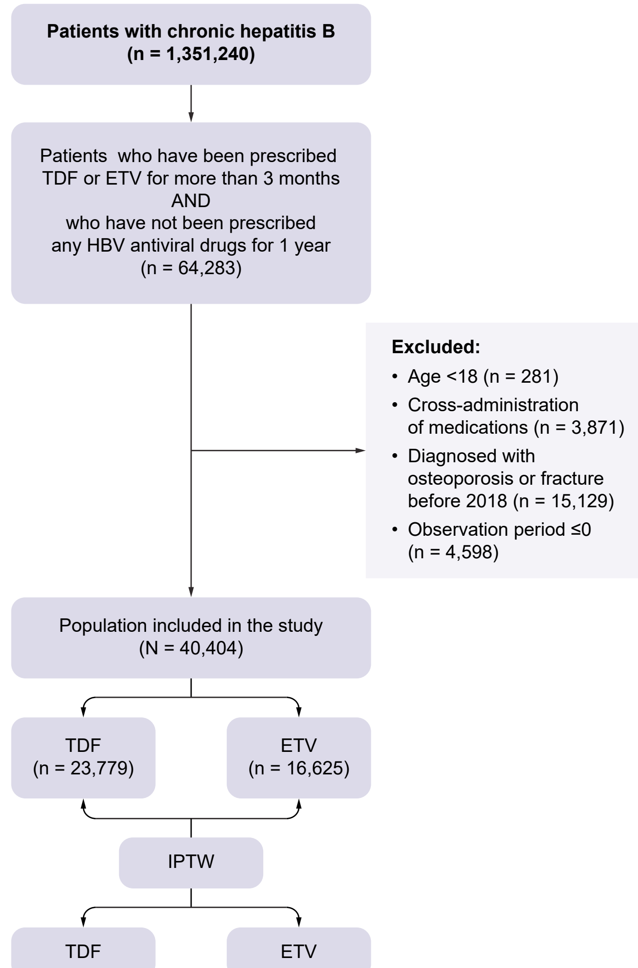

Fig. 1. Flowchart of the study population. ETV, entecavir; IPTW, inverse probability of treatment weighting; TDF, tenofovir disoproxil fumarate.

Outcomes

Patients were monitored until there was a change in medication, death, or until December 2022. The primary outcome was the occurrence of osteoporosis or osteoporotic fracture. CHB was identified using ICD-10 codes B180 or B181. Antiviral drug use was tracked using the Korea drug code, with specific codes for TDF represented by Korea drug codes 493901ATB and 686500ATB, and for ETV by Korea drug codes 487202ATB, 487202ATD, 487203ATB, and 487203ATD. Osteoporosis was defined using ICD-10 codes M80 and M81, while osteoporotic fractures were identified with ICD-10 codes S22.0, S22.1, S32.0, S32.7, S42.2, S42.3, S52.5, S52.6, S72.0, S72.1, S82.3, S82.5, and S82.6. A summary of these variables and ICD-10 codes can be found in Tables S1 and S2. To enhance the credibility of our big data analysis, we conducted a negative control outcome analysis[19] using acute appendicitis, which is unrelated to TDF, ETV, or osteoporosis. The results have been included in the supplementary information.

Although BMD tests were not used directly for diagnosis in this study, they can be used as an indirect indicator that may influence the diagnosis of osteoporosis or fracture. In Korea, BMD screening is reimbursed annually for individuals aged ≥65 years (women) and ≥70 years (men), or for those with underlying conditions or medications known to induce osteoporosis.[20]

Statistical analysis

Descriptive statistics were utilized to summarize baseline characteristics, presenting continuous variables as means ± SD and categorical variables as counts (percentages). The t test was employed for continuous variables, while the Chi-square test was used for categorical variables. The incidence rates of osteoporosis and osteoporotic fractures were calculated per 1,000 person-years, with 95% CIs based on the assumption of a Poisson distribution. Comparisons of incidence rates between the two groups were conducted using Kaplan-Meier analysis, with log-rank p values and incidence rate ratios (IRRs) also calculated. To adjust for selection bias between the TDF and ETV groups, inverse probability of treatment weighting (IPTW) was performed. IPTW was based on patient age, sex, comorbidities, and the number of years since the initiation of TDF or ETV therapy, reflecting the duration of treatment. Comorbidities and corticosteroid use were defined according to ICD-10 codes, as detailed in Tables S1 and S2. Following IPTW, Cox regression analysis was conducted to identify risk factors for the development of osteoporosis or osteoporotic fractures. All analyses were performed using SAS (Statistical Analysis System, Version 9.4), with a significance threshold set at p <0.05.

Results

Baseline characteristics of the study population

The baseline characteristics of the two groups are summarized in Table S3. The average age of participants in both groups was 48.5 years, with over two-thirds being male. The average age in the ETV group was 5 years higher than in the TDF group (TDF: 46.7 years *vs*. ETV: 51.0 years). The most prevalent comorbidities were cirrhosis (30.8%) and diabetes mellitus (20.8%). Most comorbidities, including hypertension, diabetes mellitus, chronic kidney disease, rheumatoid arthritis, and cirrhosis, were more frequent in the ETV group, while corticosteroid use was more common in the TDF group (p <0.001).

After applying IPTW, the differences between the two groups were minimized for all variables, achieving a standardized mean difference of less than 0.1 (Table S3). This adjustment for potential confounding factors ensures that there are no significant differences between the two groups concerning gender, age, and underlying conditions such as diabetes mellitus, hyperthyroidism, hyperparathyroidism, Cushing's syndrome, and corticosteroid use with respect to the occurrence of osteoporosis and fractures.

Incidence of osteoporosis or osteoporotic fracture

Patients were followed for an average of 50.8 ± 16.8 months, with no significant differences observed between the two groups (Table S3). In the TDF group (n = 23,779), a total of approximately 68,000 person-years of observation yielded 1,712 cases of osteoporosis and 509 osteoporotic fractures. In the ETV group (n = 15,531), approximately 47,000 person-years of follow-up resulted in 1,094 cases of osteoporosis and 448 osteoporotic fractures (Table 1).

The incidence of osteoporosis was higher in the TDF group after adjusting for IPTW (IRR 1.30, 95% CI 1.23–1.37, p <0.001) (Table 1). This result was reinforced by Kaplan-Meier curves and log-rank analysis, indicating a significant difference beginning 2 years after treatment initiation (log rank p <0.001) (Fig. 2). However, the difference in incidence of osteoporotic fracture between the two groups was no longer significant, with an IRR of 1.01 (95% CI 0.93–1.11, p = 0.757) (Table 1). This outcome was consistent with the Kaplan-Meier curves and log-rank analysis, which exhibited no significant difference (log rank p = 0.858) (Fig. 3).

We further analyzed osteoporotic fractures by anatomical site, including the thoracic spine, lumbar spine, humerus, forearm, and hip (Table S5). Although the mean age in the ETV group was 51.0 years – approximately 5 years older than in the TDF group (mean age 46.7 years) – the overall fracture incidence did not differ significantly between the groups. In the subgroup of patients aged 60 years or older, fractures of the lumbar spine (incidence of 0.796 per 100-person-years) and forearm (incidence of 0.462 per 100-person-years) were more frequently observed in the TDF group. Although numerical differences were noted between the groups, no statistical tests were performed for these site-specific analyses.

Risk factors for osteoporosis or osteoporotic fracture

We conducted a Cox regression analysis to identify risk factors associated with the development of osteoporosis. The analysis revealed that patients in the TDF group had a higher risk compared to those in the ETV group (hazard ratio [HR] 1.328, 95% CI 1.258–1.401, p <0.001). The HR was elevated for elderly patients over 60 years and for women. Additionally,

Table 1. Incidence of osteoporosis or osteoporotic fracture in patients treated with TDF or ETV.

	TDF (n = 23,779)	ETV (n = 15,531)	
Osteoporosis			
Person-year	66,068	46,085	
Event	1,712	1,094	
Incidence (/1,000PY)	25.91 (24.71–27.17)	23.74 (22.37–25.19)	
After IPTW			
IR (95% CI)	27.73 (26.77–28.73)	21.34 (20.50–22.20)	
IRR (95% CI)	1.30 (1.23–1.37)		p value <0.001
Osteoporotic fracture			
Person-year	68,193	47,493	
Event	509	448	
Incidence (/1,000PY)	7.46 (6.84–8.14)	9.43 (8.60–10.35)	
After IPTW			
IR (95% CI)	8.43 (7.92–8.98)	8.31 (7.80–8.85)	
IRR (95% CI)	1.01 (0.93–1.11)		p value = 0.757
Acute appendicitis (negative control)			
Person-year	68,152	47,707	
Event	332	212	
Incidence (/1,000PY)	2.25 (1.92–2.63)	1.92 (1.57–2.36)	
After IPTW			
IR (95% CI)	2.18 (1.93–2.46)	1.93 (1.70–2.20)	
IRR (95% CI)	1.12 (0.94–1.35)		p value = 0.188

ETV, entecavir; IPTW, inverse probability of treatment weighting; IR, incidence rate; IRR, incidence rate ratio; PY, person-years; TDF, tenofovir disoproxil fumarate.
IRs were calculated per 1,000 person-years with 95% CIs. After IPTW, IRRs and p values were estimated using Poisson regression. Osteoporosis incidence was significantly lower in the ETV group (p <0.001), while differences in fracture (p = 0.757) and appendicitis (p = 0.188) were not significant.

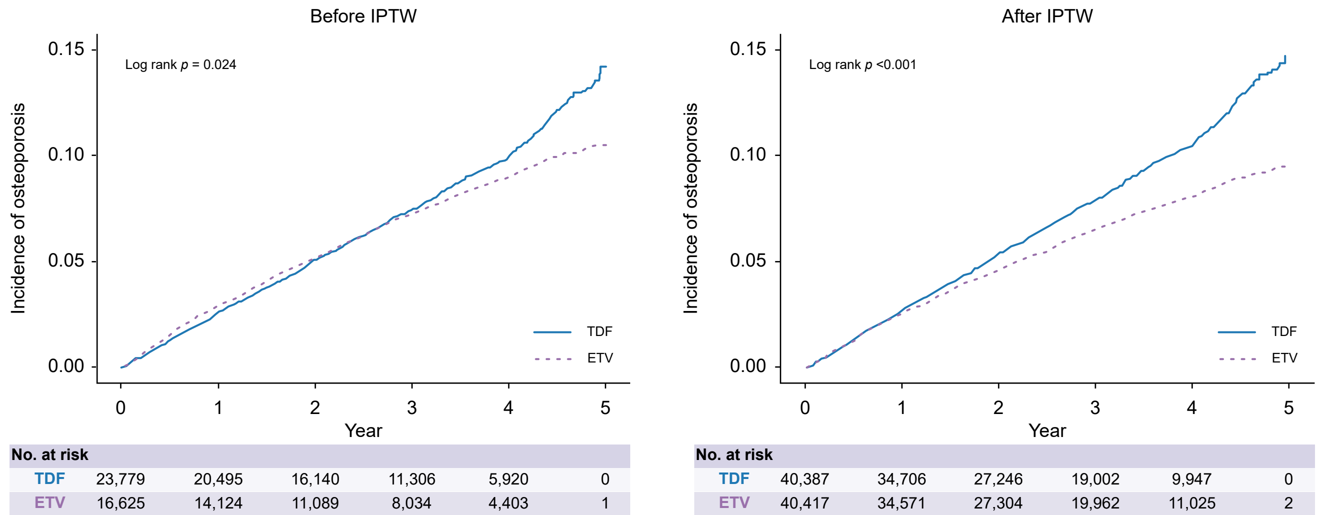

Fig. 2. Cumulative incidence of osteoporosis in patients treated with TDF or ETV. (A) Kaplan-Meier curves of osteoporosis development. (B) Kaplan-Meier curves of osteoporosis development after inverse probability of treatment weighting analysis. ETV, entecavir; IPTW, inverse probability of treatment weighting; TDF, tenofovir disoproxil fumarate.

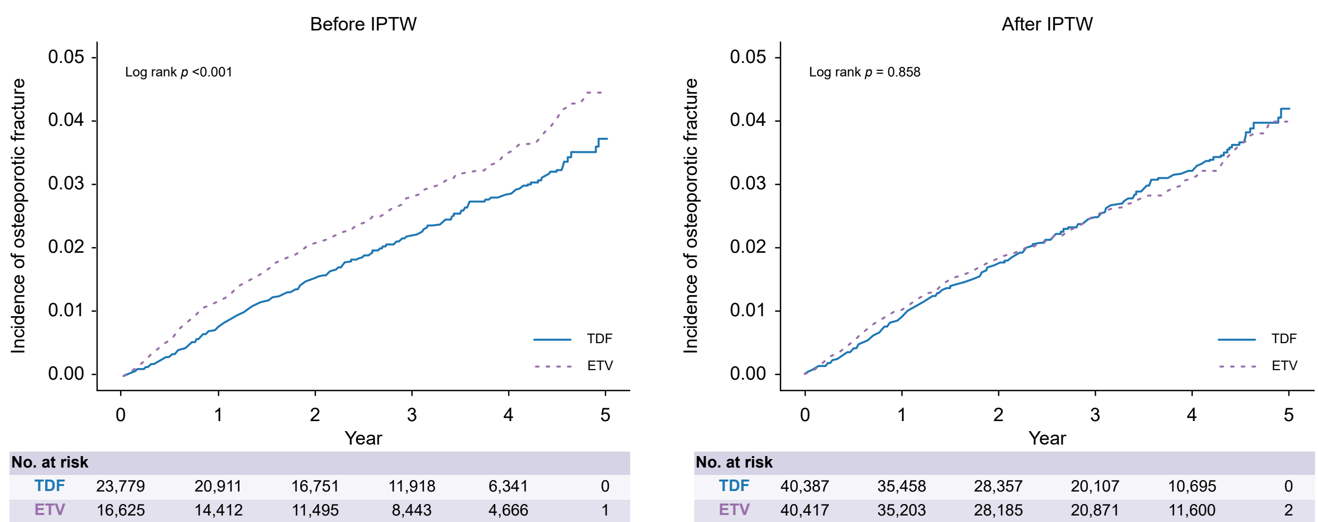

Fig. 3. Cumulative incidence of osteoporotic fracture in patients treated with TDF or ETV. (A) Kaplan-Meier curves of osteoporotic fracture development. (B) Kaplan-Meier curves of osteoporotic fracture development after inverse probability of treatment weighting analysis. ETV, entecavir; IPTW, inverse probability of treatment weighting; TDF, tenofovir disoproxil fumarate.

patients with hypertension, chronic kidney disease, hypothyroidism, hyperparathyroidism, rheumatoid arthritis, and cirrhosis were also at a higher risk (p <0.001). In contrast, corticosteroid use was linked to a reduced risk (HR 0.630, 95% CI 0.581–0.682, p <0.001) (Table 2).

Regarding osteoporotic fractures, no significant difference in risk was found between the TDF and ETV groups (HR 1.027, 95% CI 0.939–1.122, p = 0.569). However, older age (≥60 years) and female sex remained significant risk factors, with a notably higher risk observed in patients with hypertension, diabetes mellitus, asthma, rheumatoid arthritis and cirrhosis (p <0.05). Corticosteroid use continued to be associated with a lower risk (HR 0.599, 95% CI 0.523–0.687, p <0.001) (Table 3).

Subgroup analysis: patients older than 60 years

In a subgroup analysis focusing on individuals over 60 years of age, the TDF group had a significantly higher incidence of osteoporosis and osteoporotic fracture compared to the ETV group (IRR 1.250, 95% CI 1.136–1.370, p <0.001; IRR 1.163, 95% CI 1.010–1.351, p = 0.039). The differences in risk for osteoporosis and fractures became apparent after 1 and 3 years of treatment, respectively (Fig. 4; log-rank p = 0.001, p = 0.150). Additionally, Cox regression analysis indicated that TDF significantly increased the risk of osteoporosis and osteoporotic fractures (HR 1.347, 95% CI 1.224–1.484, p <0.001; HR 1.213, 95% CI 1.051–1.403, p = 0.009) (Tables 4 and S6).

Table 2. Cox regression analysis for osteoporosis risk (after IPTW).

	Univariate		Multivariate	
	HR (95% CI)	***p* values**	**HR (95% CI)**	***p* values**
Antiviral medication				
ETV	1 (reference)		1 (reference)	
TDF	1.299 (1.232–1.370)	<0.001	1.328 (1.258–1.401)	<0.001
Age (mean)				
<60	1 (reference)		1 (reference)	
≥60	2.327 (2.197–2.464)	<0.001	2.401 (2.257–2.555)	<0.001
Sex				
Female	1 (reference)		1 (reference)	
Male	0.284 (0.269–0.300)	<0.001	0.271 (0.256–0.287)	<0.001
Comorbidity				
Hypertension	1.342 (1.265–1.424)	<0.001	1.083 (1.015–1.156)	0.016
Diabetes mellitus	1.232 (1.156–1.312)	<0.001	1.067 (0.997–1.142)	0.060
Chronic kidney disease	1.426 (1.211–1.678)	<0.001	1.280 (1.060–1.493)	0.009
Hypothyroidism	1.972 (1.796–2.165)	<0.001	1.309 (1.188–1.442)	<0.001
Hyperthyroidism	1.158 (0.950–1.413)*	0.147		
Hyperparathyroidism	2.888 (2.128–3.921)	<0.001	2.207 (1.613–3.018)	<0.001
Cushing's syndrome	2.197 (0.897–5.384)	0.085		
Asthma	1.357 (1.265–1.455)	<0.001	1.046 (0.974–1.123)	0.216
Rheumatoid arthritis	2.045 (1.843–2.270)	<0.001	1.513 (1.359–1.683)	<0.001
Cirrhosis	1.080 (1.021–1.142)	0.007	1.119 (1.056–1.186)	<0.001
Corticosteroid use	0.554 (0.513–0.599)	<0.001	0.630 (0.581–0.682)	<0.001
Duration of follow-up, months	0.989 (0.987–0.991)	<0.001	0.993 (0.990–0.995)	<0.001

ETV, entecavir; HRs, hazard ratio; IPTW, inverse probability of treatment weighting; TDF, tenofovir disoproxil fumarate.
HRs and *p* values were estimated using Cox proportional hazards regression after IPTW. ETV was associated with a significantly lower risk of osteoporosis compared to TDF (p <0.001). HRs for covariates reflect direct effects under adjustment and may not be directly comparable to the total effect of primary exposures.

Subgroup analysis: impact of osteoporosis treatment on the cumulative incidence of fracture

We conducted an additional subgroup analysis to examine modifications in osteoporosis treatment and their potential influence on fracture risk. The IRR for fracture incidence between the treated and untreated groups was 5.26 (95% CI 4.64–5.96, p <0.001), indicating a higher fracture incidence in the treated compared to the untreated group. Within both the treated and untreated groups, there was no significant difference in fracture risk between the TDF and ETV medications (Fig. S1).

Discussion

In this retrospective cohort study using data from the nationwide HIRA database, we aimed to determine whether TDF increases the risk of osteoporosis and osteoporotic fractures

Table 3. Cox regression analysis for osteoporotic fracture risk (after IPTW).

	Univariate		Multivariate	
	HR (95% CI)	***p* values**	**HR (95% CI)**	***p* values**
Antiviral medication				
ETV	1 (reference)		1 (reference)	
TDF	1.012 (0.926–1.107)	0.794	1.027 (0.939–1.122)	0.569
Age (mean)				
<60	1 (reference)		1 (reference)	
≥60	3.094 (2.823–3.391)	<0.001	2.611 (2.366–2.882)	<0.001
Sex				
Female	1 (reference)		1 (reference)	
Male	0.690 (0.631–0.755)	<0.001	0.639 (0.583–0.700)	<0.001
Comorbidity				
Hypertension	1.880 (1.712–2.065)	<0.001	1.323 (1.195–1.466)	<0.001
Diabetes mellitus	1.495 (1.351–1.654)	<0.001	1.115 (1.001–1.242)	0.048
Chronic kidney disease	1.529 (1.175–1.989)	0.002	1.230 (0.939–1.611)	0.132
Hypothyroidism	1.310 (1.090–1.575)	0.004	1.038 (0.859–1.254)	0.699
Hyperthyroidism	0.831 (0.562–1.229)	0.353		
Hyperparathyroidism	1.659 (0.871–3.161)	0.124		
Cushing's syndrome	0*	0.925		
Asthma	1.500 (1.338–1.681)	<0.001	1.228 (1.094–1.378)	<0.001
Rheumatoid arthritis	1.650 (1.364–1.995)	<0.001	1.355 (1.117–1.643)	0.002
Cirrhosis	1.571 (1.435–1.719)	<0.001	1.375 (1.253–1.510)	<0.001
Corticosteroid use	0.539 (0.472 - 0.617)	<0.001	0.599 (0.523–0.687)	<0.001
Duration of follow-up, months	0.995 (0.991–0.999)	0.006	0.999 (0.996–1.003)	0.757

ETV, entecavir; HRs, hazard ratio; IPTW, inverse probability of treatment weighting; TDF, tenofovir disoproxil fumarate.
HRs and *p* values were estimated using Cox proportional hazards regression after IPTW. ETV was not significantly associated with osteoporotic fracture risk compared to TDF (p >0.05). HRs for covariates reflect direct effects under adjustment and may not be directly comparable to the total effect of primary exposures.
*The calculation is not feasible as the number of events is 0.

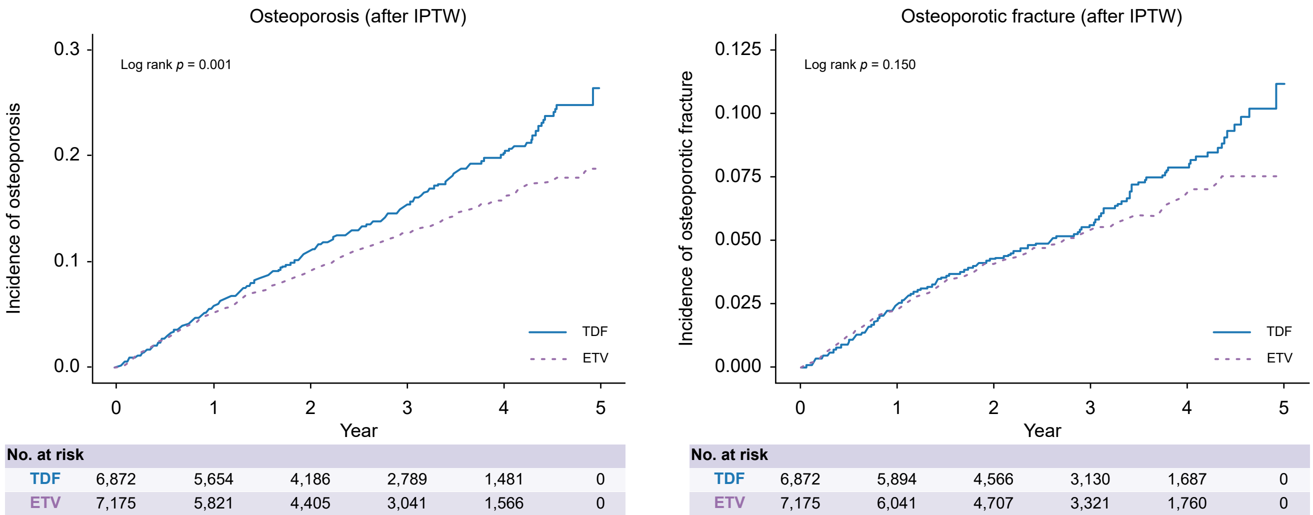

Fig. 4. Cumulative incidence of osteoporosis and osteoporotic fracture in patients aged over 60 after IPTW analysis. (A) Kaplan-Meier curves of osteoporosis development. (B) Kaplan-Meier curves of osteoporotic fracture development. ETV, entecavir; IPTW, inverse probability of treatment weighting; TDF, tenofovir disoproxil fumarate.

compared to ETV in patients with CHB. Our findings indicate that while TDF significantly increases the incidence rate of osteoporosis across all age groups, it does not elevate the risk of fractures. Cox regression analysis identified TDF as a risk factor for osteoporosis but not for fractures. In subgroup analyses of patients over 60 years old, the risk of osteoporosis and fractures was notably higher in the TDF group, with significant increases becoming apparent after 1 and 3 years of treatment, respectively.

Notably, a recent large cohort study from the Hong Kong Health Insurance Corporation corroborated our findings, indicating that TDF can increase the risk of osteoporosis and fractures compared to ETV in patients over 60, starting 2 years after the initiation of therapy.[18] While we observed an increased risk of osteoporosis with TDF use, the risk of fractures was not significantly elevated in patients of all ages. However, studies involving only patients over 60, including both the Hong Kong study and our research showed the increased risk of osteoporotic fractures after 2 to 3 years of TDF use. We propose a "two-hit" hypothesis, suggesting that osteoporosis progresses gradually with TDF use, followed by a subsequent trauma or event that triggers fractures. Moreover, individuals with pre-existing risk factors related to advanced age may be more susceptible.

The timing of fracture risk varied slightly between studies, with the Hong Kong study reporting increased fractures at 2 years, while our study noted this increase at 3 years. Differences in baseline characteristics may account for these variations; the Hong Kong study had a higher proportion of ETV users (96.1%) compared to TDF users (3.9%), whereas our study cohort had a more balanced distribution of both medications. The mean age in the Hong Kong study was 67.6 ± 6.2 years, while it was slightly younger in our study (66.0 ± 8.3 years). Additionally, the prevalence of cirrhosis was notably higher in our study (44.7%) compared to the Hong Kong study (9.7%). This suggests that while age is a known risk factor for fractures, the higher prevalence of cirrhosis in our cohort may influence outcomes. There were no significant differences between the two groups regarding other confounding variables. Presumably, osteoporosis may have been diagnosed earlier in patients in South Korea and treated with replacement therapy; however, we lacked the data to confirm this comparison.

In our analysis of risk factors for osteoporosis, TDF use was associated with a significantly higher risk compared to ETV (HR 1.328, 95% CI 1.258–1.401). Several traditional risk factors were also associated with an increased risk, including chronic kidney disease (HR 1.280, 95% CI 1.060–1.493), hypothyroidism (HR 1.309, 95% CI 1.188–1.442), hyperparathyroidism (HR 2.207, 95% CI 1.613–3.018), rheumatoid arthritis (HR 1.513, 95% CI 1.359–1.683), and cirrhosis (HR 1.119, 95% CI 1.056–1.186). Notably, in contrast to previous evidence, corticosteroid use was associated with a lower risk of both osteoporosis (HR 0.630, 95% CI 0.581–0.682) and fractures (HR 0.599, 95% CI 0.523–0.687). A possible explanation is that patients receiving corticosteroids may have undergone early BMD screening and received timely osteoporosis treatment, thereby reducing their fracture risk. Similar paradoxical findings have also been reported in other large cohort studies, where insufficient adjustment for confounding factors may have contributed to the unexpected association.[21]

We conducted a subgroup analysis to investigate whether osteoporosis treatment influenced the incidence of fractures and whether this effect differed between the TDF and ETV groups. Interestingly, fracture incidence was higher in patients who received osteoporosis treatment (IRR 5.26, 95% CI 4.64–5.96, p <0.001), which appears counterintuitive. This finding likely reflects a limitation inherent to retrospective claims data: many patients initiate osteoporosis treatment only after being diagnosed with a fracture, rather than as a preventive measure. Consequently, treatment status may reflect underlying disease severity or prior fractures, rather than functioning as an independent risk modifier.

Our findings have important implications for clinical decision-making in CHB management, particularly in older adults. The current AASLD 2018 guidelines do not recommend a specific

Table 4. Cox regression analysis for osteoporotic fracture risk in patients aged ≥60 (after IPTW).

	Univariate		Multivariate	
	HR (95% CI)	***p* values**	**HR (95% CI)**	***p* values**
Antiviral medication				
ETV	1 (reference)		1 (reference)	
TDF	1.163 (1.006–1.344)	0.041	1.213 (1.051–1.403)	0.009
Age (mean)				
≥60	1.064 (1.053–1.074)	<0.001	1.056 (1.045–1.067)	<0.001
Sex				
Female	1 (reference)		1 (reference)	
Male	0.422 (0.366–0.488)	<0.001	0.446 (0.386–0.516)	<0.001
Comorbidity				
Hypertension	1.185 (1.05–1.369)	0.021	0.949 (0.815–1.105)	0.501
Diabetes mellitus	1.177 (1.012–1.369)	0.035	1.101 (0.941–1.288)	0.230
Chronic kidney disease	1.444 (0.979–2.130)	0.064		
Hypothyroidism	1.330 (1.004–1.762)	0.047	1.089 (0.819–1.447)	0.559
Hyperthyroidism	0.434 (0.187–1.005)	0.051		
Hyperparathyroidism	0*			
Cushing's syndrome	0*			
Asthma	1.290 (1.085–1.533)	0.004	1.098 (0.922–1.308)	0.296
Rheumatoid arthritis	1.628 (1.229–2.156)	0.001	1.446 (1.089–1.920)	0.011
Cirrhosis	1.079 (0.934–1.247)	0.303		
Corticosteroid use	0.482 (0.376–0.617)	<0.001	0.517 (0.402–0.663)	<0.001
Duration of follow-up, months	0.999 (0.993–1.005)	0.697		

ETV, entecavir; HRs, hazard ratio; IPTW, inverse probability of treatment weighting; TDF, tenofovir disoproxil fumarate.
HRs and *p* values were estimated using Cox proportional hazards regression after IPTW adjustment. ETV use was associated with a significantly lower risk of osteoporotic fracture compared to TDF ($p = 0.009$). HRs for covariates reflect direct effects under adjustment and may not be directly comparable to the total effect of primary exposures.
*The calculation is not feasible as the number of events is 0.

first-line therapy for high-risk fracture groups among patients with CHB aged ≥60,[22] while the EASL 2017 guidelines suggest using ETV or TAF instead of TDF.[14] In light of our findings and those of the Hong Kong study, both of which demonstrate a significantly increased risk of osteoporosis and fractures associated with long-term TDF use – particularly after 2–3 years of treatment – clinicians should exercise caution when prescribing TDF to older patients. Although antiviral selection must consider other clinical factors such as hepatocellular carcinoma risk reduction, cardiovascular safety, and resistance profiles, our data support the consideration of ETV or TAF in patients with elevated bone risk. Furthermore, early intervention strategies such as regular BMD monitoring, adequate calcium and vitamin D supplementation, and timely re-evaluation of antiviral regimens may help mitigate skeletal complications in this population.

However, our study has several limitations. Primarily, the analysis relied on diagnostic codes and prescription data from the South Korean National Health Insurance Service, lacking laboratory data or imaging confirmation, potentially leading to underdiagnosis. However, osteoporosis diagnosis requires confirmatory testing (*e.g*. BMD assessment), and anti-osteoporosis prescriptions are strictly regulated, ensuring diagnostic validity. Additionally, baseline comorbidities and medications were assessed at the time of TDF or ETV initiation. Given the long-term follow-up period, patients' conditions may have changed. However, due to the large-scale nature of our cohort, constructing a time-dependent database that accurately reflects these changes was not feasible within the scope of this study. Moreover, this study is a retrospective cohort study, and although IPTW was used to adjust for baseline differences between the two groups, the possibility of residual confounding cannot be fully excluded. As part of a sensitivity analysis, we conducted a negative control outcome analysis using acute appendicitis. While the IRR and Kaplan–Meier curve were not statistically significant, both showed a modest trend suggesting divergence between the TDF and ETV groups. This suggests the potential presence of unmeasured confounding, and the findings should be interpreted with caution. Further prospective cohort studies are needed to validate these results.

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Abbreviations

BMD, bone mineral density; CHB, chronic hepatitis B; HIRA, Health Insurance Review and Assessment Service; IPTW, inverse probability of treatment weighting; IRR, incidence rate ratio; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.

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Conflict of interest

The authors declare that there are no conflicts of interest regarding this publication. Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Yoon E Shin contributed to investigation and writing of the original draft. Jae-Young Kim was responsible for formal analysis. Hyuk Kim contributed to investigation and writing. Jeong-Ju Yoo provided conceptualization, methodology, supervision and review. Sang Gyune Kim contributed to supervision and review. Young-Seok Kim provided supervision and review.

Data availability

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT-4.0 for translation and grammar correction. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2025.101489.

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