Introduction

Despite vaccination programmes and effective antiviral drugs, chronic hepatitis B virus (HBV) continues to be a significant global health problem. The World Health Organization (WHO) estimates worldwide, over 250 million people are positive for hepatitis B surface antigen (HBsAg) and are living with chronic HBV. These individuals are at significant risk of liver disease, including cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC), with a lifetime risk of such complications being 15–40%. With nearly 700,000 HBV related deaths in 2013, it is one of the leading causes of mortality globally.

The natural history of chronic HBV is a dynamic process, dependent on host immune and viral factors. Additional variables including age, sex, level of fibrosis at presentation, viral co-infection and the presence of metabolic cofactors impact the progression of chronic HBV to cirrhosis and its complications. The pathogenesis involves several phases, which may not occur sequentially but are defined by specific clinical parameters: hepatitis B e antigen (HBeAg) status, serum HBV DNA levels, serum alanine aminotransferase (ALT) and the presence or absence of inflammation. This characterization aims to distinguish those patients with inactive disease, that is, chronic infection, from those who have active disease, that is, chronic hepatitis, and therefore to identify those most at risk of cirrhosis and HCC, an important goal in the management of chronic HBV.

There are two classes of antiviral therapies currently approved for the treatment of chronic HBV infection: pegylated interferons (IFNs) and nucleos(t)ide analogues (NAs). These therapies...
can achieve suppression of HBV DNA replication, decreases in hepatic necroinflammation and improvement in fibrosis, thus preventing the development of cirrhosis, hepatic decompensation, HCC and ultimately HBV-related mortality. However, there are significant limitations to these treatment options. Treatment with IFN is usually restricted to those most likely to respond: HBV genotypes A and B, low HBV DNA and high ALT. HBsAg quantification may be a helpful tool for the monitoring of patients treated with IFN with a role in predicting response. Several studies have shown that the change of serum HBsAg levels during IFN therapy mimics the change of both intrahepatic covalently closed circular DNA (cccDNA) and intrahepatic HBsAg, suggesting that a decline in serum HBsAg levels is associated with the induction of an effective anti-HBV immune response. IFN requires parenteral administration and is associated with frequent, significant adverse effects such as mood disturbance, cytopenias and flu-like symptoms. IFN is contraindicated in patients with decompensated cirrhosis and those with autoimmune diseases or uncontrolled psychiatric illness. NAs, by contrast, are administered orally and are generally well tolerated. Most prior HBV management guidelines recommend entecavir or tenofovir disoproxil fumarate (TDF) as first-line oral agents. Both drugs have high antiviral potency with minimal risk of drug resistance and can be used at all stages of liver disease including in those with hepatic decompensation and those who have received a liver transplant. Regression of fibrosis, reduction in rates of hepatic decompensation and HCC are associated with sustained viral suppression in those on long-term NA therapy. Although the recommended NAs have satisfactory safety profiles, TDF has been associated with nephrotoxicity and reduction in bone mineral density (BMD) in some patients. In addition NA therapy does not usually result in HBsAg clearance, and virological relapse is common after cessation of treatment, thus the need for indefinite therapy. With all current HBV therapies there is persistence of cccDNA, which serves as the template for transcription for all viral RNAs in hepatocytes, and the presence of which is a major barrier to HBV cure. However, recent advances in understanding the HBV life cycle have enabled multiple, novel therapeutic targets to be identified and new therapies of direct-acting antiviral (DAAs) and host-targeting agents (HTAs) are in development. Tenofovir alafenamide (TAF, formerly GS-7340) is a new nucleoside analogue recently approved for the treatment of chronic HBV. Previous review articles have examined the clinical trial data for TAF and evaluated its place in the management of chronic HBV. This review provides a comprehensive overview of the phase III efficacy data for TAF, as well as the safety and tolerability outcomes and importantly includes the recently published week 96 data. We review the latest updates from the open-label phases of the ongoing phase III trials, including the bone and renal safety data after switching from TDF to TAF. The interesting ALT normalization observation is examined and we include new data on the potential clinical significance of this phenomenon.

Introduction to tenofovir alafenamide

TAF, like TDF, is a phosphonate prodrug of tenofovir (TFV), specifically developed to have enhanced antiviral potency with an improved safety profile to address the renal and bone toxicities associated with TDF. Most prior HBV management guidelines recommend entecavir or tenofovir disoproxil fumarate (TDF) as first-line oral agents. Both drugs have high antiviral potency with minimal risk of drug resistance and can be used at all stages of liver disease including in those with hepatic decompensation and those who have received a liver transplant. Regression of fibrosis, reduction in rates of hepatic decompensation and HCC are associated with sustained viral suppression in those on long-term NA therapy. Although the recommended NAs have satisfactory safety profiles, TDF has been associated with nephrotoxicity and reduction in bone mineral density (BMD) in some patients. In addition NA therapy does not usually result in HBsAg clearance, and virological relapse is common after cessation of treatment, thus the need for indefinite therapy. With all current HBV therapies there is persistence of cccDNA, which serves as the template for transcription for all viral RNAs in hepatocytes, and the presence of which is a major barrier to HBV cure. However, recent advances in understanding the HBV life cycle have enabled multiple, novel therapeutic targets to be identified and new therapies of direct-acting antiviral (DAAs) and host-targeting agents (HTAs) are in development. Tenofovir alafenamide (TAF, formerly GS-7340) is a new nucleoside analogue recently approved for the treatment of chronic HBV. Previous review articles have examined the clinical trial data for TAF and evaluated its place in the management of chronic HBV. This review provides a comprehensive overview of the phase III efficacy data for TAF, as well as the safety and tolerability outcomes and importantly includes the recently published week 96 data. We review the latest updates from the open-label phases of the ongoing phase III trials, including the bone and renal safety data after switching from TDF to TAF. The interesting ALT normalization observation is examined and we include new data on the potential clinical significance of this phenomenon.

Introduction to tenofovir alafenamide

TAF, like TDF, is a phosphonate prodrug of tenofovir (TFV), specifically developed to have enhanced antiviral potency with an improved safety profile to address the renal and bone toxicities associated with TDF. Both TAF and TDF are initially metabolized to TFV in the plasma, which in turn is metabolized, in target viral-infected cells, to the active metabolite tenofovir diphosphate (TFV-DP). Levels of circulating plasma TFV are associated with renal and bone toxicity. TAF has greater plasma stability than TDF, enabling more efficient delivery of the active metabolite TFV-DP intracellularly at much lower doses. When TAF is given at a dose of 25 mg to patients with HBV or human immunodeficiency virus (HIV) infection, circulating concentrations of plasma TFV are about 90% lower than with the approved daily dose of 300 mg TDF. This difference underpins the better safety profile of TAF compared with TDF.

Mechanism of action and pharmacokinetics of tenofovir alafenamide

TAF leaves the plasma and enters hepatocytes primarily by passive diffusion, with some uptake by the hepatic uptake transporters organic anion-transporting polypeptides 1B1 and 1B3 (OATP1B1 and OATP1B3). TAF is then primarily hydrolysed by carboxylesterase 1 (CES1) to form TFV, which undergoes phosphorylation to form the pharmacologically active metabolite TFV-DP. Potent inhibition of HBV replication occurs when HBV reverse transcriptase incorporates TFV-DP.
into HBV DNA resulting in HBV DNA chain termination.

TAF exhibits linear and dose-dependent pharmacokinetics, in patients with chronic HBV, characterized by efficient absorption ($t_{1/2} < 1$ h) and rapid plasma elimination ($t_{1/2} < 45$ min). Extensive (>80%) metabolism of TAF occurs in humans with primary metabolism in the liver by CES1 and by cathepsin A in peripheral blood mononuclear cells. In vitro, TAF is not metabolized by CYP1A2, CYP2C8, CYP2C9, CYP2C19 or CYP2D6 and undergoes minimal metabolism by CYP3A4. However, TAF is a substrate for P-glycoprotein (P-gp) and so potential drug–drug interactions can be expected with P-gp inducers such as carbamazepine, phenobarbital, rifabutin, rifampicin, rifapentine and St John’s Wort. Coadministration of these drugs with TAF is expected to decrease TAF plasma concentrations, which may result in loss of therapeutic effect, and is therefore not recommended. Likewise, drugs that inhibit P-gp may increase plasma concentrations of TAF. Excretion is largely in the faeces, with very little intact TAF (<1%) excreted through the kidneys. The European Medicines Agency (EMA) has therefore been able to approve TAF for use in chronic HBV patients with end-stage renal failure on dialysis in advance of a phase II, open-label study, currently evaluating the safety and efficacy of switching to TAF from TDF in this cohort. TFV is renally eliminated by both glomerular filtration and active tubular secretion.

There are no clinically relevant differences in the pharmacokinetics of TAF based on age, sex or ethnicity. TAF pharmacokinetics have not been studied in patients with a creatinine clearance ($CL_{CR} < 15$ ml/min but there are no clinically relevant differences in those with severe renal impairment ($CL_{CR} > 15$ but $<30$ ml/min) compared with healthy subjects with normal renal function. TAF and TDF systemic exposures are 7.5% and 11% lower, respectively, in patients with mild hepatic impairment compared with patients with normal hepatic function, and no dose adjustment is needed with hepatic impairment in patients classified as Child–Pugh class A. According to the TFV pharmacokinetics of patients with severe hepatic impairment (Child–Pugh C) treated with TAF 25 mg, TFV exposure was only modestly lower compared with healthy controls with normal hepatic function.

### Tenofovir alafenamide in chronic hepatitis B

#### Phase I data

A phase 1b trial in noncirrhotic patients with chronic hepatitis B was performed assessing safety, antiviral efficacy and pharmacokinetics. A total of 51 patients naïve to nucleoside analogues were randomized (1:1:1:1:1) to different doses of TAF (8, 25, 40 or 120 mg) or to TDF 300 mg. Over the 28-day treatment period, mean changes in serum HBV DNA were similar across the TAF groups. At week 4, mean changes in HBV DNA of $-2.81$, $-2.55$, $-2.19$, and $-2.76$ log$_{10}$ IU/ml were observed in the 8, 25, 40, and 120 mg TAF groups, respectively, and were comparable with the TDF 300 mg control group, where a $-2.68$ log$_{10}$ IU/ml change was seen. TAF was safe and well tolerated over 28 days with no participants experiencing grade 3 or 4 adverse events. TAF doses of 25 mg or lower were associated with $\geq 92\%$ reduction in circulating TFV levels compared with TDF 300 mg. There is an absence of phase II data for TAF in chronic HBV and the efficacy and safety data from this phase I was used to select a 25 mg TAF dose for two subsequent phase III trials. It is worth noting there are no dose-ranging studies for TDF in chronic HBV; these data came from TDF in HIV studies.

#### Phase III studies

Two ongoing phase III clinical trials have evaluated TAF in HBeAg-positive and HBeAg-negative chronic HBV patients. The trials have similar designs and are randomized, double blind, multinational, non-inferiority studies. For both HBeAg-positive and HBeAg-negative studies, eligible patients were at least 18-years old with plasma HBV DNA concentrations $>20,000$ IU/ml, serum ALT concentrations $>60$ U/l in men or $>38$ U/l in women and no more than 10 times the upper limit of normal (ULN), and an estimated creatinine clearance of $>50$ ml/min (by Cockcroft-Gault method). Both treatment-naïve and treatment-experienced patients were included provided they met eligibility criteria. Major exclusion criteria included evidence of hepatic decompensation, HCC and coinfection with hepatitis C, hepatitis D or HIV infection. Patients with platelet counts $\leq 50,000$ cells per $\mu l$, haemoglobin $<10$ g/dl, albumin $<3$ g/dl, direct bilirubin $>2.5$ times the ULN and aspartate aminotransferase (AST) or ALT $>10$ times the ULN were
The primary efficacy endpoint was the proportion of patients with HBV DNA < 29 IU/ml at week 48. Other prespecified efficacy endpoints were the proportion of patients with HBsAg seroconversion to anti-HBs at week 48, change from baseline in fibrosis as assessed by FibroTest at week 48 and the proportion of patients with ALT normalization at week 48. Key secondary safety endpoints at week 48 included the percentage change in hip bone mineral density (BMD), percentage change in spine BMD and change from baseline serum creatinine.44,45

Efficacy in hepatitis B e antigen-positive patients

A total of 873 patients were randomized and received treatment with either TAF 25 mg (n = 581) or TDF 30 mg (n = 292). There were no significant differences in baseline characteristics between the two treatment groups. Most patients were Asian [482 (83%) in the TAF group and 232 (79%) in the TDF group]. The commonest HBV genotype was C (52% in each group). Over a quarter of patients had been previously treated with nucleos(t)ide analogue antiviral drugs [151 (26%) in the TAF group and 77 (26%) in the TDF group]. Mean baseline HBV DNA level was 7.6 log_{10} IU/ml in both the TAF and TDF groups.44

The primary efficacy endpoint, an HBV DNA level < 29 IU/ml at week 48, was achieved by 371 (64%) of 581 patients receiving TAF, which was non-inferior to the 195 (67%) of 292 patients receiving TDF who had an HBV DNA < 29 IU/ml {adjusted between group difference \(-3.6\% \text{ [95\% confidence interval (CI) \(-9.8–2.6\%\); } p = 0.25).44 There were no significant differences in the percentage of patients receiving TAF or TDF with an HBV DNA level < 29 IU/ml in all the major subgroup analyses that included age (<50 years or \(\geq 50\) years), sex, race (Asian or non-Asian), baseline HBV DNA level (<8 log_{10} IU/ml or \(\geq 8 \log_{10}\) IU/ml), antiviral history (naïve or experienced), treatment adherence (<95% or \(\geq 95\%\)), region (East Asia, Europe, North America, other), HBV genotype, baseline ALT by central laboratory range (\(<\text{ULN}\) or \(\geq\text{ULN}\)) or baseline FibroTest score (<0.75 or \(\geq 0.75\)).

A significantly higher proportion of patients receiving TAF, with an ALT above the ULN at baseline, had a normal ALT at week 48 of treatment compared with patients receiving TDF (45% versus 36%, respectively, \(p = 0.014\)). This was based on AASLD criteria (male: ALT ≤ 30; female: ALT ≤ 19), results were not significant if based on central laboratory criteria.44 At week 96, significant higher rates of ALT normalization were seen in the TAF group where both AASLD criteria (52% in the TAF group and 42% in the TDF group, \(p = 0.0003\)) and central laboratory criteria (75% in the TAF group versus 68% in the TDF group, \(p = 0.017\)) were used.46 Small reductions in FibroTest scores at week 48 were observed in both treatment groups, but the TAF group had a significantly greater reduction from baseline score than the TDF group (mean change 0.07 versus 0.04, respectively, \(p = 0.007\)).44

There were no other significant between-group differences in secondary or other efficacy outcomes. A key prespecified secondary efficacy outcome was the proportion of patients with HBeAg loss or HBeAg seroconversion by week 48. More patients in the TAF group experienced HBeAg loss than in the TDF group (34/285 (12%) versus 8/292 (3%)) but this was not statistically significant. Similarly, the rate of HBeAg seroconversion was also numerically higher among patients receiving TAF than among those receiving TDF, but the difference did not achieve statistical significance [10% (58/565) versus 8% (23/285), respectively, \(p = 0.05\)].44 Rates of HBsAg loss by week 48 were very low and only 4 (0.7%) patients in the TAF group and 1 (0.3%) in the TDF group achieved this. There were no statistically significant differences by week 96 for HBeAg loss (22% in TAF group versus 18% in TDF group), or for
HBeAg seroconversion (1% in TAF group versus 0% in TDF group). Primary and secondary endpoints are summarised in Table 1.

**Efficacy in hepatitis B e antigen-negative patients**

A total of 426 patients were randomized and received treatment with either TAF 25 mg (n = 285) or TDF 300 mg (n = 140). Baseline characteristics of both groups were generally well balanced with no significant differences in between the TAF and TDF treatment groups. Most patients were male [173 (61%) in the TAF group and 86 (61%) in the TDF group] and Asian [205 (72%) in the TAF group and 101 (72%) in the TDF group]. The commonest HBV genotype was C (40% in the TAF group and 34% in the TDF group). About 20% of patients had been previously treated with nucleos(t)ide analogue antiviral drugs [60 (21%) in the TAF group and 31 (22%) in the TDF group]. Mean baseline HBV DNA level was 5.7 log_{10} IU/ml in the TAF group and 5.8 log_{10} IU/ml in the TDF group.

A total of 268 (94%) of 285 patients receiving TAF achieved the primary efficacy endpoint of HBV DNA < 29 IU/ml at week 48 versus 130 (93%) of 140 patients receiving TDF (adjusted between-group difference 1.8% (95% CI 3.6–7.2; p = 0.47), which demonstrates non-inferiority. The beneficial effects of TAF and TDF treatment on viral suppression were sustained at 96 weeks when the proportion of HBeAg-negative patients receiving TAF who had HBV DNA < 29 IU/ml was 90% (257 of 285 patients), compared with 91% (127 of 140 patients) of those receiving TDF [adjusted between group difference 0.6% (95% CI 7.0–5.8); p = 0.84] confirming non-inferiority at this time point.

With the exception of rates of normalization of ALT levels, based on the AASLD normal range, there were no significant between-group differences in secondary and other efficacy outcomes at week 48. At week 96, the proportion of HBeAg-negative patients receiving TAF, with normal ALT by central laboratory criteria, having had an ALT above the ULN at baseline, was significantly higher than among those receiving TDF (81% versus 71%, respectively, p = 0.038) and remained significant when using the more stringent AASLD criteria (50% versus 40%, respectively, p = 0.035). Furthermore, patients receiving TAF had higher rates of ALT normalization than patients receiving TDF at every study visit after week 4.

No patients in either treatment group had HBsAg loss at week 48, and the mean decline in quantitative HBsAg from baseline to week 48 was minimal in both groups (TAF 0.09 versus TDF 0.06 log_{10} IU/ml). Similar, small mean declines in HBsAg levels were observed at week 96 (TAF 0.14 versus TDF 0.10 log_{10} IU/ml). Primary and secondary endpoints are summarised in Table 1.

**Resistance**

In vitro, TAF has shown potent anti-HBV action against lamivudine-resistant and entecavir-resistant recombinants with mean changes in EC_{50} values < twofold compared with wild-type virus. Pooled analysis of both phase III trials showed the majority (89.2%) of patients had wild-type virus at baseline. The number of patients in both studies with resistance mutations associated with other approved nucleos(t)ide analogues was very small. In the HBeAg-negative group there were lamivudine-associated resistance mutations in five patients and mutations indicating resistance to entecavir and adefovir in one patient each. In HBeAg-positive patients there were mutations indicating resistance to lamivudine in 18 patients, to adefovir in 9 patients, and to entecavir in 4 patients. Pooled data from both phase III trials showed 1242 patients entered year 2 of the study. Of these, 132 (11%) met the criteria for resistance testing at week 96 [patients who experienced virological breakthrough (defined as HBV DNA ≥ 69 IU/ml on two consecutive visits after achieving HBV DNA < 69 IU/ml, or a ≥ 1.0 log_{10} increase in HBV DNA from nadir) or those who discontinued treatment after at least 24 weeks because of viraemia (HBV DNA ≥ 69 IU/ml)]. Of those who qualified for resistance sequence analyses, 87 were in the TAF group and 45 in the TDF group. 36 patients qualified as virological breakthrough and in 11 (31%), this was associated with nonadherence to the study medication. Overall, at week 96, no resistant isolates were detected in the TAF or TDF groups in either study.
Safety and tolerability

Both phase III studies showed TAF to be well tolerated in patients with chronic hepatitis B with most adverse events being mild to moderate in severity. At week 48, discontinuation of treatment due to adverse events was uncommon (1%) in both treatment groups. The most common adverse events overall were upper respiratory tract infection [51 (9%) of 581 patients receiving TAF versus 22 (8%) of 292 patients receiving TDF], nasopharyngitis [56 (10%) patients receiving TAF versus 16 (5%) patients receiving TDF], and headache [42 (7%) patients receiving TAF versus 22 (8%) patients receiving TDF]. The proportion of patients experiencing serious adverse events was the same in both treatment groups (4%), none of which were deemed by the investigator to be related to study treatment. There were no significant differences in the frequency of grade 3 or 4 laboratory abnormalities [18/581 (32%) patients in the TAF group versus 96/292 (33%) in the TDF group].

Table 1. Primary and secondary efficacy endpoints at 48 and 96 weeks of treatment with tenofovir alafenamide or tenofovir disoproxil fumarate for chronic hepatitis B virus patients.44–46

|                      | HBeAg positive (n = 873) | HBeAg negative (n = 425) |
|----------------------|--------------------------|--------------------------|
|                      | TAF 25 mg (n = 581)      | TDF 300 mg (n = 292)     | p-value | TAF 25 mg (n = 285) | TDF 300 mg (n = 140) | p value |
| Week 48              |                          |                          |         |                    |                        |         |
| HBV DNA < 29 IU/ml   | 371/581 [64%]            | 195/292 [67%]            | 0.25    | 268/285 [94%]      | 130/140 [93%]         | 0.47    |
| ALT normalization*   | 384/537 [72%]            | 179/268 [67%]            | 0.18    | 196/236 [83%]      | 91/121 [75%]          | 0.076   |
| central laboratory   | 257/572 [45%]            | 105/290 [36%]            | 0.014   | 137/276 [50%]      | 44/138 [32%]          | 0.0005  |
| AASLD criteria       |                          |                          |         |                    |                        |         |
| HBeAg loss           | 78/565 [14%]             | 34/285 [12%]             | 0.47    | NA                 | NA                    | –       |
| HBeAg seroconversion | 58/565 [10%]             | 23/285 [8%]              | 0.32    | NA                 | NA                    | –       |
| HBsAg loss           | 4/576 [0.7%]             | 1/288 [0%]               | 0.52    | 0/281 [0%]         | 0/138 [0%]            | –       |
| HBsAg seroconversion | 3/576 [0.5%]             | 0/288 [0%]               | 0.22    | 0/281 [0%]         | 0/138 [0%]            | –       |
| Week 96              |                          |                          |         |                    |                        |         |
| HBV DNA < 29 IU/ml   | 423/581 [73%]            | 218/292 [75%]            | 0.47    | 258/285 [90%]      | 127/140 [91%]         | 0.84    |
| ALT normalization*   | 405/537 [75%]            | 181/268 [68%]            | 0.017   | 191/236 [81%]      | 139/276 [50%]         | 0.038   |
| central laboratory   | 299/572 [52%]            | 121/290 [42%]            | 0.003   | 86/121 [71%]       | 55/138 [40%]          | 0.035   |
| AASLD criteria       |                          |                          |         |                    |                        |         |
| HBeAg loss           | 123/565 [22%]            | 51/285 [18%]             | 0.2     | NA                 | NA                    | –       |
| HBeAg seroconversion | 99/565 [18%]             | 35/285 [12%]             | 0.5     | NA                 | NA                    | –       |
| HBsAg loss           | 7/576 [1%]               | 4/288 [1%]               | 0.88    | 1/281 [0.4%]       | 0/138 [0%]            | 0.72    |
| HBsAg seroconversion | 6/576 [1%]               | 0/288 [0%]               | 0.078   | 1/281 [0.4%]       | 0/138 [0%]            | 0.72    |

*Central laboratory: ALT ≤ 43 U/l for males aged 18–69 years and ≤35 U/l for males aged ≥69 years; ALT ≤ 34 U/l for females aged 18–69 years and ≤32 U/l for female aged ≥69 years. AASLD criteria: ALT ≤ 30 U/l for males and ≤19 U/l for females. AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NA, not applicable.
At week 96, the type and frequencies of adverse events did not differ from those reported at week 48 and the most common adverse events were headache, nasopharyngitis and upper respiratory tract infection. Discontinuation rates due to adverse events remained low in both groups; 13 (2%) patients receiving TAF and 4 (1%) receiving TDF. Again, the proportion of patients experiencing serious adverse events was the same in both treatment groups (7%; 60 patients receiving TAF and 29 receiving TDF) and none were deemed by the investigator to be related to study treatment. There were no deaths during treatment.46

**Bone safety**

After 48 weeks of treatment, patients receiving TAF had significantly smaller reductions in bone mineral density (BMD) compared with patients receiving TDF. No treatment-related fractures were reported in either group.44,45 In HBsAg-positive patients the mean reduction from baseline BMD was significantly less at both the hip (mean change $-0.10\%$ *versus* $-1.72\%$, $p < 0.0001$) and the spine (mean change $-0.42\%$ *versus* $-2.29\%$, $p < 0.0001$) in the TAF group compared with the TDF group.44 Similarly, in HBsAg-negative patients the mean reduction from baseline BMD was significantly less at both the hip (mean change $-0.29\%$ *versus* $-2.16\%$, $p < 0.0001$) and the spine (mean change $-0.88\%$ *versus* $-2.51\%$, $p < 0.0001$) in the TAF group compared with the TDF group.45

A separate analysis compared the percentage of patients in each treatment group who experienced a greater than 3% reduction in BMD after 48 weeks of treatment. In the HBsAg-positive patients, a greater than 3% reduction in BMD occurred in significantly fewer TAF recipients than TDF recipients (hip: 8% *versus* 24%, respectively; spine: 18% *versus* 38%, respectively).44 The HBsAg-negative group showed similar results with significantly fewer TAF recipients experiencing a greater than 3% reduction in BMD than TDF patients (hip: 10% *versus* 33%, respectively; spine: 22% *versus* 39%, respectively).45 The presence of baseline risk factors for osteoporosis (female sex, age $\geq 50$ years, Asian race and estimated glomerular filtration rate (eGFR) $< 90$ ml/min) did not impact on the percentage of patients on TAF with a greater than 3% reduction in BMD which remained 8–10% at week 48, irrespective of number of risk factors.48 By contrast, the percentage of patients on TDF with a greater than 3% reduction in BMD at week 48 increased according to the number of baseline risk factors for osteoporosis by up to 58% for patients with all four risk factors.48

At 96 weeks, the reduced effects on BMD decline with TAF versus TDF, continued with a pooled analysis of the treatment populations showing patients receiving TAF had significantly smaller decreases compared with TDF-treated patients, at the hip ($-0.33\%$ *versus* $-2.52\%$) and the spine ($-0.75\%$ *versus* $-2.59\%$). Furthermore, the magnitude of the difference in BMD decreases between the TAF and TDF groups was significantly greater at week 96 compared with the difference in decline observed at week 48 ($p < 0.001$) when assessed at hip but not at spine.46 Furthermore, significant improvements in BMD at the hip ($-2.7\%$ to $-2.1\%$, $p < 0.001$) and at the spine ($-3.1\%$ to $-1.6$, $p < 0.001$) were observed early (at week 120) in the patients who had switched to TAF from TDF at week 96, during the open-label extension phase.49 The recently reported 1-year safety and efficacy data from the open-label phase included a specific analysis of a subset of patients with baseline risk factors for TDF use [age $\geq 60$ years, osteoporosis of hip/spine, $\geq$ stage 2 chronic kidney disease (CKD), albuminuria (UACR $> 30$ mg/g), hypophosphaemia (PO4 $< 2.5$ mg/dl), or comorbidities associated with CKD (e.g. hypertension, diabetes, obesity)]. In patients with $\geq$1 TDF risk factor who switched from TDF to TAF, hip BMD remained significantly below that seen in patients who had received continuous TAF at week 144 ($p = 0.016$). Antiviral efficacy was maintained in both groups and TDF patients switching to TAF at week 96 had increased rates of ALT normalization at week 144.50 The 96-week analysis reviewed the T scores at week 96 of those with a normal T score ($\geq 1.0$), that is, no evidence of osteopenia or osteoporosis, at baseline. At baseline, 570 patients in the TAF group and 285 patients in the TDF group had a normal T score. With regard to hip BMD, by week 96, 6% patients in the TAF group, with available data, had developed osteoporosis compared with 16% in the TDF group. No patients with a normal T score at baseline in either group developed osteoporosis and there were no treatment-related fractures in either group.46

Various surrogate biomarkers for bone metabolism were evaluated in the phase III trials and
support a reduced impact of TAF on bone safety compared with TDF. These included markers of bone resorption [C-type collagen sequence (CTX)] and formation [procollagen type 1 N-terminal propeptide (P1NP), bone-specific alkaline phosphatase (bsAP), osteocalcin]. TAF recipients showed significantly smaller changes in these biomarkers at week 48, from baseline, than those receiving TDF ($p < 0.001$) and these trends continued through to week 96.44,45

Renal safety
At 48 weeks, there were no renal-related serious adverse events or renal-related drug discontinuations in either treatment groups in both phase III trials. No patients experienced proximal renal tubulopathy including Fanconi Syndrome.44,45 At week 48, median changes in eGFR were significantly smaller in the TAF recipients compared with the TDF recipients (HBeAg-positive: $-0.6$ versus $-5.4$ ml/min; $p < 0.0001$, HBeAg-negative: $-1.8$ versus $-4.8$ ml/min; $p = 0.004$).44,45

The lower impact of TAF, compared with TDF, on renal parameters continued to week 96. A pooled analysis of both study populations showed the mean increase in creatinine from baseline of 0.003 mg/dl in patients receiving TAF was significantly smaller than the increase of 0.019 mg/dl in patients receiving TDF ($p = 0.001$). Patients receiving TAF had a significantly smaller median decrease in eGFR, by Cockcroft-Gault equation, than patients receiving TDF (1.2 ml/min versus 4.8 ml/min respectively, $p < 0.001$).46 Significantly fewer TAF recipients than TDF recipients experienced a $\geq 25\%$ reduction in eGFR (10 versus 18%; $p < 0.001$) at week 96, and analysis of factors associated with this level of decline identified diabetes mellitus, treatment with TDF, vitamin D level below the lower limit of the normal range, and baseline ALT value more than five times ULN by AASLD criteria to be independent predictors.46 Furthermore, in the open-label phase of each trial, in those patients who switched from TDF to TAF at week 96, there was a significant improvement in creatinine clearance at week 120 and the patients on long-term TAF maintained stable creatinine clearance.49 Some 1-year data, postswitch to TAF in the open-label phase, in a subset of patients with risk factors for TDF have recently been reported. At week 144, eGFR was significantly improved following switch to TAF ($p \leq 0.023$ for patients with no TDF risk factors; $p = 0.008$ for patients with $\geq 1$ TDF risk factor).50

TFV nephrotoxicity primarily occurs in the proximal tubule cells, so specific markers of tubular dysfunction were assessed. There were no significant between-group differences in urine-protein-to-creatinine or albumin-to-creatinine ratio (UACR) but significant differences were observed when more sensitive markers of proximal tubular dysfunction were assessed.46 Median percentage changes from baseline in both urine retinol-binding-protein-to-creatinine (RBP:CR) ratio and urine-$\beta$-2-microglobulin-to-creatinine ($\beta$2M:CR) ratio favoured TAF over TDF at week 48 ($p < 0.001$). Week 96 data continued to favour TAF over TDF in median change from baseline in both RBP:CR (HBeAg positive: 22.2 versus 55.6%, HBeAg negative: 18.5 versus 53.2%; both $p < 0.001$) and $\beta$2M:CR (HBeAg positive: 9.5 versus 55.7%, HBeAg negative: 10.8 versus 59.2%; both $p < 0.001$) ratios.46

Discussion
The use of IFNs and nucleos(t)ide analogues for the management of chronic hepatitis B has greatly improved patient outcomes. These therapies can achieve sustained HBV DNA suppression and reduce the progression of liver disease, ultimately preventing HCC and liver-related mortality.14–19 NAs rarely result in HBsAg clearance, however, and have a marginal effect on cccDNA production, the persistence of which remains a barrier to the complete eradication of the virus. Whilst current treatments may decrease liver related morbidity and mortality, long term therapy is usually required and can be associated with renal and bone toxicity.

Better understanding of the HBV life cycle, including information on the key nuclear enzymes involved in cccDNA formation, has enabled the identification of multiple new therapeutic targets currently under investigation. It is likely combination therapy, targeting multiple steps in the HBV life cycle with immune modulatory therapy will be needed to achieve the goal of HBV ‘cure’ and this will include a continued role for suppression of viral replication with nucleos(t)ide analogues. The development of TAF, specifically designed to deliver potent antiviral activity but with an improved safety profile compared with TDF, is therefore timely.
Two large, multinational, phase III trials have demonstrated sustained antiviral efficacy of TAF that is non-inferior to TDF in patients with both HBeAg-positive and HBeAg-negative chronic HBV infection. The initial 48-week analysis reported no significant differences between the TAF and TDF groups in terms of other secondary efficacy endpoints: the proportion of patients with HBsAg seroconversion to anti-HBs, the proportion of patients with HBeAg loss and the proportion of patients with ALT normalization (assessed by central laboratory criteria). However, the proportion of patients with ALT normalization was significantly lower in the TAF group when more stringent AASLD criteria were used for assessment. The recently published 96-week data confirm the efficacy outcomes seen at week 48 and at this time point, significantly higher rates of ALT normalization were observed in the TAF treatment groups by both central laboratory criteria and AASLD criteria. This finding was observed in both studies at most study time points so appears to be a real phenomenon.46 The exact mechanism behind this is yet to be established but the clinical significance was recently demonstrated in a large cohort study from Hong Kong that followed 21,182 patients (10,437 with and 10,745 without a normal ALT (<30U/l in males, <19U/l in females) at 12 months after antiviral treatment with TFV or entecavir) for 4.0 ± 1.7 years. Patients with normal on-treatment ALT after antiviral treatment had lower risk of hepatic events with the cumulative incidence (95% CI) of composite hepatic events at 6 years being 3.51% (3.06–4.02%) in those with a normal ALT and 5.70% (5.15–6.32%) in those without a normal ALT (p < 0.001).51

TAF and TDF were well tolerated in both phase III studies with low rates of early discontinuation (<1%) and adverse effects in both treatment groups at week 48. The changes in bone safety parameters were small but favoured TAF over TDF. Safety outcomes at week 96 were consistent with week 48 results with significant smaller declines in hip and spine BMD in patients receiving TAF than those receiving TDF.

Effects on renal safety markers were similar to BMD findings. After 2 years of treatment, significant differences in decreases in eGFR and sensitive markers of proximal tubular dysfunction support that TAF has less of an impact on renal function than TDF. It is certainly encouraging that the decrease in adverse bone and renal effects in patients receiving TAF over TDF were observed after only 48 weeks of therapy and in those patients who switched from TAF to TDF, at the end of the double-blind phase (week 96), significant improvements in bone and renal parameters occurred only 24 weeks after the switch.

Given concerns about renal and bone adverse effects with long term TDF, these safety outcomes may be relevant for all patients with chronic hepatitis B who require therapy.25,26 They are especially relevant in light of results from a recent longitudinal cohort study in Taiwan of 180,730 patients that showed patients with HBV to be at greater risk of developing osteoporosis than matched non-HBV controls, even after correction for multiple confounding factors.32 This improved safety profile allows for a broader population of HBV-infected patients to potentially benefit from TFV antiviral therapy. Those who may benefit the most, however, are likely to be older patients, those with comorbidities or risk factors for the development of renal or bone disease.

Data relating to the use of TAF in certain specific populations are currently limited. To date, there are no specific human data on the use and safety of TAF during pregnancy but animal studies did not report any adverse foetal developmental effects.32 TAF, like TDF, is classified as US Food and Drug Administration pregnancy category B drug.

Although the phase III renal safety data are encouraging, these studies did not enrol patients with clinically significant renal impairment (eGFR < 50ml/min) and the majority of patients were under 65-years old without comorbidities. Similarly, there are no efficacy or safety data for patients with decompensated or advanced liver disease (Child-Pugh class B and C). Further studies are underway to evaluate the use of TAF in these key populations. The post liver transplant population are an important group with risk factors for renal and bone disease. A recent study evaluated short-term renal and bone safety in post liver transplant patients with chronic kidney disease receiving TAF for HBV prophylaxis. Patients maintained on TDF antiviral prophylaxis were randomized 1:1 to either switch to TAF 25 mg once daily or remain on TDF. In this trial, 47 patients reached week 12 (25 in TAF
group and 22 in TDF group). Mean baseline eGFR Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) was 52 ml/min/1.73m² with 53% of patients <50 ml/min/1.73 m². The median time since liver transplant was 9 years. There were no treatment discontinuations. Switching to TAF treatment resulted in a trend toward improved serum creatinine levels (median change in mg/dl: −0.07 for TAF versus −0.02 for TDF; \( p = 0.09 \)) as early as week 12.53

The efficacy of TAF in patients with resistance mutations associated with older nucleos(t)ide analogues is unclear. Although no evidence of TAF or TDF resistance was detected in the phase III studies through 96 weeks of treatment, very small numbers of patients had baseline mutations indicating resistance to lamivudine, adefovir or entecavir and efficacy data specifically for this group is not available.

As most chronic HBV patients require lifelong therapy, the cost of drugs is an important consideration. In the United States, TAF has been approved with a similar price as TDF. Elsewhere, TAF may be much more expensive than TDF, limiting its use. With generic options for TDF and entecavir now available, it remains to be seen whether TAF will be a competitive, cost-effective alternative to the older NAs.

In conclusion, TAF is more efficient than TDF at delivering TFV into target hepatocytes with reduced impact on renal function and bone mineralization. TAF was included in the 2017 European Association for the Study of the Liver guidelines as a first-line agent for the treatment of chronic HBV infection in adults, and the recently updated 2018 AASLD guidance also recommends TAF amongst preferred antiviral therapies in adults.13,54 Similarly, the 2018 expert consensus for the management of chronic hepatitis B in Asian Americans includes TAF as a preferred therapy.55 These guidelines support a role for TAF in the management of chronic hepatitis B and as encouraging as the phase III data for TAF is, substantially longer follow up will be required to determine if and how the differences in renal and bone safety parameters translate into clinical benefit over TDF.

**Funding**

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

**Conflict of interest statement**

Dr Kosh Agarwal has received grant support from Abbvie, Merck, Gilead Sciences and advisor fees from Abbvie, Merck, Gilead Sciences, Arbutus, BMS, Janssen and Vir.

**References**

1. Schweitzer A, Horn J, Mikolajczyk RT, et al. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet 2015; 386: 1546–1555.

2. World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva, Switzerland: World Health Organization, 2015. http://www.who.int/hiv/pub/hepatitis/hepatitis-b-guidelines/en/ (accessed 14 January 2018).

3. Bosch FX, Ribes J, Cleries R, et al. Epidemiology of hepatocellular carcinoma. Clin Liver Dis 2005; 9: 191–211.

4. Fattovich G, Stroffolini T, Zagni I, et al. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology 2004; 127(5 Suppl 1):S35–S50.

5. Kao JH. Hepatitis B virus genotypes and hepatocellular carcinoma in Taiwan. Intervirology 2003; 46: 400–407.

6. Lok AS and McMahon BJ. Chronic hepatitis B: update 2009. Hepatology 2009; 50: 661–662.

7. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015; 385: 117–171.

8. Liaw YF, Tai DI, Chu CM, et al. The development of cirrhosis in patients with chronic type B hepatitis: a prospective study. Hepatology 1988; 8: 493–496.

9. Huo TT, Wu JC, Hwang SJ, et al. Factors predictive of liver cirrhosis in patients with chronic hepatitis B: a multivariate analysis in a longitudinal study. Eur J Gastroenterol Hepatol 2000; 12: 687–693.

10. Park BK, Park YN, Ahn SH, et al. Long-term outcome of chronic hepatitis B based on histological grade and stage. J Gastroenterol Hepatol 2007; 22: 383–388.

11. Yu MW, Lin CL, Liu CJ, et al. Influence of metabolic risk factors on risk of hepatocellular...
carcinoma and liver-related death in men with chronic hepatitis B: a large cohort study. *Gastroenterology* 2017; 153: 1006–1017.

12. Yu MW, Lin CL, Liu CJ, et al. Influence of metabolic risk factors on risk of hepatocellular carcinoma and liver-related death in men with chronic hepatitis B: a large cohort study. *Gastroenterology* 2017; 153: 1006–1017.

13. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; 67: 370–398.

14. Chang TT, Liaw YF, Wu SS, et al. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. *Hepatology* 2010; 52: 886–893.

15. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006; 295: 65–73.

16. Lin CL and Kao JH. Risk stratification for hepatitis B virus related hepatocellular carcinoma. *J Gastroenterol Hepatol* 2013; 28: 10–17.

17. Papatheodoridis GV, Lampertico P, Manolakopoulos S, et al. Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos(t)ide therapy: a systematic review. *J Hepatol* 2010; 53: 348–356.

18. Rijckborst V, Mj TB, Cakaloglu Y, et al. A randomized trial of peginterferon alpha-2a with or without ribavirin for HBeAg-negative chronic hepatitis B. *Am J Gastroenterol* 2010; 105: 1762–1769.

19. Sung JJ, Tsoi KK, Wong VW, et al. Meta-analysis: treatment of hepatitis B infection reduces risk of hepatocellular carcinoma. *Aliment Pharmacol Ther* 2008; 28: 1067–1077.

20. Buster EH, Hansen BE, Lau GK, et al. Factors that predict response of patients with hepatitis B e antigen-positive chronic hepatitis B to peginterferon-alfa. *Gastroenterology* 2009; 137: 2002–2009.

21. Chan HL, Wong VW, Tse AM, et al. Serum hepatitis B surface antigen quantification can reflect hepatitis B virus in the liver and predict treatment response. *Clin Gastroenterol Hepatol* 2007; 5: 1462–1468.

22. Wursthorn K, Lutgehetmann M, Dandri M, et al. Peginterferon alpha-2b plus adefovir induce strong cccDNA decline and HBsAg reduction in patients with chronic hepatitis B. *Hepatology* 2006; 44: 675–684.

23. Arends P, Rijckborst V, Zondervan PE, et al. Loss of intrahepatic HBsAg expression predicts sustained response to peginterferon and is reflected by pronounced serum HBsAg decline. *J Viral Hepat* 2014; 21: 897–904.

24. Janssen HL, van Zonneveld M, Senturk H, et al. Pegylated interferon alfa alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. *Lancet* 2005; 365: 123–129.

25. Lau GK, Piratvisuth T, Luo XX, et al. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2005; 352: 2682–2695.

26. Jafri SM and Lok AS. Antiviral therapy for chronic hepatitis B. *Clin Liver Dis* 2010; 14: 425–438.

27. American Association for the Study of Liver Diseases. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology* 2016; 63: 261–283.

28. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int* 2016; 10: 1–98.

29. Heathcote EJ, Marcellin P, Buti M, et al. Three year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. *Gastroenterology* 2011; 140: 132–43.

30. Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow up study. *Lancet* 2013; 381: 468–475.

31. Petersen J, Heyne R, Mauss S, et al. Effectiveness and safety of tenofovir disoproxil fumarate in chronic hepatitis B: a 3-year prospective field practice study in Germany. *Dig Dis Sci* 2016; 61: 3061–3071.

32. Chang TT, Liaw YF, Wu SS, et al. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. *Hepatology* 2010; 52: 886–893.

33. Lampertico P, Chan HL, Janssen HL, et al. Review article: long-term safety of nucleoside and nucleotide analogues in HBV-monoinfected patients. *Aliment Pharmacol Ther* 2016; 44: 16–34.

34. Maggi P, Montinaro V, Leone A, et al. Bone and kidney toxicity induced by nucleotide analogues in patients affected by HBV-related chronic hepatitis: a longitudinal study. *J Antimicrob Chemother* 2014; 70: 1150–1154.
35. Papatheodoridis G, Vlachogiannakos I, Cholongitas EE, et al. Discontinuation of oral antivirals in chronic hepatitis B: a systemic review. *Hepatology* 2016;63:1481–1492.

36. Buti M, Riveiro-Barciela M, Esteban R, et al. Tenofovir alafenamide fumarate: a new tenofovir prodrug for the treatment of chronic hepatitis B infection. *J Infect Dis* 2017; 216(Suppl. 8):S792–S796.

37. Abdul Basit S, Dawood A, Ryan J, et al. Tenofovir alafenamide for the treatment of chronic hepatitis B virus infection. *Expert Rev Clin Pharmacol* 2017; 10: 707–716.

38. Babusis D, Phan TK, Lee WA, et al. Mechanism for effective lymphoid cell and tissue loading following oral administration of nucleotide prodrug GS-7340. *Mol Pharm* 2013; 10: 459–466.

39. Murakami E, Wang T, Park Y, et al. Implications of efficient hepatic delivery by tenofovir alafenamide (GS-7340) for hepatitis B virus therapy. *Antimicrob Agents Chemother* 2015; 59: 3563–3569.

40. Agarwal K, Fung SK, Nguyen TT, et al. Twenty-eight day safety, antiviral activity and pharmacokinetics of tenofovir alafenamide for treatment of chronic hepatitis B infection. *J Hepatol* 2015; 62: 533–540.

41. Ruane PJ, DeJesus E, Berger D, et al. Antiviral activity, safety and pharmacokinetics/pharmacodynamics of tenofovir alafenamide as 10-day monotherapy in HIV-1 positive adults. *J Acquir Immune Defic* 2013; 63: 449–455.

42. European Medicines Agency. Vemlidy 25 mg film-coated capsules: summary of product characteristics, 2017. http://www.ema.europa.eu (accessed 4 January 2018).

43. Custodio JM, Ma G, Cuvin J, et al. Pharmacokinetics and safety of tenofovir alafenamide in subjects with severe hepatic impairment (abstract no. FRI-127/poster). *J Hepatol* 2016; 64(1 Suppl): S594–S595.

44. Chan HL, Fung S, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBsAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol* 2016; 1: 196–206.

45. Agarwal K, Seto WK, Brunetto M, et al. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection *J Hepatol* 2018; 68: 672–681.

46. Liu Y, Mitchell B, Dinh P, et al. Antiviral activity of tenofovir alafenamide against drug-resistant HBV isolates in vitro. *Hepatology* 2016; 64: 1194A.

47. Seto WK, Asahina Y, Peng CY, et al. Reduced changes in bone mineral density in chronic HBV (CHB) patients receiving tenofovir alafenamide (TAF) compared with tenofovir disoproxil fumarate (TDF) (abstract no. 67 plus oral presentation). *Hepatology* 2016; 64(Suppl 1): 35A.

48. Chan HL, Fung S, Seto WK, et al. Improved bone and renal safety of switching from tenofovir disoproxil fumarate to tenofovir alafenamide: preliminary results from two phase 3 trials in HBsAg-positive and HBsAg-negative patients with chronic hepatitis B (abstract no. PS-041 plus oral presentation). *J Hepatol* 2017; 66(Suppl): S25.

49. Gane E, Seto WK, Janssen H, et al. Safety and efficacy at 1 year after switching from tenofovir disoproxil fumarate to tenofovir alafenamide in chronic HBV patients with risk factors for TDF use (abstract no. PS-156 plus oral presentation). *J Hepatol* 2018; 68(Suppl 1): S87.

50. Wong GL, Chan HL, Tse YK, et al. Normal on-treatment ALT during antiviral treatment is associated with a lower risk of hepatic events in patients with chronic hepatitis B. *J Hepatol*. Epub ahead of print 11 May 2018. DOI: 10.1016/j.jhep.2018.05.009.

51. Chen CH, Lin CL and Kao CH. Association between chronic hepatitis B virus infection and risk of osteoporosis: a nationwide population-based and study. *Medicine (Baltimore)* 2015; 94: e2276.

52. Gane E, George B, Munn S, et al. Evaluation of renal and bone safety in post liver transplant patients with chronic kidney disease receiving tenofovir alafenamide for HBV prophylaxis (abstract no. PS-336). *J Hepatol* 2018; 68(Suppl 1): S514.

53. Terrault NA, Lok AS, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 67: 1560–1599.

54. Tong MJ, Pan CQ, Han S-H, et al. An expert consensus for the management of chronic hepatitis B in Asian Americans. *Aliment Pharmacol Ther* 2018; 47: 1181–1200.