Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in virologically suppressed patients with chronic hepatitis B: a randomised, double-blind, phase 3, multicentre non-inferiority study

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Summary

Background Treatment with tenofovir disoproxil fumarate has been associated with renal toxicity or reductions in bone mineral density, or both, in some patients with chronic hepatitis B virus (HBV) infection. Tenofovir alafenamide is a tenofovir prodrug with high intrahepatic concentrations of active drug and reduced systemic tenofovir exposures compared with tenofovir disoproxil fumarate. In patients with chronic HBV, tenofovir alafenamide has shown efficacy non-inferior to that of tenofovir disoproxil fumarate with improved renal and bone safety. With this non-inferiority study, we aimed to evaluate the efficacy and safety of tenofovir alafenamide in patients with HBV infection switching from tenofovir disoproxil fumarate who are virally suppressed.

Methods Patients with chronic HBV infection who had been receiving tenofovir disoproxil fumarate for 48 weeks or more and who had HBV DNA less than the lower limit of quantification (LLOQ) for at least 12 weeks were recruited to this randomised, multicentre, double-blind, phase 3 non-inferiority study. Patients were randomly assigned in a 1:1 ratio to receive tenofovir alafenamide 25 mg once a day or to continue tenofovir disoproxil fumarate 300 mg once a day. The primary efficacy endpoint was loss of virological control, defined as the proportion of patients who received at least one dose of study drug who had HBV DNA of at least 20 IU/mL at week 48 by the modified US Food and Drug Administration (FDA) snapshot algorithm. Key safety endpoints were changes in hip and spine bone mineral density, estimated creatinine clearance by Cockcroft-Gault, and markers of bone turnover and renal tubular function. The study was powered for non-inferiority in efficacy of tenofovir alafenamide versus tenofovir disoproxil fumarate with a 4% margin. Investigators and patients were unaware of treatment allocation and on-treatment results. This trial is ongoing and is registered with ClinicalTrials.gov, number NCT02979613.

Findings Participants in this study were enrolled between Dec 29, 2016, and Oct 20, 2017. 541 patients were screened and 490 patients were randomly assigned to switch to tenofovir alafenamide or to stay on tenofovir disoproxil fumarate. Two patients assigned to receive tenofovir alafenamide did not receive treatment; thus the full analysis set for efficacy and safety analyses consisted of 243 patients in the tenofovir alafenamide group and 245 in the tenofovir disoproxil fumarate group. At week 48, one patient from each treatment group (both <1%) had HBV DNA of at least 20 IU/mL (difference in proportion 0·0%, 95% CI –1·9 to 2·0), thereby showing non-inferior efficacy of tenofovir alafenamide to tenofovir disoproxil fumarate. Patients who received tenofovir alafenamide had significantly increased bone mineral density at hip (mean change 0·66% [SD 2·08] *vs* –0·51% [SD 1·91]; difference in least square means 1·17% [95% CI 0·80 to 1·54; p<0·0001]) and at spine (mean change 1·74% [3·46] *vs* –0·11% [3·13]; difference in least square means 1·85% [1·24 to 2·46; p<0·0001]), creatinine clearance by Cockcroft-Gault relative to tenofovir disoproxil fumarate (median change 0·94 mL/min [IQR –4·47 to 6·24] *vs* –2·74 mL/min [–7·89 to 1·88]; p <0·0001), and improved markers of bone turnover and tubular function at week 48. The most common treatment-emergent adverse events were upper respiratory tract infection (18 [7%] of 243 patients in the tenofovir alafenamide group and 16 [7%] of 245 patients in the tenofovir disoproxil fumarate group) and nasopharyngitis (13 [5%] of 243 patients in the tenofovir alafenamide group and 12 [5%] of 245 patients in the tenofovir disoproxil fumarate group). The incidence of grade 3 and above adverse events and serious adverse events was low and similar between groups. No viral resistance was observed in patients who qualified for viral sequencing.

Interpretation These findings suggest that tenofovir alafenamide can be substituted for tenofovir disoproxil fumarate in patients with HBV infection for improved safety without a loss of efficacy.

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Research in context

Evidence before the study

We searched PubMed on May 30, 2019, using the search terms "HBV", "hepatitis B virus", "chronic HBV", "tenofovir disoproxil fumarate", "tenofovir alafenamide", "bone toxicity", and "nephrotoxicity", for clinical trials published from inception to May 30, 2019, restricted to English language publications. Previous phase 3 studies in patients with chronic HBV, viraemia and elevated serum alanine aminotransferase (ALT) concentrations have shown tenofovir alafenamide to have similar efficacy to tenofovir disoproxil fumarate with improved bone and renal safety. There are no published studies that have examined switching patients who are receiving tenofovir disoproxil fumarate therapy to tenofovir alafenamide in a randomised fashion to evaluate whether efficacy is maintained and bone and renal safety are improved. Treatment guidelines from the European Association for the Study of the Liver and American Association for the Study of Liver Diseases recommend that patients with active HBeAg-negative and HBeAg-positive chronic HBV infection receive antiviral therapy of indefinite duration with entecavir, tenofovir disoproxil fumarate, or tenofovir alafenamide, which are considered first-line therapies for HBV infection. The same guidelines recommend that tenofovir alafenamide be used instead of tenofovir disoproxil fumarate in patients who are at risk for bone and renal complications with tenofovir disoproxil fumarate. Tenofovir alafenamide was developed specifically to deliver the active metabolite of tenofovir to hepatocytes at lower doses than tenofovir disoproxil fumarate. In clinical trials in patients with HIV and HBV, the lower systemic exposure to tenofovir with tenofovir alafenamide resulted in reduced renal and bone effects compared with tenofovir disoproxil fumarate. The present study was done to establish whether switching patients with chronic HBV who are virally suppressed on tenofovir disoproxil fumarate to tenofovir alafenamide would offer improvements without a loss of antiviral efficacy. To our knowledge this is the first statistically powered study to evaluate the safety and efficacy of switching to tenofovir alafenamide from tenofovir disoproxil fumarate using the US Food and Drug Administration snapshot algorithm, initially applied for use in HIV switch trials and modified for use in patients with chronic HBV infection.

Added value of this study

Our results show that in patients on long-term treatment with tenofovir disoproxil fumarate, switching to tenofovir alafenamide is as effective at suppressing HBV replication as continuing tenofovir disoproxil fumarate for one additional year. Evaluation of clinical and laboratory measures which were also used in previous studies that compared tenofovir alafenamide with tenofovir disoproxil fumarate suggests that tenofovir alafenamide might have less pronounced adverse effects on bone and renal health than tenofovir disoproxil fumarate. An unexpected finding was that in the subset of patients with elevated ALT at baseline, a higher proportion of patients receiving tenofovir alafenamide achieved normalisation of ALT concentrations according to 2018 AASLD criteria. The clinical implications of this finding are unclear.

Implications of all the available evidence

Although the short-term results of this trial are promising, the possible clinical benefits of switching to tenofovir alafenamide from tenofovir disoproxil fumarate for patients with chronic HBV infection will require confirmation in longer term follow-up studies.

Introduction

The population of patients chronically infected with hepatitis B virus (HBV)—estimated at 257 million worldwide in 2015—is ageing.[1] Between 2006 and 2015, the median age of patients with HBV in the US Medicaid system increased from 44 to 50 years. This increase is partly attributable to the widespread adoption of neonatal vaccination programmes, which have driven down the number of new HBV infections,[2,3] but also to improved patient survival as a result of advances in treatment.[4] In addition, the ageing population of patients with chronic HBV infection has an increasing prevalence of HBV-related comorbidities such as cirrhosis and hepatocellular carcinoma, as well as other comorbidities, including diabetes mellitus, hypertension, and chronic kidney disease.[1,5,6]

Oral nucleos(t)ide analogue drugs are the best tolerated treatment options for patients with chronic HBV infection and first-line treatments offering potent inhibition of viral replication coupled with a low or negligible development of resistance; however, only a small proportion of patients have HBsAg loss with these drugs (<9%), such that most patients will require lifelong treatment.[7] In an ageing cohort with existing comorbidities, even mild drug toxicities can be problematic in the context of long-term treatment.

Tenofovir disoproxil fumarate is an oral prodrug of the nucleotide analog tenofovir. Although tenofovir disoproxil fumarate is a highly effective antiviral agent with a negligible risk of resistance,[8] the relatively high dose required to achieve active hepatic concentrations of tenofovir diphosphate also produces high concentrations of circulating tenofovir, which can result in kidney and bone toxicity over long-term use.[9] Tenofovir alafenamide is an oral phosphonamidate prodrug of tenofovir with greater stability in plasma than tenofovir disoproxil fumarate. Tenofovir alafenamide provides high intracellular concentrations of tenofovir diphosphate, the active metabolite, to HBV-infected hepatocytes.[10] Patients with HBV receiving tenofovir alafenamide have circulating plasma concentrations of tenofovir approximately 90% lower than those in patients taking tenofovir disoproxil fumarate at approved doses.[11] In phase 3 trials, patients with viraemia and HBeAg-positive and HBeAg-negative

chronic HBV infection randomly assigned to tenofovir alafenamide treatment had significantly smaller decreases in bone mineral density and smaller increases in serum creatinine, as well as improvements in markers of renal tubular function and bone turnover as compared with patients receiving tenofovir disoproxil fumarate at weeks 48 and 96.[12–14] In addition, the efficacy of tenofovir alafenamide in virally suppressed patients with HBV on long-term efficient tenofovir disoproxil fumarate therapy is not known.

We did an international, multicentre, phase 3 study to evaluate the efficacy and safety of tenofovir alafenamide in virally suppressed patients with chronic HBV infection who switch treatment from tenofovir disoproxil fumarate.

Methods

Study design and participants

Patients were enrolled at 42 sites, including hospitals and clinics in eight countries (Hong Kong, South Korea, Taiwan, Canada, Italy, Spain, UK, and USA). Patients were at least 18 years of age with documented evidence of HBeAg-negative or HBeAg-positive chronic HBV infection, including those with compensated cirrhosis. Eligible patients had been receiving tenofovir disoproxil fumarate 300 mg once a day for at least 48 weeks, and as monotherapy for at least 24 weeks before screening. Eligible patients were virally suppressed (HBV DNA <lower limit of quantification [LLOQ] by local laboratory assessment) for at least 12 weeks before screening and were required to have HBV DNA <20 IU/mL (by central laboratory) at screening. Eligible patients had an estimated creatinine clearance of at least 50 mL/min (by the Cockcroft-Gault method).

Patients with hepatocellular carcinoma, evidence of hepatic decompensation, or co-infection with other viruses (HIV, hepatitis C virus [HCV], or hepatitis D virus [HDV]) were excluded, as were patients with abnormal laboratory parameters, including haemoglobin of less than 10 g/dL, absolute neutrophil count of less than 750 cells per mm³, platelet count of 50 000 per mm³ or less, aspartate aminotransferase (AST) or serum alanine aminotransferase (ALT) greater than 5×the upper limit of normal (ULN), albumin less than 3·0 mg/dL, International Normalised Ratio (INR) greater than 1·5×ULN (unless stable on anticoagulant regimen), or total bilirubin >2·5×ULN). Complete entry and exclusion criteria are provided in the appendix (pp 2–3). This study was approved by the institutional review board or independent ethics committees at all participating sites and was done in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements. Written informed consent was obtained from all patients before enrolment and any study procedures.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to receive either tenofovir alafenamide with a matching placebo of tenofovir disoproxil fumarate, or to continue taking tenofovir disoproxil fumarate with a matching placebo of tenofovir alafenamide. We used an online interactive response system (Bracket Global, San Francisco, CA, USA), for computer-generated randomisation sequences with a preset block size of four and a predefined stratification scheme. Randomisation was stratified by HBeAg (positive or negative) status and age (≥50 or <50 years). Investigators and patients were unaware of treatment allocation and on-treatment results until database lock. The treating physician obtained the next centrally stored treatment allocation by use of the interactive online response system. Access to unmasked treatment codes was provided to the sponsor via a secure file transfer protocol server system only after the data and statistical analysis plan were finalised.

Procedures

Patients received either tenofovir alafenamide 25 mg plus matching tenofovir disoproxil fumarate placebo or tenofovir disoproxil fumarate 300 mg plus matching tenofovir alafenamide matching placebo orally once daily. The duration of double-blind treatment was 48 weeks. All patients who completed 48 weeks of treatment were eligible to receive open-label tenofovir alafenamide 25 mg for an additional 48 weeks.

Adverse events were assessed by the study investigator at each study visit. Laboratory analyses (haematology, chemistry, and urinalysis; Covance Central Laboratory Services, Indianapolis, IN, USA, Geneva, and Singapore), plasma HBV DNA (Roche COBAS AmpliPrep COBAS TaqMan HBVtest, v2.0 with an LLOQ of 20 IU/mL), HBsAg (Architect HBsAg Assay with an LLOQ of 0·05 IU/mL, Abbott Laboratories, Abbott Park, IL, USA), blood and urine tests for renal and bone biomarkers, and physical examinations were done at baseline and at weeks 4, 8, 12, 24, 36, and 48. Dual energy X-ray absorptiometry scans for hip and spine bone mineral density were done at baseline and weeks 24 and 48. All scans were blindly read by a centralised laboratory (BioClinica, Newark, CA, USA). Kidney function tests included serum creatinine, estimated creatinine clearance by Cockcroft-Gault equation, and estimated creatinine clearance by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). Proteinuria was assessed qualitatively by dipstick urinalysis, quantitatively by urine protein to creatinine ratio, urine albumin to creatinine ratio, and specific proximal renal tubular proteinuria (retinol binding protein to creatinine ratio, β2-microglobulin to creatinine ratio); renal function was also assessed by renal tubular maximum reabsorption prevalence of phosphate to the glomerular filtration rate (eGFR) and fractional excretion of phosphate.

See Online for appendix

Outcomes

The primary efficacy endpoint was the proportion of patients who lost virological control (ie, HBV DNA

≥20 IU/mL) at week 48, as defined by the modified US Food and Drug Administration (FDA)-defined snapshot algorithm.[15] A full description of the snapshot algorithm criteria are provided in the appendix (p 4).

Secondary efficacy endpoints were the proportion of patients with HBV DNA less than 20 IU/mL (including the proportion with target not detected), by missing equals failure analysis, the proportions of patients with HBeAg loss and seroconversion to anti-HBe, and the proportion of patients with HBsAg loss and seroconversion to anti-HBs. The other secondary efficacy endpoints were the proportions of patients with normal ALT (ALT value at or below the upper limit of normal [ULN] at week 48 regardless of baseline value) and normalised ALT (ie, ALT ≤ULN at week 48 in the subset with ALT >ULN at baseline), and change from baseline in fibrosis as determined by serum FibroTest (BioPredictive S.A.S, Paris, France).

Sequence analysis of the HBV polymerase–reverse transcriptase for potential resistance mutations was done in patients with HBV DNA of 69 IU/mL or greater at any study visit from baseline through to the end of week 48.

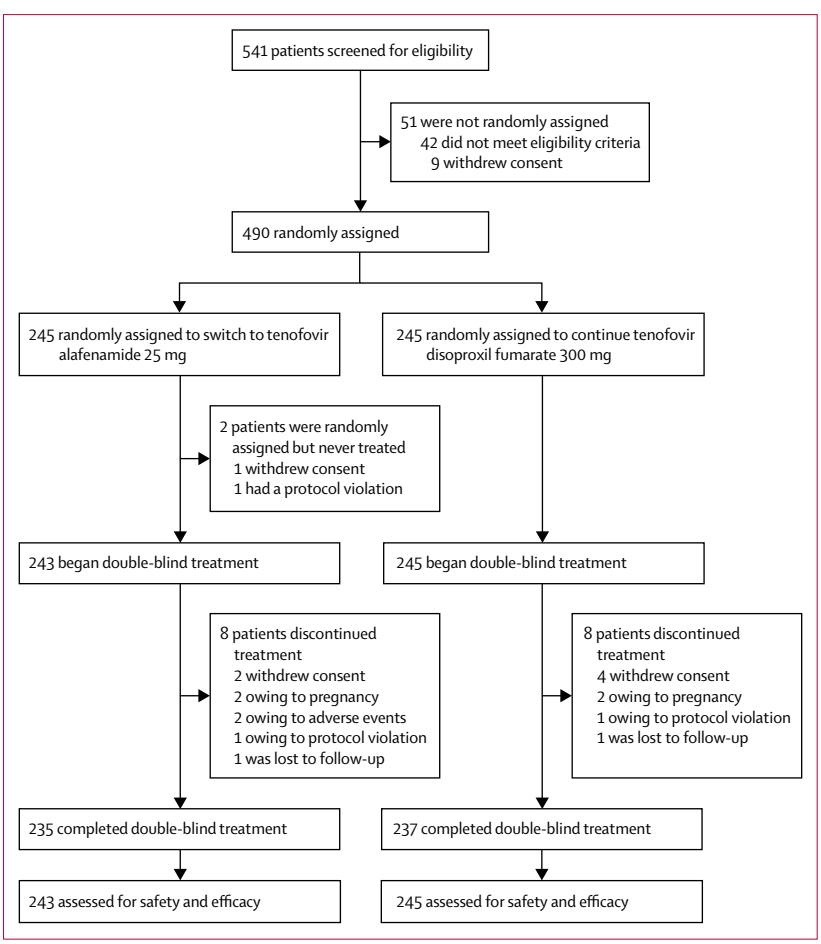

Figure 1: **Trial profile**

The primary safety endpoint was the safety and tolerability in patients switched to tenofovir alafenamide as compared with patients who continued tenofovir disoproxil fumarate treatment at week 48. The prespecified secondary safety endpoints were the percentage change from baseline in hip and spine bone mineral density and change in creatinine clearance at week 48. Bone mineral density was determined by dual-energy X-ray absorptiometry scans and creatinine clearance was estimated by means of the Cockcroft-Gault method.

Protocol-defined exploratory safety endpoints at week 48 included the percentage changes in serum markers of bone formation (procollagen type 1 N-terminal propeptide; P1NP) and bone resorption (C-type collagen sequence), and percentage changes in quantitative proteinuria markers (urine protein to creatinine ratios and urine albumin to creatinine ratios), and percentage changes in urinary proximal tubular markers (the ratios of retinol binding protein and β2 microglobulin to creatinine). We did a post-hoc assessment of changes in creatinine clearance to establish the possible effect of concomitant treatments for hypertension and or diabetes, or both on creatinine clearance, for the small subset of patients receiving at least one of these treatments during the study.

Statistical analysis

A sample size of 230 patients for each treatment group was calculated to achieve 80% power to establish non-inferiority of the primary efficacy endpoint with a 4% margin at a one-sided significance level of 0·025. This margin was calculated assuming that the expected difference in the proportion of patients with HBV DNA of 20 IU/mL or greater at week 48, as determined by the modified US FDA-defined snapshot algorithm,[15] would be 0 and the proportion of patients with HBV DNA of 20 IU/mL or greater at week 48 in the tenofovir disoproxil fumarate group would be 2·4%. The non-inferiority margin was chosen per the US FDA guidance document for switch studies in virally suppressed patients with HIV-1 infection, and the predicted response for HBV DNA at week 48 was based on results from previous phase 3 studies with tenofovir disoproxil fumarate in patients who are HBeAg-negative and HBeAg-positive.[8]

Efficacy was analysed in the full analysis set, which was defined as the set of all randomised patients who received at least one dose of study drug with patients analysed according to their randomised treatment assignment. Safety was analysed in the safety analysis set, which was defined as the set of all randomised patients who received at least one dose of study drug with patients analysed according to the treatment they actually received. For the primary efficacy endpoint and other efficacy endpoints involving proportions, the baseline stratum-weighted difference between the

	Tenofovir alafenamide 25 mg (n=243)	Tenofovir disoproxil fumarate 300 mg (n=245)
Age, years	51 (10·5)	51 (10·8)
<50	107 (44%)	109 (44%)
≥50	136 (56%)	136 (56%)
Sex		
Male	179 (74%)	166 (68%)
Female	64 (26%)	79 (32%)
Race		
Asian	195 (80%)	205 (84%)
White	38 (16%)	31 (13%)
Black	9 (4%)	8 (3%)
Other	1 (<1%)	1 (<1%)
Body-mass index, kg/m²	24·3 (4·1)	24·1 (3·5)
HBeAg status		
Positive	78 (32%)	79 (32%)
Negative	165 (68%)	166 (68%)
HBsAg, $\log_{10}$ IU/mL	2·9 (0·9)	2·9 (0·9)
Years positive for HBV	14·5 (8·9)	13·7 (9·5)
Cirrhosis history		
Yes	32 (13%)	45 (18%)
No	201 (83%)	190 (78%)
Unknown	10 (4%)	10 (4%)
FibroTest score	0·42 (0·23)	0·41 (0·21)
FibroTest score ≥0·75	24 (10%)	17 (7%)
ALT, U/L	23 (18–32)	24 (18–31)
Normal ALT by 2018 AASLD criteria	191 (79%)	192 (78%)
Normal ALT by central lab normal range	211 (87%)	226 (92%)
Creatinine clearance by Cockcroft-Gault, mL/min	90·9 (76·6–110·3)	90·3 (76·1–107·9)
Serum creatinine, mg/dL	0·86 (0·76–1·00)	0·87 (0·72–0·99)
Serum phosphorus, mg/dL	3·2 (2·9–3·5)	3·3 (2·9–3·7)
≥Grade 1 proteinuria	17 (7%)	17 (7%)
Diabetes	18 (7%)	18 (7%)
Hypertension	44 (18%)	47 (19%)
Hyperlipidaemia	32 (13%)	26 (11%)
Hip bone mineral density status		
Normal, T-score ≥−1·0	143/241 (59%)	124/244 (51%)
Osteopenia, T-score −2·5 to −1·0	89/241 (37%)	116/244 (48%)
Osteoporosis, T-score <2·5	9/241 (4%)	4/244 (2%)

(Table 1 continues in next column)

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	Tenofovir alafenamide 25 mg (n=243)	Tenofovir disoproxil fumarate 300 mg (n=245)
Spine bone mineral density status		
Normal, T-score ≥−1·0	125 (51%)	120 (49%)
Osteopenia, T-score −2·5 to −1·0	90 (37%)	97 (40%)
Osteoporosis, T-score <2·5	28 (12%)	28 (11%)
Duration of prior tenofovir disoproxil fumarate use, weeks	220 (142–297)	224 (146–320)
Previous anti-HBV therapy other than tenofovir disoproxil fumarate	154 (63%)	157 (64%)
Previous interferon therapy	32 (13%)	31 (13%)
Previous oral antiviral therapy*	122 (50%)	126 (51%)
Lamivudine	95 (39%)	96 (39%)
Adefovir dipivoxil	94 (39%)	91 (37%)
Entecavir	47 (19%)	52 (21%)
Telbivudine	21 (9%)	27 (11%)
Other (clevudine, emtricitabline–tenofovir disoproxil fumarate, or tenofovir alafenamide)	13 (5%)	10 (4%)

Data are n (%), mean (SD), or median (IQR). HBV=hepatitis B virus. ALT=alanine aminotransferase. AASLD=American Association for the Study of Liver Diseases. *Refers to previous use of any of the agents below.

Table 1: **Baseline demographic characteristics (full analysis set)**

groups and its 95% CI were calculated on the basis of the stratum-adjusted Mantel-Haenszel proportion, where stratification factors included age group (≥50 or <50 years) and baseline HBeAg status (HBeAg-negative or HBeAg-positive). For the key secondary safety endpoints, the mean percentage difference in bone mineral density changes were assessed by means of ANOVA including study treatment as a fixed effect, and the difference in the estimated creatinine clearance change was assessed by means of the Wilcoxon rank-sum test. To control for type I error in the assessment of the primary efficacy endpoint and key secondary safety and efficacy endpoints, hypothesis testing was done in a sequential order: the primary hypothesis of non-inferiority of tenofovir alafenamide relative to tenofovir disoproxil fumarate with respect to the proportion with HBV DNA of 20 IU/mL or greater at week 48 (by modified US FDA-defined snapshot algorithm) was tested first; if non-inferiority was established, multiplicity adjustments were done for the key secondary endpoints with a fall-back procedure in sequential order with prespecified two-sided α levels: mean percentage change in hip bone mineral density (α=0·02), mean percentage change in spine bone mineral density (α=0·01), median change in creatinine clearance (α=0·02), and superiority of tenofovir alafenamide relative to tenofovir disoproxil fumarate with respect to the primary efficacy endpoint (α=0; appendix p 5). SAS (version 9.2) was used for all analyses. Adverse events were coded by means of the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1. An independent data monitoring committee reviewed the progress after the last patient completed 24 weeks of treatment and provided oversight of the study.

This study is ongoing and is registered with ClinicalTrials.gov, NCT02979613.

Role of the funding source

The funder of the study had a role in data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. The initial draft of the manuscript was prepared by a professional writer employed by Gilead and the primary investigators, with input from all authors.

Results

From Dec 29, 2016, to Oct 20, 2017, 541 patients were screened and 490 enrolled and randomly assigned (245 in each group; figure 1). Of the 42 patients who were not enrolled because of not meeting eligibility criteria, the most common reasons (>3% of patients) for non-enrollment included: 12 were unwilling or unable to comply with all study requirements, 11 had not maintained tenofovir disoproxil fumarate treatment at 300 mg once a day for at least 48 weeks and as monotherapy for chronic hepatitis B for at least 24 weeks before screening with viral suppression for at least 12 weeks prior to screening, seven had creatinine clearance rates of less than 50 mL/min at screening, six lacked documented evidence of chronic HBV infection, five were co-infected with HCV, HIV, or HDV, two had malignancy within the 5 years before screening, and one each for four other reasons. Five patients were excluded because they did not meet multiple eligibility criteria. Two patients assigned to the tenofovir alafenamide group did not receive treatment and were excluded from all analyses (figure 1). The baseline demographic and clinical characteristics of the two groups were generally balanced (table 1). A slightly higher percentage of patients receiving tenofovir disoproxil

	Tenofovir alafenamide (n=243)	Tenofovir disoproxil fumarate (n=245)	Proportional difference (95% CI)	p value
Primary efficacy endpoint				
HBV DNA ≥20 IU/mL†	1 (<1%)	1 (<1%)	0·0% (−1·9 to 2·0)‡	..§
Key safety endpoints				
Percentage change from baseline in hip bone mineral density	0·66% (2·08)	−0·51% (1·91)	1·17% (0·80 to 1·54)¶	<0·0001¶
Percentage change from baseline in spine bone mineral density	1·74% (3·46)	−0·11% (3·13)	1·85% (1·24 to 2·46)¶	<0·0001¶
Change from baseline in creatinine clearance by Cockcroft-Gault, mL/min	0·94 (−4·47 to 6·24)	−2·74 (−7·89 to 1·88)	..	<0·0001‖

Data are n (%), mean (SD), or median (IQR). HBV=hepatitis B virus.*Multiplicity adjustments were performed according to the hierarchy as described in the methods and appendix. Only if the non-inferiority of the primary efficacy endpoint was established were the p values from testing the superiority of each key secondary safety endpoint and the primary efficacy endpoint compared with their respective adjusted α-level using the fallback procedure. †The proportion of patients (in the full analysis set) with HBV DNA ≥20 IU/mL at week 48 as determined by the modified US FDA-defined snapshot algorithm.[15] ‡Difference in proportion between treatment groups and their 95% CIs were calculated based on Mantel-Haenszel proportions adjusted by baseline age (<50 *vs* ≥50 years) and baseline HBeAg status. §p value (0·95) for the superiority test was from Cochran-Mantel-Haenszel test stratified by baseline age (<50 *vs* ≥50 years) and baseline HBeAg status. ¶p values, difference in least-squares means, and their 95% CI were from the analysis of variance model including treatment as a fixed effect. Only patients with non-missing hip or spine bone mineral density for the baseline visit were included in the hip or spine dual energy X-ray absorptiometry analysis set. ‖p values were from the two-sided Wilcoxon rank sum test to compare the two treatment groups.

Table 2: **Primary efficacy and key (α-controlled) safety and efficacy endpoints at week 48***

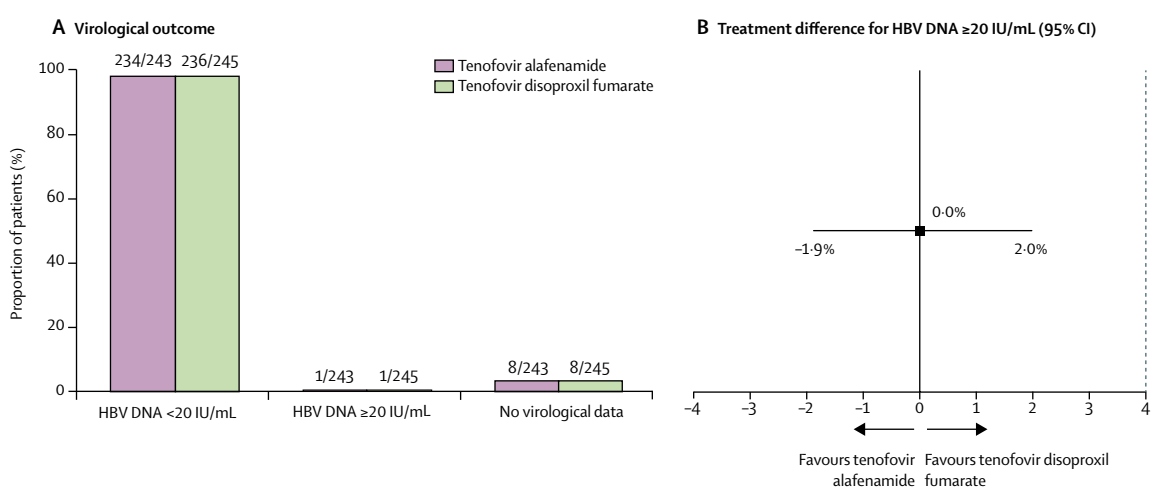

Figure 2: **Virological outcomes at week 48 as determined by the modified US FDA-defined snapshot algorithm[15]**

Difference in proportion between treatment groups and its 95% CI were calculated based on Mantel-Haenszel proportions adjusted by baseline age (<50 *vs* ≥50 years) and baseline HBeAg status. The dashed blue line indicates the prespecified non-inferiority margin of 4%. HBV=hepatitis B virus.

fumarate had a history of cirrhosis than those receiving tenofovir alafenamide, whereas a higher proportion of patients receiving tenofovir alafenamide versus patients receiving tenofovir disoproxil fumarate had a FibroTest score of at least 0·75, suggestive of cirrhosis (ie, METAVIR F4—fibrosis stage 4; table 1). The distribution of hip bone mineral density T-scores differed between treatments, with more patients receiving tenofovir disoproxil fumarate having T-scores indicative of osteopenia than patients receiving tenofovir alafenamide, and vice versa for osteoporosis and normal bone mineral density (table 1).

Nearly two-thirds of patients, had previously used anti-HBV therapies other than tenofovir disoproxil fumarate, with 248 (51%) of 488 having received other oral antiviral agents, most commonly lamivudine, adefovir dipivoxil, and entecavir (table 1). Patients had received tenofovir disoproxil fumarate for a median of approximately 4 years with a similar median duration between groups (table 1).

At week 48, one patient in each treatment group (one [<1%] of 243 in tenofovir alafenamide, and one [<1%] of 245 in tenofovir disoproxil fumarate) had HBV DNA of at least 20 IU/mL (table 2 and figure 2). The difference in proportion of 0·0% between the two groups had a 95% CI of −1·9% to 2·0%. Because the upper bound of the 95% CI was below the prespecified non-inferiority margin of 4%, the antiviral efficacy of tenofovir alafenamide was non-inferior to that of tenofovir disoproxil fumarate at week 48. Sensitivity analyses done by means of the Wilson score method had a similar result (95% CI −1·89 to 1·92). When testing was done for superiority in efficacy at week 48, after adjusting for multiplicity, the results were not significant (table 2). Excluding eight patients from each group who were without virological data in the week 48 analysis window, the percentages of patients with HBV DNA less than 20 IU/mL were 234 (96%) of 243 for patients receiving tenofovir alafenamide and 236 (96%) of 245 for those receiving tenofovir disoproxil fumarate (figure 2).

As assessed by missing equals failure analysis, 96% of patients in each group (234 of 243 in the tenofovir alafenamide group and 236 of 245 in the tenofovir disoproxil fumarate group, treatment difference 0·0% [95% CI −3·7 to 3·7]) achieved HBV DNA less than 20 IU/mL with 154 (63%) of 243 patients having target not detected in the tenofovir alafenamide group and 152 (62%) of 245 patients having target not detected in the tenofovir disoproxil fumarate group (table 3). At week 48, one patient (<1%) of 243 in the tenofovir alafenamide and one (<1%) of 245 in the tenofovir disoproxil fumarate group) had HBV DNA of 20 IU/mL or greater (both had a viral load <69 IU/mL), whereas eight patients (3%) in each group were considered to be treatment failures because of missing data. No differences in treatment response were observed between study regions (Asia *vs* Europe and North America) or within any of the subgroups analysed (appendix p 6). Results from per protocol analysis of treatment responses at week 48 were consistent (appendix p 7).

No viral resistance was detected in the three (1%) of 243 patients receiving tenofovir alafenamide and two (1%) of 245 patients receiving tenofovir disoproxil fumarate who qualified for viral sequencing; none of the patients receiving tenofovir alafenamide had HBV DNA of 69 IU/mL or more while receiving study treatment, and one patient in the tenofovir disoproxil fumarate group

	Tenofovir alafenamide (n=243)	Tenofovir disoproxil fumarate (n=245)	Proportional difference (95% CI)*	p value†
HBV DNA <20 IU/mL, target not detected	154 (63%)	152 (62%)	1·4% (−7·1 to 9·9)	0·74
ALT normal (2018 AASLD)‡	192 (79%)	184 (75%)	3·8% (−3·7 to 11·4)	0·31
ALT normal (central laboratory)‡	217 (89%)	208 (85%)	4·5% (−1·6 to 10·6)	0·14
ALT normalisation (2018 AASLD)§	26/52 (50%)	14/53 (26%)	23·8% (5·3 to 42·3)	0·014
ALT normalisation (central laboratory)§	16/32 (50%)	7/19 (37%)	14·1% (−16·4 to 44·6)	0·34
HBeAg loss¶	6/78 (8%)	5/78 (6%)	1·4% (−7·2 to 10·1)	0·73
HBeAg seroconversion¶	2/78 (3%)	0/78 (0%)	2·7% (−2·3 to 7·7)	0·13
HBsAg loss	0/243	5/245 (2%)	−2·0% (−4·4 to 0·3)	0·028
HBsAg seroconversion	0/243	0/245	0·0% (−1·5 to 1·6)‖	1·0
Log_{10} quantitative HBsAg change, IU/mL	−0·07 (0·143)	−0·10 (0·287)	0·03 (−0·01 to 0·07)**	0·15**
Change in FibroTest score	−0·02 (0·082)	−0·01 (0·082)	−0·02 (−0·03 to 0·00)**	0·018**

Data n (%) or mean (SD). Missing data was imputed as non-responders, except for change in quantitative HBsAg and change in FibroTest, which were based on observed data. HBV=hepatitis B virus. ALT=alanine aminotransferase. AASLD=American Association for the Study of Liver Diseases.*Difference in proportion between treatment groups and its 95% CI were calculated based on Mantel-Haenszel proportions adjusted by baseline age (<50 *vs* ≥50 years) and baseline HBeAg status. †p value was calculated from the Cochran-Mantel-Haenszel test stratified by baseline age (<50 *vs* ≥50 years) and baseline HBeAg status. ‡ALT normal is the proportion with ALT ≤ULN at week 48, regardless of baseline ALT status. §ALT normalisation is the proportion with ALT >ULN at baseline and ALT ≤ULN at week 48. ¶Only for patients who were HBeAg-positive at baseline. ‖Calculated using the Wilson score CI. **p value and 95% CI were calculated based on an ANOVA with treatment group and baseline strata as fixed effects.

Table 3: **Secondary efficacy responses at week 48 (full analysis set)**

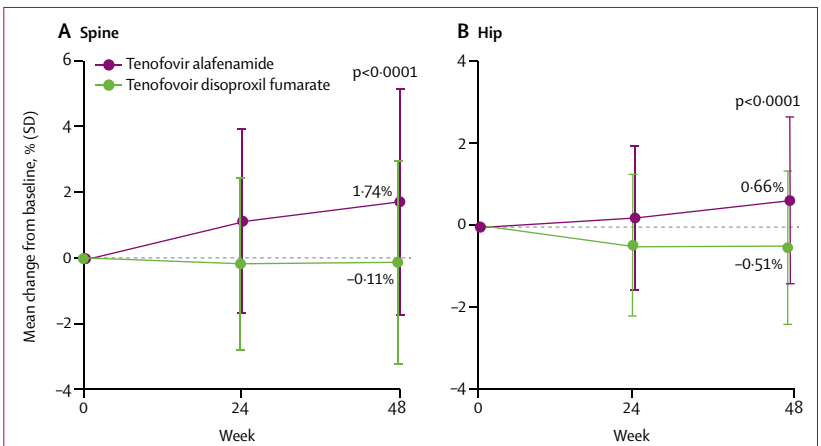

Figure 3: **Mean percentage change from baseline in spine and hip bone mineral density through to end of week 48**

	Tenofovir alafenamide 25 mg (n=243)	Tenofovir disoproxil fumarate 300 mg (n=245)	Proportional difference (95% CI)*
Any adverse event	126 (52%)	118 (48%)	3·7% (−5·6 to 13·0)
Study drug-related adverse events	21 (9%)	18 (7%)	1·3% (−3·9 to 6·5)
Grade 3 adverse events†	8 (3%)	4 (2%)	..
Pancreatitis	1 (<1%)	0	..
Gastroenteritis	0	1 (<1%)	..
Muscle rupture	1 (<1%)	0	..
Wrist fracture	1 (<1%)	0	..
Diabetes	1 (<1%)	0	..
Extremity pain	0	1 (<1%)	..
Breast cancer	1 (<1%)	0	..
Hepatocellular carcinoma	1 (<1%)	0	..
Malignant melanoma	0	1 (<1%)	..
Headache	1 (<1)	1 (<1)	..
Bipolar disorder‡	1 (<1%)	0	..
Homicidal ideation‡	1 (<1%)	0	..
Suicidal ideation‡	1 (<1%)	0	-
Serious adverse event§	11 (5%)	3 (1%)	-
Study drug-related serious adverse event	0	0	-
Premature study drug discontinuation due to adverse events	2 (1%)	0	-
Most common treatment-emergent adverse events¶			
Upper respiratory tract infection	18 (7%)	16 (7%)	-
Nasopharyngitis	13 (5%)	12 (5%)	-
Grade 3 or 4 laboratory abnormalities			
Grade 3 or 4 laboratory abnormalities in ≥1% of patients in either group‖	23/242 (10%)	18/243 (7%)	2·1% (−3·3 to 7·5)
Creatine kinase, 10·0 to <20·0 × upper limit of normal	1 (<1%)	3 (1%)	..
Hyperglycaemia, 250 to 500 mg/dL	3 (1%)	1 (<1%)	..
LDL cholesterol, >190 mg/dL	9 (4%)	4 (2%)	..
Urine erythrocytes, grade 3	2 (1%)	3 (1%)	..
Urine glucose, grade 3	3 (1%)	5 (2%)	..

Data are n (%). *Normal approximation for difference in two proportions. †There were no grade 4 adverse events. ‡These events occurred in the same patient. §11 patients receiving tenofovir alafenamide had the following serious adverse events: angina pectoris, pancreatitis, muscle rupture, tendon injury, wrist fracture, rotator cuff syndrome, hepatocellular carcinoma, breast cancer, lipoma, bipolar disorder, homicidal ideation, suicidal ideation, bladder stone, and cervical dysplasia. Three patients receiving tenofovir disoproxil fumarate had the following serious adverse events: herpes zoster, hepatocellular carcinoma, and varicose veins. ¶Adverse events occurring in at least 5% of patients in any arm. ‖None of the laboratory abnormalities listed were grade 4 in severity.

Table 4: **Adverse events and grade 3 or 4 laboratory abnormalities at week 48 (safety analysis set)**

(ie, all occurred at the baseline visit; see appendix p 8 for further details).

Of the 78 patients receiving tenofovir alafenamide who were HBeAg-positive at baseline, six (8%) had HBeAg loss at week 48, as compared with five (6%) of 78 HBeAg-positive patients receiving tenofovir disoproxil fumarate. Two (3%) of the 78 patients receiving tenofovir alafenamide had HBeAg seroconversion as compared with none receiving tenofovir disoproxil fumarate (table 3). With each treatment, mean declines in quantitative HBsAg concentrations were small and similar at week 48 (table 3). No patients receiving tenofovir alafenamide had HBsAg loss at week 48, whereas five (2%) of 245 patients continuing tenofovir disoproxil fumarate achieved this endpoint (p=0·028; difference in proportions, 95% CI −2·0% [−4·4 to 0·3]), although none of the patients with HBsAg loss had anti-HBs seroconversion. Four (80%) of the five patients with HBsAg loss in the tenofovir disoproxil fumarate group had low (<1 IU/mL) concentrations of HBsAg present at baseline.

The proportion of patients with normal ALT values at week 48 was numerically higher in patients receiving tenofovir alafenamide versus patients receiving tenofovir disoproxil fumarate by both central laboratory and 2018 AASLD criteria (table 3 and appendix p 9). Of the 32 patients in the tenofovir alafenamide group with ALT levels over the ULN at baseline by central laboratory criteria, 16 (50%) had normalised ALT at week 48 as compared with seven (37%) of 19 receiving tenofovir disoproxil fumarate (difference in proportions 95% CI 14·1% [−16·4 to 44·6]; p=0·34). Of the 52 patients in the tenofovir alafenamide group with baseline ALT levels over the ULN by 2018 AASLD criteria, 26 (50%) had normalised ALT at week 48, as compared with 14 (26%) of the 53 patients in the tenofovir disoproxil fumarate group (p=0·014; difference in proportions, 95% CI 23·8% [5·3 to 42·3]; table 3 and appendix p 9).

Fibrosis response (mean [SD] change in FibroTest scores at week 48) declined slightly more in patients receiving tenofovir alafenamide versus patients receiving tenofovir disoproxil fumarate (table 3). Similarly, categorical shifts (eg, cirrhosis category to moderate to severe fibrosis category) from baseline to week 48 were assessed, a higher proportion of patients receiving tenofovir alafenamide showed improvements in FibroTest score categories (appendix p 10) compared with patients receiving tenofovir disoproxil fumarate.

At week 48, patients receiving tenofovir alafenamide had a mean increase from baseline in bone mineral density of 0·66% (SD 2·08) at the hip and 1·74% (3·46) in the spine, as compared with mean decreases from baseline in bone mineral density of −0·51% (1·91) at the hip and −0·11% (3·13) in the spine in patients continuing tenofovir disoproxil fumarate (p<0·0001 for both hip and spine comparisons, difference in least squares mean for hip 1·17% [95% CI 0·80–1·54] and spine 1·85% [1·24–2·46]; table 2 and figure 3). Categorical percentage changes and clinical status in hip and spine bone mineral density over 48 weeks are shown in the appendix (pp 11, 12).

At weeks 12, 24, and 48, patients receiving tenofovir alafenamide had median percentage decreases from baseline in C-type collagen sequence, a serum biomarker of bone resorption, and P1NP, a serum biomarker of bone formation, which were significantly different from the patients receiving tenofovir disoproxil fumarate, who showed either no change or small median percentage increases at these same timepoints (appendix p 11).

Overall, study treatment was well tolerated in both groups. No patients discontinued tenofovir disoproxil

fumarate treatment prematurely, and two patients in the tenofovir alafenamide group had treatment stopped owing to adverse events (table 4): one 52-year-old woman discontinued tenofovir alafenamide treatment on day 191 after being diagnosed with breast cancer, and one 35-year-old man discontinued tenofovir alafenamide treatment on day 7 owing to alopecia reported by the investigator to be treatment-related, and which resolved approximately 9 months after tenofovir disoproxil fumarate treatment was reinstituted. Three patients required dose reduction owing to an adverse event during the study: two patients receiving tenofovir alafenamide (a 55-year-old man for seasonal allergies and a 35-year-old man for pancreatitis) and one patient receiving tenofovir disoproxil fumarate (a 56-year-old man for decreased creatinine clearance). Hepatocellular carcinoma developed in one patient in the tenofovir alafenamide group and one in the tenofovir disoproxil fumarate group. There were no deaths during the double-blind treatment phase.

Overall, the percentages of patients who had any treatment-emergent adverse event were similar in the two groups: 126 (52%) of 243 patients receiving tenofovir alafenamide and 118 (48%) of 245 receiving tenofovir disoproxil fumarate (table 4). The percentages of patients with study drug-related adverse events were also similar: 21 (9%) of 243 patients receiving tenofovir alafenamide and 18 (7%) of 245 patients receiving tenofovir disoproxil fumarate. Adverse events occurring in at least 5% of patients were upper respiratory tract infection (18 [7%] of 243 patients receiving tenofovir alafenamide and 16 [7%] of 245 patients receiving tenofovir disoproxil fumarate) and nasopharyngitis (13 [5%] of 243 patients receiving tenofovir alafenamide and 12 [5%] of 245 patients receiving tenofovir disoproxil fumarate).

14 patients had serious adverse events: 11 (5%) of 243 patients receiving tenofovir alafenamide and three (1%) of 245 receiving tenofovir disoproxil fumarate (table 4). None of the serious adverse events were considered to be related to treatment. One patient, an 83-year-old man in the tenofovir alafenamide group with a history of hypertension and hyperlipidaemia, died of cardiac arrest on study day 356, or day 20 of the open-label extension phase. 12 (2%) of 488 patients overall had grade 3 adverse events (table 4). No patient had a grade 4 adverse event.

There were three bone fractures reported, all of which were probably due to trauma (one wrist fracture in the tenofovir alafenamide group, which was also a serious adverse event, and one patient with a fractured humerus and rib in the tenofovir disoproxil fumarate group). No patient discontinued or interrupted treatment because of a bone-associated adverse event.

No patients had a renal-related adverse event, serious adverse renal event, or an event of proximal tubulopathy, including Fanconi syndrome. Three patients (two [1%] of 243 patients receiving tenofovir alafenamide and one [<1%] of 245 patients receiving tenofovir disoproxil fumarate) had a confirmed decrease in creatinine clearance below 50 mL/min during the study. All three patients had baseline creatinine clearance values just above the entry criterion of 50 mL/min, and none had a confirmed decline below 45 mL/min during treatment.

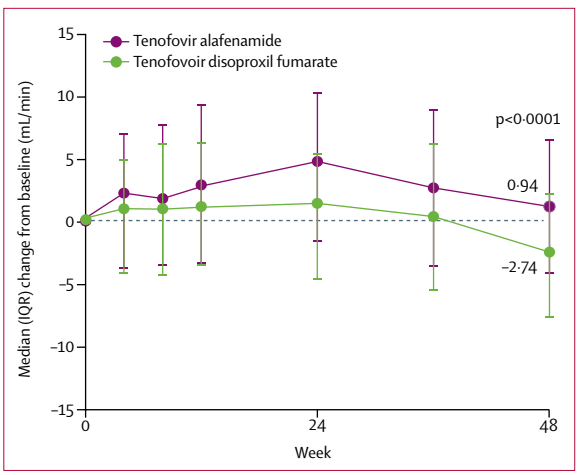

Figure 4: **Change in creatinine clearance (Cockcroft-Gault method) over 48 weeks**

	Tenofovir alafenamide 25 mg (n=243)	Tenofovir disoproxil fumarate 300 mg (n=245)	p value*
Serum creatinine change, mg/dL	0·00 (−0·05 to 0·05)	0·02 (−0·03 to 0·06)	0·0063
Serum phosphorus change, mg/dL	0·0 (−0·3 to 0·3)	0·0 (−0·2 to 0·2)	0·70
≥Grade 1 proteinuria	33/242 (14%)	54/243 (22%)	0·013§
≥1 stage worsening in chronic kidney disease stage†	15/234 (6%)	32/237 (14%)	<0·0001§
≥1 stage improvement in chronic kidney disease stage‡	28/112 (25%)	9/116 (8%)	<0·0001§

Data are median (IQR) or n (%). *p values were from the two-sided Wilcoxon rank sum test to compare the two treatment groups based on observed data. †Denominators are all patients with stage ≥1 chronic kidney disease at baseline and non-missing data at week 48 (see appendix p 15 for details). ‡Denominators are all patients with stage ≥2 chronic kidney disease at baseline and non-missing data at week 48 (see appendix p 15). §p value was from a rank analysis of covariance adjusting for baseline grade or stage.

Table 5: **Renal safety at week 48 (safety analysis set)**

A median increase from baseline in creatinine clearance was observed in the tenofovir alafenamide group at week 48 compared with a decrease in the tenofovir disoproxil fumarate group; the difference was significant (p<0·0001; table 2 and figure 4). Similar results were observed when change in creatinine clearance was assessed by the CKD-EPI method (appendix p 15). At week 48, patients who were switched to tenofovir alafenamide had no change from baseline in median serum creatinine, whereas patients who continued tenofovir disoproxil fumarate had a small increase; no changes in median serum phosphorus concentrations were observed over 48 weeks in either group (table 5). Apparent differences between treatment groups at week 48 were seen in shifts from baseline in chronic kidney disease staging (table 5; appendix pp 14, 15). To establish

the possible effect of concomitant treatments for hypertension or diabetes, or both on creatinine clearance by Cockcroft-Gault, we did a post-hoc assessment of change in creatinine clearance by Cockcroft-Gault for the small subset of patients receiving at least one of these treatments during the study. At week 48, the median change from baseline in creatinine clearance by Cockcroft-Gault was +1·76 (IQR –1·07 to 7·35) mL/min in the tenofovir alafenamide group and –1·69 (–7·30 to 1·98) mL/min in the tenofovir disoproxil fumarate group (p=0·00034). The better renal function in the tenofovir alafenamide group as compared with the tenofovir disoproxil fumarate group was consistent with results in the overall study population. We note, however, that both groups in the overall study population had declines in creatinine clearance after week 24 (figure 4).

A lower proportion of patients receiving tenofovir alafenamide than patients receiving tenofovir disoproxil fumarate had at least grade 1 proteinuria (by dipstick) at week 48 (33 [14%] of 242 *vs* 54 [22%] of 243; p=0·013; table 5). The median percentage change in urine protein to creatinine ratios also appeared to be smaller in the tenofovir alafenamide group than in the tenofovir disoproxil fumarate group at week 48 (appendix p 16); however, the median percentage change in urine albumin to creatinine ratios did not differ between groups. In patients switched to tenofovir alafenamide, median percentage decreases were seen in the urinary markers of proximal tubular dysfunction (retinol binding protein to creatinine ratio and β_2-microglobulin to creatinine ratio), which differed from the median percentage increases occurring in the patients who continued their tenofovir disoproxil fumarate treatment (appendix p 16).

The incidence of grade 3 laboratory abnormalities (there were no grade 4 abnormalities seen in ≥1% of patients) was similar between groups (23 [10%] of 242 patients receiving tenofovir alafenamide *vs* 18 [7%] of 243 patients receiving tenofovir disoproxil fumarate; table 4). The only grade 3 laboratory abnormalities occurring in at least 2% of patients were increased LDL cholesterol (nine [4%] of 243 in the tenofovir alafenamide group *vs* four [2%] of 245 in the tenofovir disoproxil fumarate group), and glucosuria (three [1%] of 243 in the tenofovir alafenamide group *vs* five [2%] of 245 in the tenofovir disoproxil fumarate group; table 4).

In the group of patients who were switched to tenofovir alafenamide, median increases in fasting lipid parameters were seen at week 48 compared with little or no changes in these metabolic parameters in the group that continued taking tenofovir disoproxil fumarate (appendix pp 17–18).

Discussion

We have previously shown that in patients with chronic HBV and viraemia, who were mostly treatment-naive and either HBeAg-negative or HBeAg-positive, the antiviral efficacy of tenofovir alafenamide is non-inferior to that of tenofovir disoproxil fumarate, and the bone and renal safety profile is superior to tenofovir disoproxil fumarate at weeks 48 and 96.[12–14] In this large, randomised, phase 3 switch trial, which to our knowledge is the first of its kind to apply the US FDA-defined snapshot algorithm to patients chronically infected with HBV, we establish that virologically suppressed patients who switch from tenofovir disoproxil fumarate to tenofovir alafenamide for 48 weeks had virological efficacy that is non-inferior to that of patients continuing tenofovir disoproxil fumarate. Patients in both groups had very low incidences of treatment failure, and significantly more patients receiving tenofovir alafenamide had improved kidney function and increases in hip and spine bone mineral density compared with patients in the tenofovir disoproxil fumarate group. At 48 weeks, 234 (96%) of 243 patients receiving tenofovir alafenamide and 236 (96%) of 245 patients receiving tenofovir disoproxil fumarate were virally suppressed, with a 0·0% difference in proportions between treatment groups, and similar proportions of patients who were virally suppressed had no detectable HBV DNA present. No viral resistance developed in either group. Further, similar treatment response rates were observed across subgroups. The rate of serological responses was low in both groups and similar rates of HBeAg loss were seen at 48 weeks between the two groups, but HBsAg loss was significantly higher in the tenofovir disoproxil fumarate group than in the tenofovir alafenamide group. The reasons for these differences are unclear, but we note that the relevant percentages of tenofovir alafenamide and tenofovir disoproxil fumarate patients with HBsAg loss are small (0 [0%] of 243 *vs* five [2%] of 245 patients; table 3). Finally, the proportion of patients who had normal serum ALT at week 48 was numerically higher in the tenofovir alafenamide group, with higher prevalence of ALT normalisation by the most recent AASLD criteria. We note that although all patients were virally suppressed at screening, 21–22% had abnormal ALT and that similar proportions of patients (51 [21%] of 243 in the tenofovir alafenamide group and 61 [25%] of 245 in the tenofovir disoproxil fumarate group) had abnormal ALT at week 48 despite less than 1% (one patient of 243 in the tenofovir alafenamide group and one of 245 in the tenofovir disoproxil fumarate group) of patients receiving treatment having not achieved full viral suppression. Although the reasons for the persistence of serum ALT elevations in patients who are virally suppressed is not clear, these prevalences are in line with other reports.[16]

The primary efficacy endpoint for this study and the non-inferiority margin were chosen after discussions with the FDA on the basis of existing HIV guidelines for antiretroviral switch studies.[15] Since the population in this study was virally suppressed patients with chronic HBV receiving tenofovir disoproxil fumarate, the primary efficacy endpoint was selected to be HBV DNA of at least LLOQ by the modified US FDA-defined snapshot algorithm, rather than the proportion achieving viral

suppression (HBV DNA <LLOQ), which was the primary endpoint in previous tenofovir alafenamide versus tenofovir disoproxil fumarate studies in patients with viraemia.[12–14] The observed prevalence of the primary endpoint of 0·4% was lower than the expected 2·4%, which is probably because of the study population (patients with long-term suppression on tenofovir disoproxil fumarate treatment, which selected for individuals who were good pill takers and had shown reasonably good tolerability to tenofovir disoproxil fumarate). Our prespecified non-inferiority margin of 4% was chosen on the basis of the expected prevalence of 2·4%, however in this analysis the proportion of virological failures was low and equivalent between groups, and the upper bound of the 95% CI would have met a non-inferiority margin as low as 2%.

In comparison with the viraemic population enrolled in the two phase 3 tenofovir alafenamide registrational studies,[12,13] patients in this study are older (mean age of 51 years), have more comorbidities, and a higher proportion are HBeAg-negative—all characteristics which are reflective of the patient population receiving oral antiviral treatment for chronic HBV infection.[3,4] Switching to tenofovir alafenamide in patients who were virally suppressed while taking tenofovir disoproxil fumarate long-term (median duration approximately 4 years) was safe and well tolerated. In comparison with week 48 results in patients with viraemia, the overall incidence of adverse events, serious adverse events, and adverse events leading to treatment discontinuation were lower in this switch trial, which is not surprising given that this was a stable, treatment-experienced population.[12,13] In this study, similar incidences of adverse events, serious adverse events, and laboratory abnormalities were observed in both treatment groups, and only two (1%) of 243 patients in the tenofovir alafenamide group discontinued treatment owing to an adverse event. After 48 weeks of double-blind treatment, hepatocellular carcinoma developed in two patients (one [<1%] of 243 in the tenofovir alafenamide group and one [<1%] of 245 in the tenofovir disoproxil fumarate group). At 48 weeks, patients who were switched to tenofovir alafenamide had improved bone and kidney parameters compared with those who continued tenofovir disoproxil fumarate treatment. These differences are relevant given that most patients with chronic HBV infection require life-long therapy, and with increasing age, have an increasing prevalence of comorbidities. This consideration is especially important for patients with comorbidities affecting bone and kidney function.

In this study, patients switched to tenofovir alafenamide had increases in fasting lipid parameters, compared with those continuing tenofovir disoproxil fumarate treatment, wherein these parameters remained relatively stable. The increases in fasting lipids in the tenofovir alafenamide group were not unexpected given that tenofovir disoproxil fumarate has a well-known lipid lowering effect, which has been shown in patients with HIV and chronic HBV, as well as in healthy individuals, and appears to be related to plasma concentrations of tenofovir.[14,17,18] Although tenofovir alafenamide treatment resulted in increases in fasting total and LDL cholesterol concentrations, the increases were modest. Only a small percentage of patients had clinically important (grade 3 or 4) increases in LDL cholesterol (nine [4%] of 243 patients in the tenofovir alafenamide group *vs* four [2%] of 245 patients in the tenofovir disoproxil fumarate group); the elevations were transient, and typically occurred in patients with pre-existing hyperlipidaemia or elevated baseline concentrations. Notably, switching to tenofovir alafenamide was associated with greater increases in HDL cholesterol compared with continued tenofovir disoproxil fumarate treatment and the ratio of total cholesterol to HDL cholesterol was only slightly increased in patients receiving tenofovir alafenamide. Though the increases in lipid parameters observed were not considered to be clinically significant, long-term follow-up of lipid profiles in patients who are switched from tenofovir disoproxil fumarate to tenofovir alafenamide might be warranted.

Although tenofovir disoproxil fumarate is a highly efficacious first-line treatment for chronic HBV infection, its use has been associated with declines in bone mineral density.[19–22] The exact mechanism of bone loss has not been elucidated; however, increases in certain markers of bone turnover in patients with HIV have suggested that increases in both osteoblast and osteoclast activity occur with tenofovir disoproxil fumarate treatment.[22,23] In this study, mean percentage increases in hip and spine bone mineral density occurred in patients who were switched to tenofovir alafenamide, compared with mean percentage decreases in hip and spine bone mineral density in patients continuing on tenofovir disoproxil fumarate. The positive bone mineral density changes we observed with tenofovir alafenamide in this study are consistent with previously reported results in virally suppressed patients with HIV who switched to a tenofovir alafenamide-based antiretroviral regimen from regimens containing tenofovir disoproxil fumarate.[24,25] We also found that markers of bone turnover were decreased following the switch to tenofovir alafenamide, whereas these markers remain upregulated in patients continuing tenofovir disoproxil fumarate. These data support the notion that the bone loss and the increased prevalence of bone turnover associated with long-term tenofovir disoproxil fumarate use can be reversed when patients are switched to tenofovir alafenamide, a finding that is consistent with recommendations for the use of tenofovir alafenamide in updated HBV practice guidelines.[7,26]

Long-term use of tenofovir disoproxil fumarate has been linked with cases of kidney injury, including acute renal failure, proximal tubulopathy, and in rare instances, Fanconi syndrome.[27–30] Previous studies of tenofovir disoproxil fumarate in patients with chronic HBV infection who were treatment-naive, for up to 10 years

noted renal laboratory abnormalities in 2% of patients.[8,31] The primary mechanism by which tenofovir disoproxil fumarate is believed to disrupt renal function is through dose-dependent accumulation of tenofovir from blood into proximal tubular cells via organic anion transporters 1 and 3 (OAT1 and OAT3). Tenofovir disoproxil fumarate when given in a dose of 300 mg once daily is immediately cleaved following oral absorption to tenofovir by tissue and plasma esterases. In contrast to tenofovir disoproxil fumarate, tenofovir alafenamide has greater plasma stability with 90% lower systemic exposures of tenofovir when given at the approved dose of 25 mg once daily.[10,11] In addition, tenofovir alafenamide itself is not a substrate for renal tubular uptake by OAT1 or OAT3.[32] This, together with the significantly reduced tenofovir exposures, provides a plausible mechanistic explanation for the differential effects observed in renal parameter changes when patients with viraemia are treated with tenofovir alafenamide compared with tenofovir disoproxil fumarate, and when patients maintained on tenofovir disoproxil fumarate treatment are switched to tenofovir alafenamide.[12–14,24,25] Consistent with this, in our study, an increase from baseline in creatinine clearance was observed in the tenofovir alafenamide group compared with a continued decline in the tenofovir disoproxil fumarate group; the difference between treatments was significant as early as week 24. Furthermore, patients who switched to tenofovir alafenamide had a significantly lower incidence of proteinuria and improved markers of renal tubular function, including urine retinol binding protein to creatinine and β2-microglobulin to creatinine ratios, both of which are sensitive and specific indicators of renal tubular dysfunction. These results suggest that the deleterious changes in renal laboratory parameters that occur with long-term tenofovir disoproxil fumarate use are reversible when patients switch to tenofovir alafenamide. Our results are also consistent with reports in HIV-positive patients who were switched from tenofovir disoproxil fumarate-based to tenofovir alafenamide-based regimens,[24,25] and our findings are also in line with the HBV treatment guidelines.[7,26]

This study has limitations. Although our sample size was large enough to show non-inferiority in efficacy of switching from tenofovir alafenamide to tenofovir disoproxil fumarate, the 48-week duration might not be long enough to reflect potential long-term differences in the incidences of clinically important renal and bone events. Follow-up of patients during the 48 week open-label tenofovir alafenamide extension phase (ie, through to the end of week 96) is ongoing. Given that patients with HBV infection and eGFR less than 50 mL/min are common in clinical practice, the results of this trial, which enrolled only patients with eGFR of at least 50 mL/min, cannot be generalised to the population at large. Because this study is not yet complete, some secondary endpoints were not included herein; these results will be reported in future publications. Additionally, patients with decompensated cirrhosis (Child-Pugh-Turcotte B or C) and those with moderate or severe renal impairment including patients with end-stage renal disease on haemodialysis were not assessed in this study. A phase 2 open-label switch study with tenofovir alafenamide that includes these important patient populations with chronic HBV (NCT03180619) is also ongoing.

In conclusion, in virally suppressed patients with chronic HBV infection receiving long-term tenofovir disoproxil fumarate treatment, we have shown that switching to tenofovir alafenamide is safe and effective, and that tenofovir disoproxil fumarate-associated renal and bone abnormalities are improved on switching to tenofovir alafenamide.

Contributors

JFF, AG, AL, VS, SKT, and GMS designed and oversaw study conduct. PL, MB, SF, SHA, W-LC, WYT, AR, C-YC, ET, HB, XM, HT, S-KY, KA, Y-SL, and HLYC served as investigators for this study. GW provided statistical analysis, and YL provided resistance analysis.

Declaration of interests

PL has participated on the advisory boards of Gilead Sciences, Roche, Bristol-Myers Squibb, Glaxo Smith Kline, Merck Sharp & Dohme, Arrowhead, Alnylam, MYR Pharmacueticals, Eiger, and AbbVie. MB has participated on the advisory boards of, and has served as a speaker for, Gilead, Merck Sharp & Dohme, Bristol-Myers Squibb, Janssen, and AbbVie. SF declares no conflicts of interest. SHA has participated on the advisory boards of Bristol-Myers Squibb, Gilead, AbbVie, and Merck Sharp & Dohme, and has received research support from Bristol-Myers Squibb, Gilead Sciences, and Roche. W-LC has participated on the advisory boards of Gilead, AbbVie, Bristol-Myers Squibb, Merck Sharp & Dohme, and PharmaEssentia, and has served as a speaker for Gilead, AbbVie, Bristol-Myers Squibb, Merck Sharp & Dohme, PharmaEssentia, and Roche. WYT has received personal fees from Bayer HealthCare, Gilead Science Korea, AbbVie, Ono Pharma Korea, Eisai Korea, Bukwang Pharmaceutical, Merck Sharp & Dohme, Korea, Yuhan, and Samil Pharmaceutical. AR has served as an advisor for, is on the speaker's bureau for, received grants from, and consults for AbbVie, Gilead, Merck, and Intercept, is on the speaker's bureau for Celgene, has received grants from Janssen and Assembly, and has consulted for Bristol-Myers Squibb, Janssen, and Novartis. C-YC declares no conflicts of interest. ET declares no conflicts of interest. HB has served as a speaker for and has received research grants from Gilead. XM has served as a consultant for Gilead Sciences, and has served as an investigator for a trial sponsored by Assembly Biosciences. JFF, AG, AL, YL, GW, VS, SKT, and GMS are employees of and hold stock in Gilead Sciences. HT has served as a speaker and advisor for, received research grants from, holds stock in Gilead Sciences, and has received research grants from Intercept and Assembly. S-KY declares no conflicts of interest. KA has participated on the advisory boards of and has served as a speaker for AbbVie, Achillion, Bristol-Myers Squibb, Glaxo Smith Kline, Gilead, Intercept, Janssen, Merck, Novartis, and Roche, has served as a consultant for AbbVie, Achillion, Bristol-Myers Squibb, Glaxo Smith Kline, Gilead, Intercept, Janssen, Merck, Novartis, and Roche, and has received grants from BMS, Gilead, and Roche. Y-SL has served on the advisory boards of Bayer, Bristol-Myers Squibb, and Gilead, has received research support from Bayer, Bristol-Myers Squibb, Gilead Sciences, and Novartis, and has served as a speaker for Bayer and Gilead. HLYC has served as an advisor and speaker for AbbVie, Bristol-Myers Squibb, Gilead and Roche, has served as an advisor for Janssen, and has served as a speaker for Merck Sharp & Dohme.

Data sharing

Gilead shares anonymised individual patient data on request or as required by law or regulation with qualified external researchers. Approval of such requests is at Gilead's discretion and dependent on the nature of the request, the merit of the research proposed, availability of

the data and the intended use of the data. Requests should be sent to datarequest@gilead.com.

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