

Assessment of Bone Mineral Density in Tenofovir-Treated Patients With Chronic Hepatitis B: Can the Fracture Risk Assessment Tool Identify Those at Greatest Risk?

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Background. Tenofovir disoproxil fumarate (TDF) is an established nucleotide analogue in the treatment of chronic hepatitis B. Bone mineral density loss has been described in TDF-treated patients with human immunodeficiency virus infection, but limited data exist for patients with chronic hepatitis B. Dual X-ray absorptiometry (DEXA) was used to determine bone mineral density changes in TDF-exposed patients. We evaluated the accuracy of the Fracture Risk Assessment Tool (FRAX) as an alternative to DEXA in clinical practice.

Methods. A total of 170 patients were studied: 122 were exposed to TDF, and 48 were controls. All patients underwent DEXA, and demographic details were recorded. FRAX scores (before and after DEXA) were calculated.

Results. TDF was associated with a lower hip T score ($P = .02$). On univariate and multivariate analysis, advancing age, smoking, lower body mass index, and TDF exposure were independent predictors of low bone mineral density. In addition, the pre-DEXA FRAX score was an accurate predictor of the post-DEXA FRAX treatment recommendation (100% sensitivity and 83% specificity), area under the curve 0.93 (95% CI, .87–.97, $P < .001$).

Conclusions. TDF-treated patients with chronic hepatitis B have reduced bone mineral density, but the reduction is limited to 1 anatomical site. Age and advanced liver disease are additional contributing factors, underlining the importance of multifactorial fracture risk assessment. FRAX can accurately identify those at greatest risk of osteoporotic fracture.

Keywords. chronic hepatitis B; tenofovir; bone mineral density; DEXA; FRAX.

The third-generation nucleos(t)ide analogues, tenofovir and entecavir, now represent first-line treatments in

the management of chronic hepatitis B [1, 2]. While drug cost represents a barrier to early treatment and long-term use, the majority of physicians have greater concerns about the potential toxicities associated with lifelong or indefinite-duration nucleos(t)ide therapy [3].

Tenofovir disoproxil fumarate (TDF) is an acyclic nucleotide analogue of adenosine monophosphate, which has emerged as a highly effective agent in the treatment of chronic hepatitis B. Recommended by all the major liver disease organizations clinical practice guidelines [1, 2], TDF's place as a first-line antiviral is supported by the lack of any documented resistance to the drug [4] and its ability to reverse liver fibrosis [5].

The vast experience with TDF stems from its use in human immunodeficiency virus (HIV)-infected cohorts [6]. Although generally considered safe and well

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tolerated [7, 8], concerns have emerged around the potential long-term side effects associated with prolonged use [9]. These concerns focus primarily on the reported adverse impact on bone mineral density (BMD). Evaluation of TDF in randomized, controlled clinical trials revealed that it decreased BMD in HIV-infected patients [7, 10, 11], and cases of bone fractures and or osteomalacia have also been reported [12–15]. Observational data from the veterans HIV-infected cohort demonstrated that, during the highly active antiretroviral therapy era, TDF increased the risk of osteoporotic fracture and cumulative TDF exposure was independently predictive of an increased risk of osteoporotic fracture [16]. The potential mechanisms of bone toxicity remain unclear; possible mechanisms include proximal renal tubular dysfunction with resulting hypophosphatemia [17], and more recently, TDF was reported to alter osteoblast gene expression and function [18, 19].

Data are lacking on the effect of TDF therapy on BMD in cohorts with chronic hepatitis B virus (HBV) infection. Moreover, there are obvious limitations in extrapolating data around bone toxicity from HIV-infected cohorts to subjects with chronic HBV infection. Notably, reduced BMD has been reported in a proportion of healthy HIV-negative men who have sex with men, suggesting that some degree of bone loss may predate HIV infection in individuals for whom certain high-risk activities, including amphetamine and inhalant use, were associated with low BMD [20]. Similarly, identifying classical risk factors for reduced BMD are important when considering BMD loss in the context of treatment. This is pertinent in patients with chronic HBV infection from HBV-endemic areas, where ethnicity, the duration of chronic HBV infection, and the development of chronic liver disease are likely factors contributing to changes in BMD.

In addition to formally measuring BMD, we were interested in alternative modalities to assess fracture risk in patients with chronic hepatitis B. The World Health Organization (WHO) developed the Fracture Risk Assessment Tool (FRAX) as a simple and practical Internet-based tool that integrates clinical information in a quantitative manner to calculate a 10-year risk of fracture [21]. The aim of this study was to determine, for the first time, the impact of TDF therapy on BMD in a cohort with chronic HBV mono-infection. We assessed all identifiable factors associated with BMD loss in patients with chronic hepatitis B, using dual-energy X-ray absorptiometry (DEXA). Additionally, we sought to evaluate the accuracy and utility of the FRAX score as a screening method or even as an alternative to DEXA, to assess fracture risk in a real-life clinical setting.

PATIENTS AND METHODS

Study Design and Patients

Patients with chronic hepatitis B undergoing treatment with TDF or being considered for TDF therapy were offered

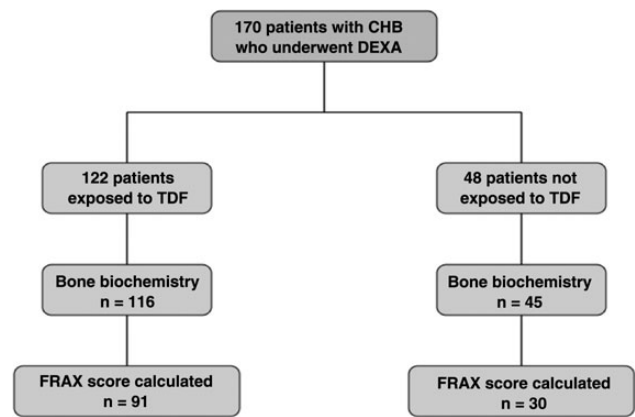


Figure 1. Study design and overview, including the number of patients analyzed in the tenofovir disoproxil fumarate (TDF)-exposed group and the unexposed control group and the interventions performed in each group. Abbreviations: CHB, chronic hepatitis B; DEXA, dual X-ray absorptiometry; FRAX, Fracture Risk Assessment Tool.

DEXA as standard of care in light of the concerns about changes in BMD reported in TDF-treated HIV-infected cohorts (Figure 1).

Patients with ≥ 12 months of TDF exposure were offered DEXA and included in the analysis. A control group comprising patients without TDF exposure but being considered for TDF were also offered DEXA and included for comparison. All patients included in the analysis were documented to be hepatitis C virus, hepatitis delta virus, and HIV negative. By electronic case note review, cross-sectional data, including demographic characteristics (age and sex), treatment duration, body mass index (BMI), fibrosis stage, other comorbidities, use of concomitant drugs, alcohol use and smoking history, were extracted (Table 1).

Bone Mineral Density Measurement

All DEXA scans were performed with a Hologic Discovery scanner and analyzed by the same physician. BMD is reported in 3 measurements: grams/square centimeters; the Z score, defined as the number of standard deviations above or below the mean for the patient's age, sex, and ethnicity (the Z score thus reflects changes in BMD, which are age matched); and the T score, which provides the number of standard deviations above or below the mean for a healthy 30-year-old individual of the same sex and ethnicity for the patient studied. Patients are classified as Black, Asian, or white, and T scores are calculated with this adjustment. Moreover, the WHO guidelines use the T score to define bone health: a T score of ≥ 1 indicates a normal BMD, a T score of -1 to -2.5 indicates osteopenia, and a T score of -2.5 or less indicates osteoporosis. In this study and for the calculation of the FRAX score, T scores are used to reflect changes in BMD.

Table 1. Baseline Characteristics at Time of Bone Mineral Density Estimation by Dual X-ray Absorptiometry (DEXA) for the Study Cohort

Variable	All Patients (n = 170)	Patients Not Receiving TDF (n = 48)	Patients Receiving TDF (n = 122)	P Value ^a
Age, y	43 (34–49)	36 (31–44)	45 (35–50)	.002
Male sex	121 (71.2%)	31 (64.6%)	90 (73.8%)	.316
Ethnicity				
Asian	109 (64.1%)	76	33	.597
Black	33 (19.4%)	26	7	
White	28 (16.5%)	20	8	
Comorbidities	22 (12.9%)	5 (10.4%)	17 (13.9%)	.717
Concomitant drug use	9 (5.3%)	1 (2.1%)	8 (6.6%)	.428
Current smoking	13 (7.6%)	5 (10.4%)	8 (6.6%)	.594
Alcohol use	28 (16.5%)	8 (16.7%)	20 (16.4%)	.852
BMI ^b	25.9 (23.1–29.4)	26.1 (23.0–29.6)	25.9 (23.4–29.2)	.795
Fibrosis severity				
Mild	77	31	46	.007
Moderate	41	8	33	
Severe	38	6	32	
Cirrhosis	41 (24.1%)	6	35	.043
HBeAg status				.208
Negative	125	30	95	
Positive	39	14	25	
HBV DNA load, log IU/mL	1.3 (1.3–8.6)	4.3 (3.5–5.7)	1.3 (1.3–1.3)	<.001
Serum calcium level, mmol/L	2.20 (2.16–2.26)	2.23 (2.17–2.30)	2.20 (2.16–2.24)	.0408
Serum phosphate level, mmol/L	1.13 (0.99–1.27)	1.19 (1.02–1.34)	1.12 (0.98–1.24)	.1368
Serum ALP level, mmol/L	74 (60–95)	67 (54–91)	76 (63–94)	.0844
ALT level, IU/L	34 (24–48)	39 (27–58)	31 (23–47)	.0485
Creatinine level, μ mol/L	82 (70–93)	79 (66–88)	84 (70–93)	.197
eGFR level, mL/min	88 (77–90)	90 (89–97)	86 (76–90)	.026
Vitamin D level, nmol/L	33 (20–46)	28 (16–41)	35 (24–46)	.106

Data are proportion (%) of subjects or median value (interquartile range). All serological/biochemical tests were performed at the time of DEXA.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; eGFR, estimated glomerular filtration rate; HBeAg, hepatitis B virus e antigen; HBV, hepatitis B virus; TDF, tenofovir disoproxil fumarate.

^a Calculated by the χ^2 test, for categorical variables, and the Mann–Whitney test, for continuous variables, which were nonparametric.

^b Body mass index (BMI) is calculated as the weight in kilograms divided by the height in square meters.

Bone Biochemical Measurements

Bone biochemistry was analyzed to determine whether these laboratory values could be used to predict BMD changes. Measurements for adjusted serum calcium (sCa) level (normal range, 2.2–2.6 mmol/L), serum phosphate (sPo) level (normal range, 0.8–1.5 mmol/L), and serum alkaline phosphatase (sALP) level (normal range, 30–130 IU/L) were recorded. Biochemical parameters were obtained at baseline, before treatment in the TDF-exposed group, and at the time of the DEXA, to establish any correlation between changes in bone biochemistry and BMD measurements. In addition, serum 25-hydroxyvitamin D (vitamin D) level (normal range, 75–150 nmol/L; vitamin D insufficiency is defined as 50–75 nmol/L, and vitamin D deficiency is defined as <50 nmol/L) was recorded for patients, when available, to document preexisting vitamin D deficiency and its potential impact on BMD measurements.

FRAX Score

The FRAX score calculates a 10-year risk of fracture, based on key clinical factors. These are composed of 12 fields, which include; subject age (in years), sex, weight (in kilograms), height (in centimeters), history of previous fracture, history of parental hip fracture, corticosteroid exposure (defined as a dose of 7.5 mg of prednisolone or the equivalent in the preceding 3 months), a concomitant diagnosis of rheumatoid arthritis, a secondary cause of osteoporosis, alcohol intake of >3 units/day, and current smoking. All patients were considered to have a secondary cause of osteoporosis because they all had chronic liver disease (ie, chronic hepatitis B). Data on family history, smoking habits, and alcohol habits were derived from clinical case records.

The clinical FRAX scores were calculated using the Internet-based tool, initially without the DEXA-measured BMD (the pre-DEXA FRAX score), and patients were risk stratified using the

age-adjusted National Osteoporosis Guideline Group (NOGG) recommendations. This allows stratification into low, medium, or high risk for developing a major osteoporotic condition (which includes the shoulder, forearm, or spine) or hip fracture over a 10-year period. On the basis of the pre-DEXA FRAX score, low-risk patients can be safely reassured, medium-risk patients can be offered DEXA, and high-risk patients can be treated prophylactically for osteoporosis. FRAX scores were then recalculated with the BMD T score (the post-DEXA FRAX score). We used the NOGG recommendation with the post-DEXA FRAX score, which stratifies patients as low risk (ie, individuals who are not currently requiring treatment for osteoporosis) or high risk (ie, individuals for whom treatment for osteoporosis is recommended).

Statistical Analysis

Continuous variables were assessed for normality using the D'Agostino Pearson test. Subsequent comparison between variables was by the Student's *t* test (1-way analysis of variance) or the Mann-Whitney (Kruskal-Wallis) test for ≥ 2 variables. Categorical variables were compared using the χ^2 test. Predictors of low T score (≤ 1) were assessed by logistic regression in both univariate and multivariate mode. In multivariate regression, the enter method was used, and well-established risk factors—age, sex, smoking status, and alcohol use status—were incorporated into multivariate models. Ethnicity was already incorporated into the T score used as the primary outcome. Missing data were managed by multiple imputation. Predictors with $>10\%$ missing values were not included in multivariate analysis.

The use of the pre-DEXA FRAX score was assessed by receiver operating characteristic (ROC) curve analysis to predict a moderate or high post-DEXA FRAX score, which is established as an indication for risk factor modification and treatment to prevent BMD loss and future fracture. The Hanley and McNeill method was used to determine the area under the ROC (AUROC) and whether it was significantly different from the null hypothesis value of 0.5.

Statistically significant differences were defined as those with a *P* value of $<.05$, and all *P* values were reported as 2 sided.

Ethical Considerations

We offer DEXA as standard of care in this dedicated chronic hepatitis B treatment clinic, where patients are exposed to or being considered for TDF treatment. In line with this, we did not require formal ethical approval according to the guidelines of the UK National Research Ethics Service.

RESULTS

One-hundred and seventy patients were included for analysis (Figure 1 and Table 1), of whom 122 (71.8%) were treated with TDF. Forty-eight of 170 patients had no exposure to TDF and comprised 13 (27%) who were treated with pegylated

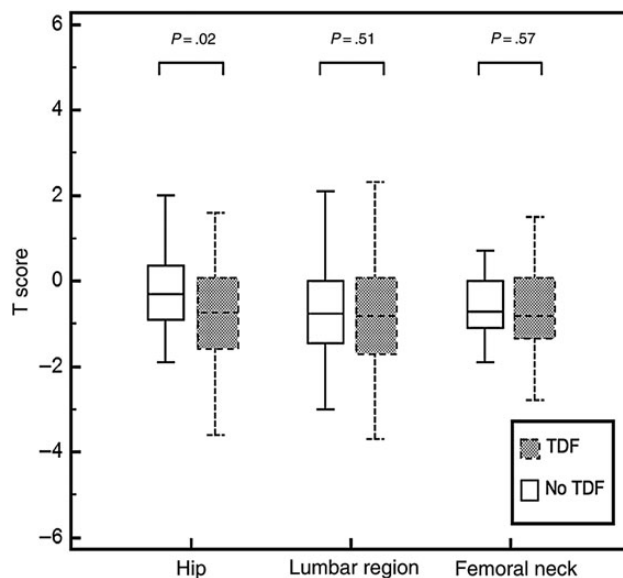


Figure 2. Box and whisker plots indicating bone mineral density changes, by T score at each site (hip, lumbar and femoral neck [FN]) in the tenofovir disoproxil fumarate (TDF)-exposed group and the unexposed control group.

interferon, 5 (10%) who were treated with entecavir, and 30 (63%) who were treatment naive. Characteristics of the whole cohort were similar between those who were and those who were not treated with TDF, except that patients receiving TDF tended to be older with more-advanced liver disease and a reduced estimated glomerular filtration rate (Table 1).

Prevalence of BMD Loss in Patients With Chronic HBV Infection

Osteopenia, defined by DEXA results as a T score between -1 and -2.5 , was recorded in 62 patients (36.5%) at the lumbar site, 59 (34.7%) at the hip, and 58 (34.1%) at the femoral neck. Osteoporosis (defined as a T score of -2.5 or less) was found in 11 patients (6.5%) at the lumbar site, 5 (2.9%) at the hip site, and 5 (2.9%) at the femoral neck. A total of 102 patients had a T score of -1 or less at any site, and 33 had a T score of -1 or less at all 3 anatomical sites.

In this cohort, BMD showed variable correlation between the 3 different sites and was highest between the hip and femoral neck: lumbar BMD versus femoral neck BMD, $r = 0.59$; lumbar BMD versus hip BMD, $r = 0.65$; and hip BMD versus femoral neck BMD, $r = 0.89$.

TDF Exposure Is Associated With a Lower T Score at the Hip Site

TDF use was not associated with reductions in BMD at the lumbar or femoral neck sites but was associated with significantly lower T scores at the hip (Figure 2). In the TDF-treated group, osteopenia was present in 46 of 122 TDF-treated patients (37%) at the lumbar site, 49 (40%) at the hip, and 43 (35%) at the

Table 2. Variables Associated With T Scores of -1 or Less or Greater Than -1 at the Hip

Variable	T Score		Univariate		Multivariate	
	-1 or Less (n = 64)	Greater Than -1 (n = 106)	OR (95% CI)	P Value ^a	OR (95% CI)	P Value
Age, y	46 (26–64)	38 (20–64)	1.06 (1.02–1.09)	.001	1.06 (1.02–1.11)	.006
Male sex	50 (78.1%)	71 (67.0%)	1.95 (.94–4.05)	.102	1.37 (.56–3.36)	.528
BMI ^b	25.0 (16.4–38.9)	26.6 (19.5–46.0)	0.92 (.86–.99)	.030	0.88 (.81–.97)	.013
Current smoking	9 (14.1%)	4 (3.8%)	4.17 (1.23–14.17)	.032	5.58 (1.38–22.57)	.016
Tenofovir use	54 (84.4%)	68 (64.2%)	3.02 (1.38–6.60)	.008	2.95 (1.14–7.45)	.026
Cirrhosis	18 (28.1%)	23 (21.7%)	1.41 (.69–2.88)	.445	0.67 (.27–1.64)	.372
Other drug use	5 (7.8%)	4 (3.8%)	2.16 (.56–8.36)	.432	1.68 (.35–8.04)	.517
Comorbidities	10 (15.6%)	12 (11.3%)	1.45 (.59–3.58)	.566	1.18 (.38–3.62)	.776
Alcohol use	13 (20.3%)	15 (14.2%)	1.55 (.68–3.50)	.403	1.30 (.48–3.54)	.602
Vitamin D level, nmol/L ^c	37 (7–95)	29 (5–75)	1.02 (.99–1.04)	.113	1.01 (.99–1.03)	.452
Creatinine level, μ mol/L	85 (71–96)	81 (68–92)	1.00 (.99–1.00)	.285	...	
eGFR, mL/min	90 (77–104)	86 (76–100)	0.99 (.98–1.02)	.781	1.01 (.98–1.03)	.540
HBV DNA load, log IU/mL	1.3 (1.3–1.3)	1.3 (1.3–3.5)	0.81 (.65–1.00)	.050	...	
HBeAg negative	12 (18.8%)	27 (25.5%)	0.76 (.35–1.65)	.493	...	
Serum calcium level, mmol/L	2.21 (2.17–2.27)	2.20 (2.15–2.26)	24.3 (.26–2.25)	.167	...	
Serum phosphate level, mmol/L	1.15 (0.98–1.27)	1.16 (1.01–1.27)	0.62 (.12–3.31)	.578	...	
Serum ALP level, mmol/L	81 (62–100)	73 (59–88)	1.00 (.99–1.01)	.404	...	
ALT level, IU/L	34 (24–46)	34 (24–48)	0.99 (.98–1.01)	.932	...	

Data are proportion (%) of subjects or median value (interquartile range). Multivariate analysis is by logistic regression modeling with the enter method: null model, -2 log likelihood 214; full model, -2 log likelihood 178 ($\chi^2 = 36.3$; $P = .0002$).

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; CI, Confidence Interval; eGFR, estimated glomerular filtration rate; HBeAg, hepatitis B virus e antigen; HBV, hepatitis B virus; OR, odds ratio.

^a Univariate P values are by the χ^2 test, for categorical variables, and the Mann–Whitney test, for continuous variables, which were nonparametric.

^b Body mass index (BMI) is calculated as the weight in kilograms divided by the height in square meters.

^c Incomplete data (>10% missing values) were addressed using multiple imputation for multivariate modeling.

femoral neck. In the non-TDF-exposed patients, osteopenia was observed in 16 of 48 patients (33%) at the lumbar site and in 15 (31%) at the femoral neck; of note, significantly less osteopenia was seen at the hip in the non-TDF-treated group (10 [21%]; $P = .02$), compared with the TDF-treated group.

This association was investigated further by multivariate modeling for the binary outcome variable T score of -1 or less (Table 2). On logistic regression, independent predictors of a T score of -1 or less were TDF use (odds ratio [OR], 2.90; $P = .027$), advancing age (OR, 1.06 per 1-year increase in age; $P = .006$), smoking (OR, 5.58; $P = .016$), and lower BMI (OR, 0.88 per unit decrease; $P = .01$). Prior exposure to lamivudine therapy in the TDF-exposed cohort was also studied; this had no impact on BMD changes at any site (data not shown). The impact of cirrhosis did not prove significant for BMD loss. Fibrosis stage was classified as mild, moderate, or severe in patients who underwent liver biopsy ($n = 156$); we could not demonstrate a univariate association with fibrosis severity and BMD loss at the hip. (Supplementary Table 1)

Duration of TDF Exposure and BMD Loss

All TDF-exposed patients received TDF therapy for a minimum of 12 months. We sought to establish whether duration of

exposure was associated with greater reductions in BMD over time, a factor that would have clear implications for the long-term use of the drug. Of the 122 patients who had a minimum of 12 months of exposure, 44 underwent DEXA after a minimum of 24 months of exposure, including 17 patients who had received therapy for >30 months at the time of DEXA. There was no significant correlation between duration of exposure to TDF and reduction in BMD at any site (Supplementary Table 2). While there was a significant reduction in BMD at the hip with TDF therapy, this appeared to be independent of drug duration beyond 12 months of exposure. These data are in line with a previously published study of HIV-infected patients in which a relatively early reduction in BMD was found at some anatomical sites among TDF recipients but did not appear to be progressive over time [17].

Biochemical Parameters and BMD Loss

As TDF was associated with significant reductions in BMD at the hip, we sought to establish any correlation between serum biochemistry variables—sCa, sPO, and sALP levels—and changes in BMD at the time of DEXA. No correlation was found between any of these parameters and changes in BMD at the hip or at any other site (Supplementary Table 3). There

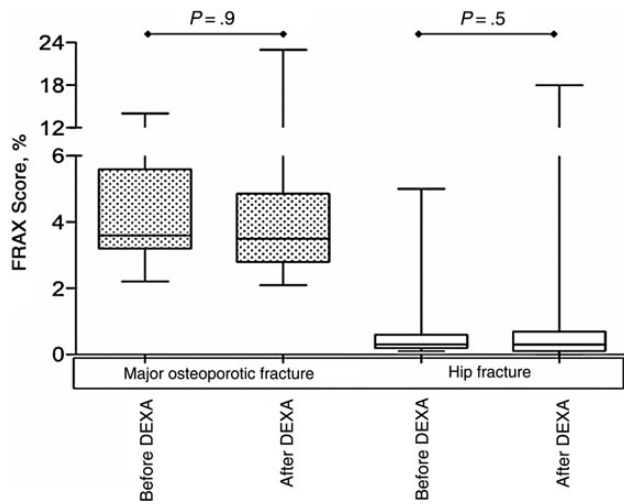


Figure 3. Box and whisker plots comparing Fracture Risk Assessment Tool (FRAX) scores before and after dual X-ray absorptiometry (DEXA) to determine the risk of developing a major osteoporotic or hip fracture in all patients.

was, however, a trend toward higher sALP levels in patients who were prescribed TDF, but this was not statistically significant ($P = .07$). The sALP level peaked after a minimum of 12 months of TDF exposure, but this was not progressive in line with BMD changes. These data highlight the limitations of bone biochemistry findings, as previously reported, in the assessment and monitoring of changes in BMD [22, 23].

Utility of FRAX to Assess Fracture Risk Over Time

Complete FRAX scores were available for 121 of 170 patients. Pre-DEXA FRAX scores ranged from 2.2% to 14.0% (median, 3.6%) for the 10-year probability of a major osteoporotic fracture, while post-DEXA FRAX scores ranged from 2.1% to 23.0% (median, 3.5%). Using the pre-DEXA FRAX score, patients may be classified to be at low, intermediate, or high risk of experiencing a major osteoporotic fracture, using age-dependent NOGG cutoffs; in this cohort 30 of 121 patients (24.8%) were categorized as medium or high risk, and 75.2% were categorized as low-risk (Figure 3).

Post-DEXA FRAX scores are categorized as above or below an intervention threshold, as well as by age-dependent NOGG cutoffs; patients with post-DEXA FRAX scores above this threshold are recommended to commence pharmacological osteoporosis prophylaxis. In this cohort, 12 of 121 patients (9.9%) had values above the intervention threshold, according to post-DEXA FRAX scoring.

We explored the ability of the pre-DEXA FRAX score to predict which patients subsequently had post-DEXA FRAX scores above the intervention threshold, with the aim of characterizing the added utility of DEXA scanning in different pre-DEXA risk categories. By ROC curve analysis, for the whole cohort, the

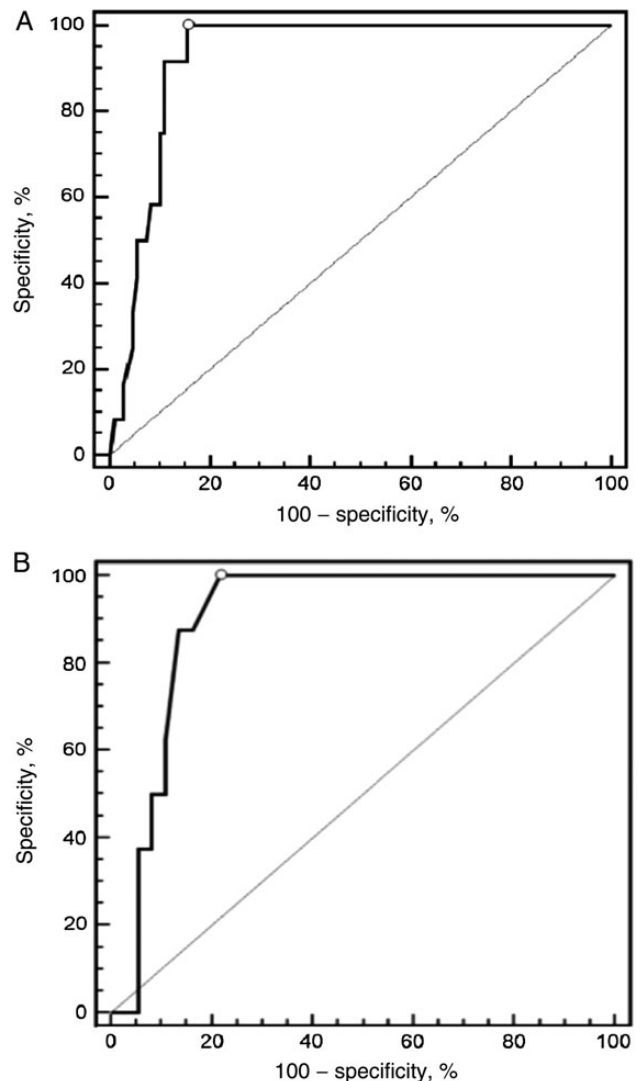


Figure 4. A, Receiver Operating Characteristic (ROC) curve indicating the ability of the Fracture Risk Assessment Tool (FRAX) score before dual X-ray absorptiometry (DEXA) to predict the post-DEXA FRAX score in the whole cohort. The area under the ROC curve (AUROC) was 0.93 (95% confidence interval [CI], .87–.97; $P < .001$), with a sensitivity of 100% (95% CI, 73%–100%) and a specificity of 83% (95% CI, 75%–90%). B, ROC curve indicating the ability of the pre-DEXA FRAX score to predict the post-DEXA FRAX score in a subgroup analysis of patients with low bone mineral density (defined as a T score of less than -1). The AUROC was 0.90 (95% CI, .81–.99; $P < .001$), with a sensitivity of 100% (95% CI, 63%–100%) and a specificity of 78% (95% CI, 62%–90%).

pre-DEXA FRAX score had good ability to distinguish between patients with and those without recommendation for subsequent treatment: area under the curve [AUC], 0.93 (95% confidence interval [CI], .87–.97; $P < .001$). No patients classified as low risk on the basis of pre-DEXA FRAX score had post-DEXA FRAX scores above the intervention threshold; a medium or high risk pre-DEXA FRAX score had a 100% sensitivity (95% CI, 73%–100%) and 83% specificity (95% CI, 75%–90%) for

post-DEXA FRAX-based treatment recommendation, with a positive likelihood ratio of 6 (95% CI, 4–9) and a negative likelihood ratio of 0 (Figure 4A). Subgroup analysis for patients with low BMD (ie, a T score of less than –1) demonstrated an AUROC of 0.90 (95% CI, .81–.99; $P < .001$), with a sensitivity of 100% (95% CI, 63%–100%) and a specificity of 78% (95% CI, 62%–90%), at a cutoff pre-DEXA FRAX score of 0.6, thus highlighting the strong performance of FRAX in patients with reduced BMD (Figure 4B).

DISCUSSION

These data raise the possibility that use of TDF for treatment of chronic hepatitis B may be associated with BMD loss, in line with previous reports on BMD changes in HIV-infected cohorts. A recent study reported a <2% decline in BMD in TDF-treated patients with chronic hepatitis B [24]. Our data demonstrated a similar effect but only at the hip. These BMD changes must be interpreted in the context of the treatment group, who were ostensibly older with more-advanced disease. Preferential bone loss in certain anatomical sites has been attributed to a possible loss of muscle strength, to which bone adapts; therefore, the pattern of bone loss varies between individuals [25].

Consistent with previous reports, we demonstrated classic risk factors: advancing age, lower BMI, and smoking were all associated with significant reductions in BMD on multivariate analysis [26, 27]. Recent data propose a relationship between low BMD and nutritional/renal status [28, 29]. This emphasizes the potential differences between patient populations, which should be considered when evaluating changes in BMD. Similarly, the lack of any progressive decline in BMD with duration of exposure, in line with published data from TDF-treated HIV patients [17], emphasizes the importance of patient characteristics in BMD loss. In addition, a recent study demonstrated a plateau in the decline of hip BMD after 72 weeks of TDF therapy; thus, we conclude that therapy-associated decline in BMD appears early after treatment initiation but is not a progressive phenomenon [24].

These are important findings in terms of the management of chronic HBV infection. Continued suppression of viral replication through effective long-term nucleos(t)ide therapy translates into better outcomes, reducing the risk of development of cirrhosis and hepatocellular carcinoma [30, 31]. Owing to the high risk of relapse after nucleos(t)ide withdrawal, the majority of patients will require lifelong therapy [32, 33], with an inherent risk of toxicity associated with long-term use. In addition, the natural progression of treatment strategies is likely to involve earlier initiation of treatment, to avert the development of the long-term sequelae of chronic hepatitis B [34]. There is a growing argument to offer earlier treatment, which is based on the efficacy and high genetic barrier to resistance to the third-generation nucleos(t)ides, specifically TDF [35, 36]. A recent

study reported on the safety and tolerability of TDF in adolescents with chronic HBV infection, and interestingly, no significant decrease in spine BMD was observed over 72 weeks of therapy, although the longer-term effects of TDF introduction at a younger age remain unknown [37]. Decisions around the timing and initiation of antiviral therapy in chronic hepatitis B will have to give due consideration to the potential influence of TDF on BMD.

Classic risk factors for the development of an osteoporotic fracture appear to be more important and should be formally assessed. Here, we demonstrate the utility of the FRAX score in the management of chronic hepatitis B, as previously shown in HIV-infected cohorts [17]. We clearly demonstrate that FRAX provides a robust tool for the assessment of fracture risk in patients receiving or being considered for TDF therapy. FRAX would have obvious advantages in clinical practice because it is a simple Internet-based tool that can assess fracture risk, yielding consideration of alternative therapies if the FRAX score prompted concerns around bone health. Importantly, we showed that the pre-DEXA FRAX score could determine a risk profile for continuing TDF therapy without resorting to DEXA in all patients. In our cohort, over three quarters (75.2%) of patients were at low risk for a major osteoporotic and hip fracture, obviating the need for DEXA. Conversely, for the remaining patients (24.8%) with a medium or high risk, DEXA or treatment for osteoporosis would be warranted, based on their FRAX score. We demonstrate that the pre-DEXA FRAX score is highly sensitive and specific in predicting post-DEXA FRAX outcome measures. When DEXA was performed to calculate the post-DEXA FRAX score, we confirmed that none of the patients for whom a low risk was revealed by the pre-DEXA FRAX score fell into the high-risk category, in which osteoporosis treatment would be indicated. No high-risk patients were missed on the basis of the pre-DEXA FRAX score, underlining its potential utility in this clinical setting. Prevalence of osteoporosis in chronic viral hepatitis is reported to be as high as 53% [38], thus underlining the importance of assessing bone health in these patients. Our data suggest that the FRAX score could obviate the need for DEXA, eliminating the associated costs of baseline and longitudinal monitoring of BMD in the majority of patients.

Our data do not support the utility of the sALP level or any other biochemical parameter as a surrogate for bone regeneration and turnover. Although a trend toward higher sALP levels was noted and peaked at month 12 of therapy, this trend was not significant, precluding its use as a benchmark for renal phosphate loss and reduced BMD. Another important factor to consider in terms of reduced BMD is vitamin D deficiency [39, 40]. However, we found that vitamin D deficiency was not significantly associated with BMD loss on univariate or multivariate analysis. Widely available and inexpensive markers, such as the urine protein:creatinine index, could also be used to identify patients at risk of TDF-related BMD complications. In

addition, an association between bone status and HLA super-types (HLA-DQ3) has been demonstrated [41], suggesting the potential utility of using genetic factors to predict TDF-associated BMD changes.

We acknowledge the limitations of this study, specifically the lack of baseline and longitudinal DEXA data to correlate BMD loss over time with TDF exposure. Further studies will be required to confirm whether there is a direct meaningful effect of TDF on BMD loss. Nonetheless, consistent with studies from HIV-infected cohorts, our findings raise concerns about the potential negative impact of TDF on BMD in a cohort with chronic hepatitis B. This study underlines the importance of FRAX and its potential role in the identification of patients with chronic HBV infection who are at risk of a major osteoporotic fracture. We conclude that FRAX represents a cheap and highly effective tool, which should be incorporated into clinical practice to identify those at greatest risk. Our data suggest that this strategy would obviate the need for DEXA in the majority of cases and could identify patients for whom DEXA and pharmacological intervention must be considered in the decision about which first-line antiviral treatment regimens to initiate.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (<http://jid.oxfordjournals.org>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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