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ADIS DRUG EVALUATION

Tenofovir Alafenamide: A Review in Chronic Hepatitis B

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Abstract Tenofovir alafenamide (AF) [Vemlidy®], an oral prodrug of tenofovir, was developed to optimize the antiviral potency and clinical safety of the active moiety tenofovir diphosphate (selective reverse transcriptase nucleotide inhibitor). In two identically designed, ongoing, multinational trials in treatment-naive and -experienced adult patients with hepatitis B e antigen (HBeAg)-positive or -negative chronic hepatitis B virus (HBV) infection, once-daily tenofovir AF 25 mg provided effective and sustained viral suppression (120-week analysis), and was generally well tolerated. In the primary 48-week analysis, tenofovir AF was noninferior to once-daily tenofovir disoproxil fumarate (DF) 300 mg in terms of the proportion of patients achieving viral suppression (HBV DNA <29 IU/mL) and was associated with significantly higher alanine aminotransferase (ALT) normalization rates than tenofovir DF based on AASLD criteria (but not central laboratory criteria). In pooled analyses and/or individual trials, ALT normalization rates by AASLD and central laboratory criteria were significantly higher in tenofovir AF than tenofovir DF recipients at most assessed timepoints up to 96 weeks. Given the bone and renal safety concerns associated with long-term tenofovir DF treatment, the more favourable pharmacological profile of tenofovir AF permits a marked reduction in the dosage of this tenofovir prodrug and thereby reduces systemic exposure to tenofovir, potentially improving the bone and renal safety of tenofovir AF versus tenofovir DF. Long-term clinical experience will more definitively establish the relative bone and renal safety of these tenofovir prodrugs. With its potential for an improved safety profile, tenofovir AF is an important emerging first-line option for the treatment of chronic HBV infection in adults and adolescents (aged ≥12 years and with a bodyweight of ≥35 kg).

Tenofovir alafenamide: clinical considerations in chronic hepatitis B
Its favourable pharmacokinetic profile (vs. tenofovir DF) reduces systemic exposure to tenofovir and thereby potentially improves renal and bone safety
Noninferior antiviral efficacy to tenofovir DF at 48 weeks, with sustained viral suppression at 120 weeks
Significantly higher ALT normalization rates (vs. tenofovir DF) at most assessed timepoints
No resistant isolates detected after 96 weeks' therapy
Generally well tolerated; more favourable outcomes for markers of renal and bone safety parameters than tenofovir DF during 96 weeks' treatment

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1 Introduction

Globally, chronic hepatitis B virus (HBV) infection constitutes an important healthcare issue because of the increased risk of liver-related morbidity and mortality associated with persistent viraemia [1–4]. An estimated 2 billion individuals have evidence of a past or present infection; of whom, an estimated 240 million are chronically infected [i.e. presence of hepatitis B surface antigen (HBsAg) for >6 months] [1, 2]. In Europe, chronic HBV infection affects an estimated 0.5–0.7% of the population and is amongst the four leading causes of primary liver cancer and liver cirrhosis [5]. Acute viral hepatitis infections and associated serious hepatic complications cause an estimated 1.4 million deaths per year, 47% of which are attributable to HBV infection [1, 2].

The pathogenesis of chronic HBV infection is a dynamic process involving several phases that may not occur sequentially, with the specific course of the disease dependent upon host and viral factors, as well as the efficacy of treatment strategies [3]. In the early phases of chronic HBV infection, patients are typically hepatitis B e antigen (HBeAg)-positive, reflecting infection with wild-type HBV. However, during the course of the disease, some patients will become HBeAg-negative as a result of the emergence of nucleotide substitutions in the precore and/or basic core promoter regions of the HBV genome; this typically represents a later and more severe phase of the disease [3].

The ultimate goal of therapy in chronic HBV infection is to prevent progression of the disease to cirrhosis and hepatocellular carcinoma (HCC) [major disease-related complications affecting 20–30% of patients], with effective and sustained viral suppression shown to slow disease progression and reduce the risk of these life-threatening complications [2–4]. Tenofovir disoproxil fumarate (tenofovir DF), an ester prodrug of tenofovir, is an effective and generally well tolerated first- [3] or second-line [6] treatment option for HBV infection (and HIV [2]; typically as part of combination therapy); however, in some patients, its use is associated with renal toxicity (e.g. renal dysfunction, Fanconi syndrome) and a loss of bone mineral density (BMD) [7, 8]. Consequent to these safety concerns, tenofovir alafenamide (tenofovir AF) [Vemlidy®], a prodrug of tenofovir, was developed to optimize the antiviral potency and clinical safety of tenofovir. The favourable pharmacological profile of tenofovir AF compared with tenofovir DF (e.g. intracellular vs. plasma activation of the prodrug [9–11]), reduces systemic exposure to the active moiety tenofovir diphosphate (Sect. 3) [12] and, consequently, may improve bone and renal safety (high systemic exposure to tenofovir diphosphate is associated with tubular dysfunction [8, 13]). This narrative review discusses the clinical use of oral tenofovir AF in treatment-naive and-experienced patients with HBeAg-positive or -negative chronic HBV infection (from an EU perspective), and summarizes the pharmacological properties of tenofovir AF.

2 Pharmacodynamic Properties

Tenofovir AF is the phosphonoamidate prodrug of the reverse transcriptase nucleotide inhibitor tenofovir diphosphate [9–11]. Tenofovir AF enters primary hepatocytes via passive diffusion and the hepatic uptake transporters OATP1B1 and OATP1B3 [9]. After uptake into primary hepatocytes, tenofovir AF is primarily hydrolyzed by carboxylesterase 1 to the monophosphate analogue of tenofovir, which is then phosphorylated to tenofovir diphosphate [9–11]. Incorporation of tenofovir diphosphate into HBV DNA by HBV reverse transcriptase inhibits HBV replication, leading to DNA chain termination [14]. Inhibition of DNA reverse transcriptase by tenofovir diphosphate is specific for HBV and human immunodeficiency virus (HIV-1 and HIV-2). Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases, including mitochondrial DNA polymerase γ, with no evidence of mitochondrial toxicity in vitro [14, 15].

In HepG2 cells, tenofovir AF exhibited similar in vitro activity across all HBV genotypes (A to H) against a panel of wild-type HBV clinical isolates, with 50% effective concentrations (EC_{50}) of tenofovir AF ranging from 34.7 to 134.4 nmol/L [16]. Four of five adefovir-resistant isolates and all lamivudine- and entecavir-resistant isolates were sensitive to tenofovir AF (a >twofold change vs. wild-type HBV is considered reduced susceptibility). One adefovir-resistant isolate with a double mutation (rtA181V and rtN236T) showed a 3.7-fold reduction in sensitivity (vs. wild-type HBV) to tenofovir AF ($p < 0.001$). In vitro activity of tenofovir AF against these resistant HBV isolates was consistent with that observed with tenofovir [16].

Tenofovir AF did not exhibit renal transporter-dependent cytotoxicity in vitro, potentially leading to an improved renal safety profile [13]. Unlike tenofovir, tenofovir AF did not interact with the renal transporters OAT1 and OAT3, with no difference in the intracellular accumulation of tenofovir AF in human kidney-derived cultured cells expressing OAT1 or OAT3 versus accumulation in matched transporter-null cells. By contrast, tenofovir DF is rapidly converted in the plasma to tenofovir, with the active uptake of systemic tenofovir by the renal transporters OAT1 and OAT3 (selectively expressed on renal proximal tubule cells; PTCs) leading to dose-dependent accumulation of tenofovir in PTCs [13, 17]. Although the

exact mechanism responsible for tenofovir DF-associated renal toxicity remains unknown [8], results from case studies suggest that proximal tubular toxicity may be a potential pathogenic mechanism [8, 18].

After 4 weeks' treatment, mean reductions in serum HBV DNA from baseline were similar in the tenofovir AF (8, 25, 40 or 120 mg/day) and tenofovir DF (300 mg/day) arms in a randomized, dose-response, phase 1b trial in treatment-naive adults with chronic HBV infection (mean change −2.19 to −2.81 vs. −2.68 $\log_{10}$ IU/mL) [12]. There were no significant differences in viral suppression rates between the four tenofovir AF groups or between each individual group and the tenofovir DF group [12]. See Sect. 4 for discussion of the efficacy of tenofovir AF during longer-term treatment in pivotal phase 3 trials [19, 20].

No isolates resistant to tenofovir AF or tenofovir DF were detected during 96 weeks of treatment in the pivotal phase 3 trials, based on individual trials [19–22] and a pooled 48-week analysis ($n = 866$ and 432; abstract plus poster) [23]. At baseline, the majority (89.2%) of patients carried wild-type HBV polymerase reverse transcriptase [23]. After 48 weeks, ≈3% of patients in each treatment arm qualified for resistance sequence analyses [i.e. patients treated for ≥24 weeks who experienced virological breakthrough (defined as HBV DNA level of ≥69 IU/mL on two consecutive visits after achieving a HBV DNA level of <69 IU/mL, or a ≥1.0 $\log_{10}$ increase in HBV DNA from nadir) or who discontinued treatment at ≥24 weeks because of viraemia (HBV DNA ≥69 IU/mL)]. Almost half of the patients (17 of 38) who qualified for resistance analyses were non-adherent to study drug treatment [23]. At 96 weeks, no resistant isolates were detected in the tenofovir AF or tenofovir DF treatment group, irrespective of whether patients were HBeAg-positive (abstract plus poster presentation) [22] or HBeAg-negative (poster plus oral presentation) [21].

3 Pharmacokinetic Properties

Tenofovir AF exhibited linear, dose-proportional pharmacokinetics across a dose range of 8–120 mg in adult patients with chronic HBV infection [12]. In the fasted state, peak plasma concentrations of tenofovir AF were attained ≈0.5 h postdose in adults with chronic HBV infection [15]. Exposure to tenofovir AF after a single dose was increased by 65% after a high fat meal; hence, tenofovir AF should be taken with food. Tenofovir AF was ≈80% bound to human plasma proteins in samples collected during clinical trials. Tenofovir shows minimal binding (<1%) to human plasma proteins, with binding independent of concentration over a range of 0.01–25 μg/mL [15].

At recommended doses, systemic exposure to tenofovir was reduced by 92% after administration of tenofovir AF 25 mg compared with exposure after tenofovir DF 300 mg in patients with chronic HBV infection (mean area under the plasma concentration-time curve from time zero to infinity 176.1 vs. 2267.5 ng · h/mL) [12]. This reduction in exposure to tenofovir following tenofovir AF may, in turn, lead to improved bone (Sect. 5.1) and renal (Sect. 5.2) safety.

Tenofovir AF undergoes extensive metabolism (>80% of an oral dose) in humans [15], with in vitro studies indicating it is mainly hydrolyzed to its major metabolite tenofovir via carboxylesterase-1 in hepatocytes and via cathepsin A in peripheral blood mononuclear cells and macrophages [9, 10]. In vivo, tenofovir is subsequently phosphorylated to its active form tenofovir diphosphate [15]. In vitro, tenofovir AF is not metabolized by CYP1A2, CYP2C8, CYP2C9, CYP2C19 or CYP2D6, and undergoes minimal metabolism by CYP3A4 [15].

Renal excretion of intact tenofovir AF is a minor pathway (<1%), with the prodrug mainly eliminated after metabolism to tenofovir [15]. Tenofovir is eliminated renally by glomerular filtration and active tubular secretion. The median plasma half-lives of tenofovir AF and tenofovir were 0.51 and 32.37 h, respectively [15].

There are no clinically relevant effects on the pharmacokinetics of tenofovir AF based on age [15], gender [15], ethnicity [15] or hepatic impairment [15, 24]. There were also no clinically relevant differences in the pharmacokinetics of tenofovir AF or tenofovir in patients with severe renal impairment [creatinine clearance (CL_{CR}) >15 to <30 mL/min] (Sect. 6) [15, 25].

Tenofovir AF is associated with some established or potentially clinically significant drug interactions [15]. Since tenofovir AF is a substrate for P-glycoprotein (P-gp), drugs that induce P-gp, such as carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine and St. John's wort, are expected to decrease absorption of tenofovir AF; concomitant administration of tenofovir AF with most of these agents is not recommended. Drugs that inhibit P-gp or BCRP, for which tenofovir AF is also a substrate, may increase absorption and plasma concentrations of tenofovir AF [15]. Local prescribing information should be consulted for comprehensive information.

4 Therapeutic Efficacy

The efficacy of tenofovir AF in treatment-naive or -experienced adult patients (aged ≥18 years) with HBeAg-positive or -negative chronic hepatitis B (with plasma HBV DNA levels of ≥20,000 IU/mL) was evaluated in two identically designed, ongoing, randomized, double-blind, multinational, noninferiority trials [19, 20]. Other key inclusion criteria were a serum alanine aminotransferase (ALT) level of ≥60 U/L for men and ≥38 U/L for women

Table 1 Efficacy of oral tenofovir alafenamide in treatment-naïve and-experienced adult patients with chronic hepatitis B in pivotal double-blind, multinational, phase 3 noninferiority trials. Results for the primary efficacy analysis at 48 weeks

Study	Regimen (mg once daily)	HBV DNA <29 IU/mL (% pts)[a] [FAS]	Normalization ALT (% pts) [no. of pts]		HBeAg loss[b] (% pts) [no. of pts]	HBeAg seroconversion[b] (% pts) [no. of pts]	HBsAg loss[c] (% pts) [no. of pts]
			By central laboratory[d]	By AASLD[e]			
In HBeAg-positive pts							
Chan et al. [20]	TAF 25 + PL	64 NI [581]	72 [537]	45* [572]	14 [565]	10 [565]	1 [576]
	TDF 300 + PL	67 [292]	67 [268]	36 [290]	12 [285]	8 [285]	<1 [288]
In HBeAg-negative pts							
Buti et al. [19]	TAF 25 + PL	94 NI [285]	83 [236][f]	50** [276][f]	NA	NA	0 [281]
	TDF 300 + PL	93 [140]	75 [121][f]	32 [138][f]	NA	NA	0 [138]

NA not applicable, *NI* noninferior vs. TDF, *PL* placebo, *pts* patients, *TAF* tenofovir alafenamide, *TDF* tenofovir disoproxil fumarate

* $p = 0.014$, ** $p = 0.0005$ vs. TDF

[a] Primary endpoint

[b] In evaluable pts who were HBeAg seropositive and negative for (or missing data) anti-HBe at baseline; specified key secondary endpoints

[c] In evaluable pts who were HBsAg seropositive and negative for (or missing data) anti-HBs at baseline

[d] Assessed in pts with baseline ALT above the Central Laboratory ULN: for men, ≤43 U/L if aged <69 years and ≤35 U/L if aged ≥69 years; for women, ULN ≤34 U/L if aged <69 years and ≤32 U/mL if aged ≥69 years

[e] Assessed in pts with a baseline ALT above the AASLD ULN of <30 U/L for men and <19 U/L for women

[f] Prespecified secondary efficacy endpoint

[i.e. ≥2× the upper limit of normal (ULN) of the AASLD range] and ≤10× the ULN by central laboratory range, and an estimated CL_{CR} of ≥50 mL/min (by Cockcroft-Gault) [19, 20]. Key exclusion criteria included the presence of HCC, evidence of clinical hepatic decompensation, co-infection with hepatitis C or D virus or with HIV, and specified abnormalities in haematological and liver function tests. Within each trial, there were no significant differences in baseline characteristics between the tenofovir AF and tenofovir DF groups [19, 20]. The mean baseline HBV DNA level in patients with HBeAg-positive disease was 7.6 $\log_{10}$ IU/mL [20] and that in patients with HBeAg-negative disease was 5.8 $\log_{10}$ IU/mL [19]. Where reported, 7 and 8% of patients in the tenofovir AF and tenofovir DF groups had liver cirrhosis at baseline, with 65% of patients in both groups having no liver cirrhosis and the cirrhosis status of the remaining patients unknown [20]. In both trials (NCT0194071 [20]; NCT01940341 [19]), patients received once-daily tenofovir AF 25 mg or tenofovir DF 300 mg for up to 144 weeks [double-blind phase; initially 96 weeks (i.e. 2 years; per amendment 1 and 2), then amended to 144 weeks (i.e. 3 years; per amendment 3)], after which time all participants were eligible to receive open-label tenofovir AF 25 mg/day until week 384 (i.e. a trial duration of 8 years).

The primary efficacy endpoint was the proportion of patients with a HBV DNA level of <29 IU/mL (i.e. viral suppression) at week 48, as assessed in the full analysis set (FAS; $n = 873$ [20] and 425 [19]). Noninferiority of tenofovir AF to tenofovir DF was established if the lower bound of the 95% CI was greater than −10, with key secondary safety (bone and renal parameters; see Sect. 5) and efficacy endpoints tested in a hierarchical manner.

4.1 In Hepatitis B e Antigen (HBeAg)-Positive Patients

At 48 weeks, the antiviral efficacy of tenofovir AF was noninferior to that of tenofovir DF in terms of the proportion of patients achieving a HBV DNA level of <29 IU/mL in the primary FAS analysis (Table 1), with an adjusted between-group difference (BGD) of −3.6% (95% CI −9.8 to 2.6) [20]. At 48 weeks, 183 of 581 tenofovir AF recipients and 88 of 292 tenofovir DF recipients did not achieve a HBV DNA level of <29 IU/mL; in both treatment groups, 78% of patients who failed to achieve viral suppression had a HBV DNA level of ≥69 IU/ml and 22% had a HBV DNA level of 29 to <69 IU/mL. In both groups, most patients who did not achieve viral suppression were viraemic (i.e. HBV DNA ≥29 IU/mL) throughout the 48-week period. Results in pre-specified per-protocol analyses were consistent with those in the primary FAS analysis, with a BGD of −2.6% (95% CI −8.9 to 3.6) in the proportion of patients achieving a HBV DNA level of <29 IU/mL [20]. There were also no significant BGDs in the proportion of patients achieving a HBV DNA of <29 IU/mL at 48 weeks in pre-specified FAS subgroup analyses, including based on age (aged <50 or ≥50 years),

gender, race (Asian or non-Asian), baseline HBV DNA level (<8 or ≥8 $\log_{10}$ IU/mL), previous antiviral therapy (naive or experienced), study drug adherence (<95 or ≥95%), HBV genotype, baseline ALT by central laboratory range (≤ULN or >ULN) or baseline FibroTest score (<0.75 or ≥0.75) [20].

The beneficial effects of tenofovir AF and tenofovir DF therapy were sustained at 72 [26] and 96 [22] weeks (abstract plus posters). At 96 weeks, 73% of tenofovir AF recipients and 75% of tenofovir DF recipients had HBV DNA levels of <29 IU/mL, with higher rates of ALT normalization in the tenofovir AF group by central laboratory (75 vs. 68%; $p = 0.017$) and AASLD (52 vs. 42%; $p = 0.003$) criteria [22]. There were no statistically significant differences between these respective groups in terms of rates for HBeAg loss (22 vs. 18%), HBeAg seroconversion (18 vs. 12%; $p = 0.05$), HBsAg loss (1 vs. 1%) and HBsAg seroconversion (1 vs. 0%) at 96 weeks [22].

There were generally no significant BGDs in terms of secondary/other efficacy outcomes at 48 weeks in evaluable patients, including outcomes tabulated in Table 1 [20]. For specified key secondary outcomes, relatively few patients experienced HBeAg loss or HBeAg seroconversion by week 48 with no correlation observed between HBeAg loss and ALT flare (i.e. a confirmed serum ALT >2 × baseline value and >10 × ULN, ±associated symptoms). Very few patients showed HBsAg loss at 48 weeks (Table 1) or HBsAg seroconversion [three tenofovir AF recipients (1%) and no tenofovir DF recipients]. Significantly more tenofovir AF than tenofovir DF recipients achieved normalization of ALT levels at 48 weeks based on AASLD normal ranges, although there was no significant BGD in rates of normalization of ALT levels based on central laboratory normal ranges (Table 1). The mean reduction (i.e. improvement) from baseline (mean score 0.34 and 0.32) in FibroTest score significantly favoured tenofovir AF over tenofovir DF treatment (mean change −0.07 vs. −0.04; $p = 0.007$). The clinical relevance of this small reduction in FibroTest score in both groups and of the BGD are uncertain, with the FibroTest providing a noninvasive measure for assessing fibrosis stage [20].

In a post hoc analysis of all patients exhibiting HBeAg loss at 48 weeks ($n = 112$ across both treatment arms), factors shown to be associated with HBeAg loss after 48 weeks of treatment were older age [odds ratio (OR) per year 1.03; 95% CI 1.01–1.03; $p = 0.002$], a lower baseline HBV DNA level (OR per $\log_{10}$ IU/mL 0.74; 95% CI 0.64–0.87; $p < 0.001$) and a higher baseline ALT by central laboratory range (OR per U/L 1.01; 95% CI 1.00–1.01; $p < 0.001$) [abstract plus poster] [27]. HBV DNA suppression occurred earlier and was more rapid in those who showed HBeAg loss at week 48 than in those who did not ($n = 783$), with a significantly higher proportion of patients with HBeAg loss having HBV DNA levels of <29 IU/mL at all timepoints (except week 12) from 4 weeks onwards ($p < 0.05$ at week 4, 8 and 16; $p < 0.001$ at all subsequent timepoints up to 48 weeks) [27].

4.2 In HBeAg-Negative Patients

Tenofovir AF was noninferior to tenofovir DF in terms of the proportion of patients achieving a HBV DNA level of <29 IU/mL at 48 weeks in the FAS analysis (adjusted BGD 1.8%; 95% CI −3.6 to 7.2), with ≈93% of patients in both groups achieving this primary outcome (Table 1) [19]. Results in prespecified per-protocol analyses were consistent with those in the FAS analysis, with a BGD in the percentage of patients achieving this primary outcome in the per-protocol analysis of 0.5% (95% CI −3.3 to 4.4%). In prespecified FAS subgroup analyses, there were no significant BGDs in antiviral efficacy in terms of the primary outcome based on age (aged <50 or ≥50 years), gender, race (Asian or non-Asian), baseline HBV DNA level (<7 or ≥7 $\log_{10}$ IU/mL) or previous antiviral therapy (naive or experienced) [19].

The beneficial effects of tenofovir AF and tenofovir DF treatment on viral suppression were sustained at 72 [26] and 96 weeks [21]. At 96 weeks, viral suppression rates in the tenofovir AF and tenofovir DF groups were 90 and 91%, respectively [21].

With the exception of rates of normalization of ALT levels based on the AASLD normal range, there were no significant BGDs in secondary and other outcomes at 48 weeks (Table 1) [19]. In both groups, there were minimal reductions in HBsAg levels by week 48, with no patients achieving HBsAg loss (Table 1) [19]. At 48 weeks, the mean reduction from baseline in FibroTest score favoured tenofovir AF treatment over tenofovir DF (mean change −0.05 vs. −0.03; $p = 0.028$; baseline mean score 0.37 in both groups) [abstract plus poster] [28].

At 96 weeks, ALT normalization rates in the tenofovir AF group were significantly higher than those in the tenofovir DF group by central laboratory (81 vs. 71%; $p = 0.038$) and AASLD (50 vs. 40%; $p = 0.035$) criteria [21].

4.3 Pooled Analyses of Phase 3 Trials

Several post hoc analyses of pooled data from the two identically designed phase 3 trials have been undertaken, all of which are available as abstract and/or poster/oral presentations [26, 28–34].

Tenofovir AF treatment was associated with higher early antiviral plus biochemical response rates than tenofovir DF, with a significantly higher proportion of tenofovir AF recipients achieving ALT normalization (by AASLD

criteria) plus HBV DNA suppression at 12 weeks (9 vs. 5%; $p = 0.01$; $n = 831$ and 416) [30]. Independent predictors for achieving this composite early response were tenofovir AF treatment (OR 2.78; $p = 0.0022$), lower baseline HBV DNA level (OR per $\log_{10}$ IU/mL 0.53; $p < 0.0001$), HBeAg-negative status at baseline (OR 3.12; $p = 0.0006$), male gender (OR 2.48; $p = 0.0023$) and the absence of cirrhosis (OR 7.35; $p = 0.0077$) [30].

At 48 weeks, patients who achieved viral suppression at 12 weeks were significantly more likely to achieve ALT normalization by AASLD criteria (49 vs. 42% of patients who did not achieve viral suppression at 12 weeks; $p = 0.02$; $n = 279$ and 965), but not by central laboratory criteria (79 vs. 73%; $n = 228$ and 905), and HBeAg loss (22 vs. 13%; $p = 0.03$; $n = 72$ and 758) [29]. There was no significant difference in HBeAg seroconversion rates at 48 weeks between patients who achieved early viral suppression and those who did not (17 vs. 9%). In patients with HBV viral suppression at 12 weeks, the median reduction in HBsAg level after 48 weeks was lower than in patients with 12-week HBV DNA levels of ≥29 IU/mL (−0.04 vs. −0.21 IU/mL; $p < 0.001$) [29].

ALT normalization rates were significantly higher in the tenofovir AF than in the tenofovir DF group at all assessed timepoints from 4 weeks onwards based on the AASLD normal range ($p \leq 0.001$ at all timepoints from week 16–64; $p < 0.005$ at week 8, 12 and 72) and from week 12–72 (except week 16) based on the central laboratory normal range ($p < 0.005$ at week 32 and 36; $p \leq 0.001$ at week 24, 28 and 64; $p < 0.05$ at all other timepoints) [31]. Patients who had no risk factors for metabolic syndrome (i.e. body mass index ≥25 kg/m^2, diabetes, hypertension and hyperlipidaemia) were more likely to achieve ALT normalization (by AASLD criteria), with significantly higher ALT normalization rates in the tenofovir AF group than in the tenofovir DF group in patients who had no risk factors (57 vs. 42%; $p < 0.001$; $n = 439$ and 212), but not in those who had one (42 vs. 33%; $n = 270$ and 144) or at least two (31 vs. 23%; $n = 102$ and 57) risk factors [31].

At week 48, mean reductions from baseline in FibroTest scores significantly favoured tenofovir AF over tenofovir DF treatment in patients with baseline scores of 0.00–0.48 (i.e. category F0-F2; mean change −0.04 vs. −0.01; $p < 0.01$; $n = 579$ and 289) and 0.49–0.74 (i.e. category F3–F4; mean change −0.11 vs. −0.08; $p < 0.04$; $n = 162$ and 78), with no significant BGD in those with baseline scores of 0.75–1.00 (i.e. category F5–F6; mean change −0.15 vs. −0.12; $n = 67$ and 41) [28]. For the most part, these small mean reductions in FibroTest scores appeared to be driven by changes in the apolipoprotein A1 component of the score. Higher baseline ALT levels (i.e. >5 × ULN by AALSD criteria; OR 3.76; $p < 0.0001$) and lower baseline HBsAg levels (OR 0.57; $p < 0.0001$) were the strongest predictors for improvement in FibroTest score. Overall, 14.7% of patients in the tenofovir AF group and 13.2% of patients in the tenofovir DF group experienced an improvement in fibrosis stage for FibroTest categories corresponding to F0–F2, F3–F4 and F5–F6 [28].

During the first 48 weeks of treatment, there were no differences in the rate of decline in HBsAg levels between the tenofovir AF and tenofovir DF groups [32]. Over this period, reductions in HBsAg levels were greater in HBeAg-positive than HBeAg-negative patients, with HBeAg-negative patients having minimal reductions in HBsAg levels regardless of treatment duration. The probability of achieving a >0.5 $\log_{10}$ reduction in HBsAg level at 48 weeks was higher in patients with HBV genotype B (vs. non-B genotypes; OR 5.92; $p < 0.0001$) and lower in patients with HBV genotype D (vs. non-D genotypes; OR 0.31; $p < 0.0001$) [32].

At 48 weeks, 50 of 1246 evaluable patients had a HBV DNA level of ≥2000 IU/mL [i.e. viral persistence; $n = 35$ (4%) in the tenofovir AF group and 15 (4%) in the tenofovir DF group], with 25 of these patients continuing to have viral persistence at 72 weeks [26]. Independent predictive factors for viral persistence at 48 weeks were a higher baseline HBV DNA level (≥8 $\log_{10}$ IU/mL; OR 4.98; $p < 0.0001$), HBeAg-positive status at baseline (OR 4.79; $p = 0.043$), HBV genotype D (vs. non-D genotypes; OR 2.60; $p = 0.007$), prior antiviral therapy (OR 1.99; $p = 0.046$) and antiviral treatment adherence (OR per % adherence 0.78; $p = 0.002$). There was no difference between treatment arms for viral persistence rates at 48 weeks [26].

During the initial 24 weeks of the open-label extension phase (i.e. week 96–120), in patients who switched from tenofovir DF to tenofovir AF at week 96, there was a significant increase from week 96 to week 120 in the percentage of patients achieving ALT normalization by central laboratory (78% after 96 weeks' tenofovir DF vs. 89% after switching to tenofovir AF; $p < 0.001$) and AASLD laboratory (47 vs. 63%; $p < 0.001$) criteria [34]. During this open-label period, viral suppression was maintained in patients who switched from tenofovir DF to tenofovir AF (88% at week 96 and 120) and in those who continued tenofovir AF treatment throughout the 120-week period (88% at week 96 and 90% at week 120) [34].

In a pooled analysis in women of child bearing potential (WOCBP; $n = 365$) [32% of whom had a HBV DNA level of >1 × 10^8 IU/mL at baseline], 77% of WOCBP who had a baseline HBV DNA level of <2 × 10^5 IU/mL achieved viral suppression after 12 weeks of tenofovir AF or tenofovir DF, with 54% of all WOCBP achieving complete viral suppression at week 24 (abstract) [33].

5 Tolerability and Safety

Tenofovir AF was generally well tolerated in the ongoing phase 3 trials in patients with chronic hepatitis B [19, 20], including during longer-term treatment [72-week analysis of pooled data (median duration of exposure 88 weeks) [15]; 96-week data from individual trials [21, 22]). During 48 weeks of tenofovir AF treatment, most (≈96%) treatment-emergent adverse events (TEAEs) were of mild to moderate severity, with very few patients (1%) discontinuing treatment because of an adverse event [19, 20]. There was no difference in the nature and incidence of TEAEs or discontinuation rates because of TEAEs between the tenofovir AF and tenofovir DF groups [19, 20]. In both trials, the most common TEAEs occurring in the tenofovir AF and tenofovir DF groups were headache (7 vs. 8% [20]; 14 vs. 10% [19]), upper respiratory tract infection (9 vs. 8% [20]; 12 vs. 7% [19]) and nasopharyngitis (10 vs. 5% [20]; 11 vs. 11% [19]). Based on the pooled 72-week analysis, the most frequently reported adverse reactions occurring during longer-term treatment with tenofovir AF were headache (11% of patients), nausea (6%) and fatigue (6%) [15]. As reported in the EU summary of product characteristics, headache is a very common (i.e. incidence ≥10%) adverse reaction occurring during tenofovir AF treatment and common (i.e. incidence ≥1 to <10%) adverse reactions were diarrhoea, vomiting, nausea, abdominal pain, abdominal distension, flatulence, fatigue, dizziness, rash, pruritus, increased ALT and arthralgia [15].

Relatively few patients experienced serious TEAEs (4% of patients in both treatment groups [20]; 5% in the tenofovir AF group vs. 6% in the tenofovir DF group [19]) after 48 weeks' treatment, with none of these considered by investigators to be treatment related [19, 20]. In patients with HBeAg-positive HBV, serious TEAEs occurring in more than one patient were HCC and dizziness, each of which occurred in two patients receiving tenofovir AF [20]. Those occurring in patients with HBeAg-negative HBV were HCC (one tenofovir AF recipient and three tenofovir DF recipients), ureteric calculus (two tenofovir AF recipients) and cellulitis (two tenofovir DF recipients) [19]. No treatment-related deaths occurred in either trial [19, 20].

There was no significant BGD in the incidence of treatment-emergent grade 3 or 4 laboratory abnormalities at 48 weeks [32% of tenofovir AF vs. 33% of tenofovir DF recipients ($n = 577$ and 288) [20]; 29 vs. 21% ($n = 282$ and 140) [19]]. Grade 3 or 4 laboratory abnormalities occurring in ≥5% of patients in either group in either trial were ALT >5 × ULN (11 and 13% [20]; 3 and 3% [19]), aspartate aminotransferase >5 × ULN (3 and 7% [20]; 3 and 3% [19]), amylase >2 × ULN (2 and 2% [20]; 5 and 2% [19]), occult blood (8 and 8% [20]; 6 and 5% [19]), urine erythrocytes (8 and 10% [20]; 7 and 7% [19]) and urine glucose (5 and 1% [20]; 5 and 1% [19]).

5.1 Bone Safety

No treatment-related fracture events occurred in the tenofovir AF or tenofovir DF groups after 48 weeks of treatment in phase 3 trials [19, 20].

After 48 weeks' treatment, tenofovir AF recipients had significantly less decline in BMD than tenofovir DF recipients in phase 3 trials [19, 20], albeit reductions in BMD were relatively small in both groups [19, 20]. In patients with HBeAg-positive HBV infection, mean percentage reductions from baseline in BMD at the hip (adjusted BGD 1.62%; 95% CI 1.27–1.96) and lumbar spine (adjusted BGD 1.88%; 95% CI 1.44–2.31) were significantly ($p < 0.0001$) smaller with tenofovir AF [20]. Similarly, in patients with HBeAg-negative disease, mean percentage declines in BMD at the hip (adjusted BGD 1.87%; 95% CI 1.42–2.32; $p < 0.0001$) and lumbar spine (adjusted BGD 1.64%; 95% CI 1.01–2.27; $p < 0.0001$) favoured tenofovir AF over tenofovir DF recipients [19].

These benefits were maintained during up to 96 weeks' treatment [21, 22, 35, 36], including in individual trials [21, 22]. For example, in a pooled 96-week analysis, tenofovir AF treatment was associated with significantly ($p < 0.0001$) smaller mean percentage changes in BMD at the hip (−0.33 vs. −2.52%) and spine (−0.75 vs. −2.59%) than tenofovir DF (abstract plus poster) [36].

Significantly ($p \leq 0.0004$) fewer tenofovir AF than tenofovir DF recipients experienced a >3% reduction in hip (7.6 vs. 23.6% [20]; 10 vs. 33% [19]) or lumbar spine (18.2 vs. 37.5% [20]; 22 vs. 39% [19]) BMD at 48 weeks. In a 48-week pooled analysis of both trials, the percentage of tenofovir AF recipients with a >3% decline in BMD at the hip (7.6–10.2%) or lumbar spine (17.2–26.5%) was relatively constant irrespective of stratification according to the presence of osteoporosis risk factors at baseline (i.e. presence of ≤1, 2, 3 or 4 risk factors) [35]. By contrast, the proportion of tenofovir DF recipients with a >3% BMD decline at the hip (20.5% in those with ≤1 risk factor to 57.6% with 4 risk factors) and lumbar spine (29.9 to 63.6%) at 48 weeks increased in patients at higher-risk of osteoporosis at baseline. Indeed, treatment with tenofovir AF was the only baseline predictor associated with having a <3% decline in hip or lumbar spine BMD at 48 weeks in multivariate analyses [35].

The beneficial effects of tenofovir AF on bone safety parameters were maintained after 96 weeks treatment in a pooled analysis [36] and individual trials [21, 22], and at week 120 (i.e. during the 96-week double-blind phase and first 24 weeks of the open-label phase) [34] (all abstracts).

For example, in the pooled 96-week analysis, significantly ($p < 0.0001$) fewer tenofovir AF than tenofovir DF recipients experienced a >3% reduction in spine (25 vs. 45% of patients) or hip (14 vs. 39%) BMD over 96 weeks [36]. Of note, in evaluable patients who switched from tenofovir DF to open-label tenofovir AF at the end of the 96-week double-blind phase, there were significant improvements in mean BMD at the hip (mean change +0.71%; $p = 0.0004$; $n = 58$) and spine (mean change +1.41%; $p < 0.0001$; $n = 60$) from week 96 to 120 [34]. Patients treated with tenofovir AF during the double-blind and open-label periods had stable BMD values from baseline to week 120 [34].

Further support for a reduced impact of tenofovir AF over tenofovir DF on bone safety is provided by changes at 48 weeks in surrogate biomarkers of bone metabolism, including biomarkers of bone resorption [C-type collagen sequence (CTX)], formation [procollagen type 1 *N*-terminal propeptide (P1NP), bone-specific alkaline phosphatase (bsAP), osteocalcin] and metabolism [parathyroid hormone (PTH)] [19, 20]. For example, in patients with HBeAg-positive disease, mean percentage changes from baseline at 48 weeks improved and/or were significantly ($p < 0.001$) smaller in tenofovir AF recipients for serum CTX (+4.2 vs. +39.0% in tenofovir DF recipients), serum P1NP (−6.0 vs. +19.3%), bsAP (−9.2 vs. +8.7%) and osteocalcin (+4.8 vs. +28.5%), with numerically smaller increases from baseline in mean serum PTH levels (by 6.7 vs. 8.5 pg/mL) [20]. Reductions in bone biomarkers of resorption and formation strongly correlated with decreases in BMD, with the strongest correlation observed for P1NP and osteocalcin (both $p < 0.001$) [37]. After 96 weeks' treatment, there were minimal changes in markers of bone turnover in the tenofovir AF group, with tenofovir AF treatment having significantly ($p < 0.001$) less impact on CTX and P1NP markers than tenofovir DF (similar changes were also observed for the other bone formation markers; no data reported) [36].

5.2 Renal Safety

In the pivotal phase 3 trials [19, 20], renal-related serious adverse events were rare in both treatment groups after 48 weeks' treatment, with no patients experiencing proximal renal tubulopathy, including Fanconi syndrome. A potential risk of nephrotoxicity resulting from chronic exposure to low levels of tenofovir due to dosing with tenofovir AF cannot be excluded [15].

After 48 weeks' treatment, tenofovir AF was typically associated with smaller changes in renal safety parameters than tenofovir DF, suggesting that tenofovir AF has less impact on renal function [19, 20]. Median changes in estimated glomerular filtration rates (eGFR) at 48 weeks were significantly smaller in the tenofovir AF than tenofovir DF group in patients with HBeAg-positive (−0.6 vs. −5.4 mL/min; $p < 0.0001$) [20] and HBeAg-negative (−1.8 vs. −4.8 mL/min; $p = 0.004$) [19] HBV infections. At baseline, mean eGFR values in the tenofovir AF and DF groups were 113.7 and 112.5 mL/min in HBeAg-positive patients [20], with corresponding baseline eGFR values of 104.7 and 100.3 mL/min in HBeAg-negative patients [19]. Tenofovir AF was also associated with a significantly smaller mean increase in serum creatinine level in patients with HBeAg-positive HBV infection (0.01 vs. 0.03 mg/dL; $p = 0.02$) [20], although there was no significant BGD for mean increases in patients with HBeAg-negative disease (0.01 vs. 0.02 mg/dL) [19]. In pooled analyses, significantly ($p = 0.002$) fewer tenofovir AF than tenofovir DF recipients had a >25% reduction in eGFR (8.7 vs. 14.5%) or a ≥1 stage (Chronic Kidney Disease stages) worsening in renal function (6.7 vs. 10.6%) at 48 weeks (abstract plus poster) [38]. In multivariate analyses, factors associated with a ≥25% decline in eGFR were tenofovir DF treatment, a higher baseline eGFR and a baseline FibroTest score of >0.75 [38].

The beneficial effects of tenofovir AF over tenofovir DF in terms of renal safety parameters were maintained after 96 weeks' treatment in patients with HBeAg-positive [22] and HBeAg-negative disease [21]. In HBeAg-positive patients, the mean change in serum creatinine level from baseline to 96 weeks was significantly smaller in the tenofovir AF than in the tenofovir DF group (0.002 vs. 0.023 mg/dL; $p < 0.001$) [22]. The median change in eGFR was also smaller in the tenofovir AF than in the tenofovir DF group at 96 weeks (−1.8 vs. −5.0 mL/min; $p < 0.001$), with fewer tenofovir AF recipients experiencing a >25% decline in eGFR (10 vs. 18%; $p = 0.002$) or having a confirmed eGFR of <50 mL/min (0 vs. 2%; $p = 0.004$) [22]. In patients with HBeAg-negative disease, there were no significant BGDs at 96 weeks for mean changes in serum creatinine levels or the percentage of patients with a confirmed eGFR of <50 mL/min; however, median changes in eGFR (−0.6 vs. −3.6 mL/min; $p = 0.011$) and the percentage of patients with a ≥25% decline in eGFR (11 vs. 18%; $p = 0.046$) favoured tenofovir AF over tenofovir DF [21].

In a pooled analysis of patients who switched from tenofovir DF to tenofovir AF at the end of the double-blind phase of each trial (i.e. week 96), there was a significant improvement at week 120 in CL_{CR} in the overall group ($p = 0.02$) and in those with a CL_{CR} of <90 mL/min at week 96 (mean CL_{CR} 76 mL/min at week 96 vs. 81 mL/min at week 120; $p < 0.0001$) [34].

For markers of proximal tubular dysfunction, tenofovir AF recipients had significantly ($p < 0.001$ vs. tenofovir DF) smaller median percentage changes in the urine retinol-binding protein to creatinine (RBP: CR) ratio and urine

β_2-microglobulin to creatinine (β2M: CR) ratio at week 48 (considered to be more sensitive markers for tubular dysfunction), with no significant BGDs in the urine protein to creatinine ratio (UPCR) or urine albumin to creatinine ratio (UACR) [19, 20]. At 72 weeks, tenofovir AF was associated with smaller reductions in estimated CL_{CR} and smaller increases in UPCR and UACR than tenofovir DF in both studies (no data reported) [15]. After 96 weeks' treatment in HBeAg-positive patients, tenofovir AF was associated with significantly ($p < 0.001$) less change from baseline in the RBP: CR (median change 22.2 vs. 55.6%) and β2M: CR (median change 9.5 vs. 55.7%) ratio than tenofovir DF, with no statistically significant differences for median changes in UPCR (median change 7.2 vs. 13.8%) and UACR (median change 28.4 vs. 33.3%) [22]. Similar results were observed at 96 weeks in HBeAg-negative patients, with median changes in RBP: CR (median change 18.5 vs. 53.2%) and β2M: CR (median change 10.8 vs. 59.2%) ratios significantly favouring tenofovir AF over tenofovir DF treatment [21].

6 Dosage and Administration

In the EU, oral tenofovir AF is indicated for the treatment of chronic HBV infection in adults and adolescents (aged ≥12 years and with a bodyweight of ≥35 kg) [15]. The recommended dosage is 25 mg once daily. In HBeAg-positive patients without cirrhosis, treatment should continue for at least 6–12 months after HBe seroconversion (HBeAg loss and HBV DNA loss with anti-HBe detection) is confirmed or until HBs seroconversion or until there is a loss of efficacy. Regular reassessment is recommended after treatment discontinuation to detect virological relapse. In HBeAg-negative patients without cirrhosis, treatment should be given until at least HBs seroconversion or until there is evidence of a loss of efficacy. With prolonged treatment of >2 years, regular reassessment is recommended to confirm that continuing the selected therapy remains appropriate for the patient [15].

Discontinuation of anti-hepatitis B therapy, including tenofovir AF, may result in acute exacerbations of hepatitis B [15]. Most cases are self-limiting, but severe exacerbations, including fatal outcomes, may occur. Hepatic function should be monitored closely with both clinical and laboratory follow-up for ≥6 months in patients who discontinue anti-hepatitis B therapy. If appropriate, resumption of anti-hepatitis B therapy may be warranted [15].

No dosage adjustment is required in patients with an estimated CL_{CR} of ≥15 mL/min or patients with a CL_{CR} of <15 mL/min who are receiving dialysis [15]. Tenofovir AF is not recommended in patients with an estimated CL_{CR} of <15 mL/min who are not receiving haemodialysis. There are no efficacy or safety data in HBV-infected patients with decompensated liver disease and who have a Child Pugh score >9. These patients may be at higher risk of experiencing serious hepatic or renal adverse reactions. Hence, hepatobiliary and renal parameters should be closely monitored in this patient population [15].

Local prescribing information for tenofovir AF should be consulted for detailed information, including its use in special populations, contraindications and drug interactions.

7 Place of Tenofovir Alafenamide in the Management of Chronic Hepatitis B

During the last three decades, the introduction of potent antiviral agents, such as conventional and pegylated interferon (IFN)-α and nucleos(t)ide analogues (e.g. adefovir, entecavir, lamivudine, telbivudine and tenofovir DF), for the management of chronic hepatitis B have significantly improved patient outcomes [2, 39–41]. These agents provide sustained HBV suppression and reduce the progression of liver disease and development of HCC, thereby potentially preventing premature death and/or the need for liver transplantation [3, 4, 39–41]. However, a clinical cure (i.e. clearance of HBsAg) for chronic HBV infection remains elusive, as the persistence of covalently closed circular DNA in the nucleus of infected hepatocytes means that complete eradication of HBV infection is not usually possible [3, 4, 39–41].

Current EASL [3] guidelines recommend the use of entecavir, tenofovir AF and tenofovir DF as first-line, long-term treatment in adult patients with HBeAg-positive or negative chronic HBV infection, with pegylated-IFN or a nucleos(t)ide analogue recommended for treatment of finite duration. UK NICE [6] guidelines recommend pegylated IFN-α2a as first-line therapy and entecavir and tenofovir DF as second-line options in adults, children and adolescents with HBeAg-positive or -negative chronic HBV infection. The most recent 2017 EASL guidelines recommend a conservative approach to treatment in children, with no specific recommendations for one agent over another (recommended treatments are entecavir, tenofovir AF, tenofovir DF and pegylated-IFNα) [3]. The approval of tenofovir AF is too recent for it to have been considered in current NICE guidelines [6].

The choice of therapy for an individual patient is dependent on several factors, including the individual properties of the drug (e.g. its efficacy, safety, resistance rates and route of administration) and patient characteristics (e.g. patient's age, severity of liver disease) [3, 4]. A key consideration in the choice of treatment is the potential for emergence of drug resistance during long-term therapy with nucleos(t)ide analogues. Tenofovir DF and entecavir

(first-line options [3, 6]) have a high genetic barrier to resistance, with no resistance to tenofovir DF detected after 8 years' treatment [42] and drug resistance to entecavir occurring in 1% of patients during long-term treatment (>5 years [4]), albeit the frequency of the emergence of resistance to entecavir increases in patients harbouring lamivudine-resistant isolates [3, 4]. As with tenofovir DF, no isolates resistant to tenofovir AF were detected during 96 weeks of treatment in the pivotal phase 3 trials (Sect. 2). Conversely, long-term use of lamivudine, adefovir or telbivudine is associated with high rates of drug resistance, with lamivudine and adefovir having a low genetic barrier to resistance and telbivudine a moderate barrier to resistance [3, 4]. Compared with nucleos(t)ide analogues, the advantages of IFN-α therapy are a finite duration of therapy, an absence of resistance and higher rates of HBe and HBs seroconversion. However, these immunomodulatory agents only have moderate antiviral efficacy (about one-third of patients respond [43]), are costly, associated with frequent adverse events and require subcutaneous administration. Conversely, the nucleos(t)ide analogues have the convenience of oral administration and are more potent antivirals and better tolerated than IFN-α therapy [3, 4].

In two identically designed, ongoing (planned duration of 8 years), multinational, phase 3 trials, tenofovir AF provided effective and sustained viral suppression in treatment-naive and -experienced patients with HBeAg-positive or -negative chronic HBV infection (Sect. 4). At 48 weeks (primary analysis), the antiviral efficacy of tenofovir AF was noninferior to that of tenofovir DF in both HBeAg-positive (Sect. 4.1) and -negative (Sect. 4.2) patients, with viral suppression maintained at 96 weeks. There were generally no significant differences between the tenofovir AF and tenofovir DF groups in terms of secondary/other efficacy outcomes at 48 weeks, including rates of HBeAg and HBsAg loss and ALT normalization rates (by central laboratory criteria). However, according to more stringent AASLD criteria, ALT normalization rates were significantly higher in tenofovir AF than tenofovir DF groups at 48 weeks. In pooled post hoc analyses of these trials, relative to tenofovir DF, tenofovir AF was associated with higher early antiviral plus biochemical response rates at 12 weeks, higher ALT normalization rates at virtually all assessed timepoints up to 96 weeks and greater mean reductions (improvements) from baseline in FibroTest scores at 48 weeks (albeit changes in FibroTest score in both treatment groups were small) (Sect. 4.3). The beneficial effects of tenofovir AF on viral suppression and ALT normalization rates were maintained at 96 weeks, with higher ALT normalization at 96 weeks by central laboratory and AASLD criteria in patients with HBeAg-positive (Sect. 4.1) or HBeAg-negative (Sect. 4.2) chronic hepatitis B. In a pooled analysis of patients who switched from tenofovir DF to tenofovir AF at the end of the 96-week double-blind period of each trial, viral suppression was maintained at week 120, with a significant increase in the proportion of patients achieving ALT normalization by central laboratory and AASLD criteria (Sect. 4.3).

Tenofovir AF was generally well tolerated in these ongoing trials, including during longer-term treatment (≤96 weeks treatment), with most TEAEs of mild to moderate severity and very few patients discontinuing treatment because of an adverse event (Sect. 5). In general, there was no difference in the nature and incidence of TEAEs or discontinuation rates because of TEAEs between the tenofovir AF and tenofovir DF groups at 48 weeks. Based on a pooled 72-week analysis, the most frequently (incidence ≤11%) reported adverse reactions occurring during tenofovir AF treatment were headache, nausea and fatigue.

Concerns have been raised about potential renal and bone safety issues with long-term use of tenofovir DF. In phase 3 trials in patients with chronic HBV infection (48 week analyses), no patients experienced a treatment-related fracture (Sect. 5.1) and renal-related serious adverse events were rare with both tenofovir AF and tenofovir DF treatment (Sect. 5.2), with no patients experiencing proximal renal tubulopathy (including Fanconi syndrome). After up to 96 weeks treatment, the bone and renal safety profile of tenofovir AF was better than that of tenofovir DF based on markers of bone (Sect. 5.1) and renal safety (Sect. 5.2). Furthermore, in a pooled analysis of patients who switched from tenofovir DF to tenofovir AF at the end of the double-blind phase, there was a significant improvement at week 120 in CL_{CR} in the overall group and in those with a CL_{CR} of <90 mL/min at week 96 (Sect. 5.2). The favourable pharmacological profile of tenofovir AF compared with tenofovir DF (Sects. 2, 3) also suggests a potential for an improved clinical safety profile with tenofovir AF. Long-term data from the two pivotal ongoing phase 3 trials and post-marketing surveillance in the real-world setting will more definitely establish the relative renal and bone safety of the two tenofovir prodrug formulations.

Data relating to the use of tenofovir AF in pregnant women (<300 pregnancy outcomes) and in patients with renal impairment are currently limited [15]; further data from ongoing clinical experience should help to define the role of tenofovir AF therapy in these patient populations. Although data from pregnant women treated with tenofovir AF are limited, extensive data from pregnant women treated with tenofovir DF (>1000 exposure outcomes) indicates no malformative or fetal/neonatal toxicity was associated with the use of tenofovir DF [15]. Further evidence comes from a randomized, open-label, multicentre trial evaluating the efficacy (in preventing mother-to-child transmission of HBV infection) and safety of tenofovir DF (vs. usual care with antiviral therapy) in mothers who have

a HBV DNA level of >20,000 IU/mL [44]. In this trial, the risk of viral transmission to infants was significantly reduced (5 vs. 18% of infants in the control group; $p = 0.007$; $n = 97$ and 100) and safety profiles were similar in the tenofovir DF and control group, including the rate of birth defects (2 vs.1%; $n = 95$ and 88) [44]. The use of tenofovir AF may be considered during pregnancy [15].

In conclusion, tenofovir AF provided effective and sustained viral suppression, and was generally well tolerated in two identically designed, multinational trials in treatment-naive and -experienced patients with HBeAg-positive or -negative chronic HBV infection. In the primary 48-week analysis, tenofovir AF was noninferior to tenofovir DF in terms of the proportion of patients achieving viral suppression and was associated with significantly higher ALT normalization rates than tenofovir DF based on AASLD criteria (but not central laboratory criteria). In pooled analyses and/or individual trials, ALT normalization rates by AASLD and central laboratory criteria were significantly higher in tenofovir AF than tenofovir DF recipients at most assessed timepoints up to 96 weeks. Given the bone and renal safety concerns associated with long-term tenofovir DF treatment, the more favourable pharmacological profile of tenofovir AF permits a marked reduction in the dosage of this tenofovir prodrug and thereby reduces systemic exposure to tenofovir diphosphate, potentially improving the bone and renal safety of tenofovir AF versus tenofovir DF. Long-term clinical experience will more definitively establish the relative bone and renal safety of these two tenofovir prodrugs. With its potential for an improved safety profile, tenofovir AF is an important emerging first-line option for the treatment of chronic HBV infection in adults and adolescents (aged ≥12 years and with a bodyweight of ≥35 kg).

Data Selection Tenofovir alafenamide: 115 records	
Duplicates removed	24
Excluded at initial screening (e.g. press releases; news reports; not relevant drug/indication)	28
Excluded during initial selection (e.g. preclinical study; reviews; case reports; not randomized trials)	2
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	16
Cited efficacy/tolerability articles	17
Cited articles not efficacy/tolerability	27
Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were Tenofovir alafenamide, Vemlidy, GS-734, chronic hepatitis B, chronic HBV, CHB Records were limited to those in English language. Searches last updated 27 April 2017	

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Compliance with Ethical Standards

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Conflicts of interest Henry L. Y. Chan is an advisor and speaker for AbbVie, Bristol Meyers Squibb, Gilead and Roche, and a speaker for Echosens and Novartis. Lesley J. Scott is a salaried employee of Adis/Springer and declares no relevant conflicts of interest.

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