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CADTH COMMON DRUG REVIEW

Clinical Review Report

TENOFOVIR ALAFENAMIDE (VEMLIDY)

(Gilead Sciences Canada, Inc.)

Indication: Treatment of chronic hepatitis B in adults with compensated liver disease

Service Line:	CADTH Common Drug Review
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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

AASLD	American Association for the Study of the Liver Disease
ALT	alanine aminotransferase
AE	adverse event
BMD	bone mineral density
CHB	chronic hepatitis B
CDEC	CADTH Canadian Drug Expert Committee
CDE	CADTH Common Drug Review
CHB	chronic hepatitis B
CI	confidence interval
CLF	Canadian Liver Foundation
CSR	clinical study report
DB	double-blind
DXA	dual-energy X-ray absorptiometry
EASL	European Association for the Study of the Liver
FAS	full analysis set
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCB	hepatitis C virus
HepCBC	Hepatitis C Education and Prevention Society
ITT	intention-to-treat
LDL-C	low-density lipoprotein cholesterol
LOCF	last observation carried forward
PP	per-protocol
RCT	randomized controlled trial
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
ULN	upper limit of normal

Drug	Tenofovir alafenamide (Vemlidy)
Indication	Treatment of chronic hepatitis B in adults with compensated liver disease
Reimbursement request	As per indication
Dosage form(s)	25 mg tablet
NOC date	May 17, 2017
Manufacturer	Gilead Sciences Canada, Inc.

Executive Summary

Introduction

Hepatitis B virus (HBV) belongs to the Hepadnaviridae family of small, enveloped, primarily hepatotropic DNA viruses. HBV has nine genotypes, A to J, with different prevalence in geographic regions, i.e., genotype A is seen mainly in northwest Europe, North America, India, and Africa.[1,2] In low-endemic regions, transmission is primarily through high-risk sexual behaviour and intravenous drug use, and, therefore, the infection is found predominantly in adolescents and adults.[1] Globally, approximately 2 billion people have serological evidence of HBV, and 250 million are chronically infected.[2] Approximately one-third of all cases of liver cirrhosis and half of all cases of hepatocellular carcinoma are attributable to chronic hepatitis B (CHB).[3] There do not appear to be any reliable estimates of prevalence and incidence of CHB in Canada; however, the estimated prevalence of CHB and chronic hepatitis C combined is approximately 600,000.[4-6]

The Canadian Association for the Study of the Liver consensus guidelines recommend antiretroviral treatment for CHB patients with the following clinical characteristics: hepatitis B e antigen (HBeAg)-positive patients with high levels of HBV DNA (> 20,000 IU/mL) with alanine aminotransferase (ALT) greater than the upper limit of normal (ULN) for three to six months; HBeAg-negative patients with lower levels of HBV DNA (> 2,000 IU/mL) and ALT greater than the ULN for three to six months; or patients with either HBeAg-positive or HBeAg-negative status who have significant liver inflammation and fibrosis.[7] These recommendations are in agreement with those of other major organizations, such as the European Association for the Study of the Liver,[8] and the American Association for the Study of the Liver Disease.[9] The preferred first-line antiretroviral treatments for CHB patients in Canada have been tenofovir disoproxil fumarate (TDF), entecavir, and pegylated interferon, according to the clinical expert consulted by CDR for this review.

Tenofovir alafenamide (TAF) is a prodrug of tenofovir. The antiviral properties of tenofovir are due to its inhibition of HBV polymerase, which, in turn, inhibits DNA synthesis and viral replication. TAF is indicated for the treatment of chronic hepatitis B in adults with compensated liver disease. The Health Canada–recommended dose of TAF is one 25 mg tablet once daily, taken with or without food.

The objective of this report was to perform a systematic review of the beneficial and harmful effects of tenofovir alafenamide for the treatment of adults with CHB and compensated liver disease.

Results and Interpretation

Included Studies

Two manufacturer-sponsored multinational double-blind (DB) randomized controlled trials (RCTs), Study 108 (N = 426) and Study 110 (N = 875) were included in this systematic review. Both studies randomized patients with CHB in a 2:1 ratio to either TAF or TDF. The designs of both studies were similar, with the exception that Study 108 included patients who were HBeAg-negative and Study 110 included patients who were HBeAg-positive. Both studies were initially planned for a DB treatment phase of 48 weeks; however, this was extended, first, to 96 weeks and then to 144 weeks, under two protocol amendments. These protocol amendments were in response to a request from the FDA for longer-term efficacy and safety data. The clinical study report available to CDR at the time of this report had complete follow-up to 96 weeks. The primary outcome of both studies was the proportion of patients who achieved undetectable HBV DNA (< 29 IU/mL) by week 48, testing the noninferiority of TAF to TDF, with the margin for noninferiority set at –10% for the lower boundary of the 95% confidence interval (CI) of the difference between TAF and TDF. Secondary outcomes included those related to bone mineral density (hip and spine) and assessment of renal function (serum creatinine and proteinuria), as well as HBeAg seroconversion (Study 110 only).

Key critical appraisal issues included the fact that neither study was designed to assess clinical outcomes such as mortality and CHB-related morbidity. The assessment of bone health relied on a surrogate measure, bone mineral density, instead of clinical outcomes such as fractures. Many important efficacy outcomes, such as fibrosis and ALT, as well as all of the 96-week data, were not adjusted for multiplicity and, thus, are at risk of type I error.

Efficacy

The included studies were not powered to assess mortality or morbidity related to HBV, and there were no deaths across the studies and very few morbidity-related events. The proportion of patients achieving the primary outcome was similar between TAF and TDF groups in Study 108, at both week 48 (94.0% versus 92.9%, respectively) and week 96 (90.2% versus 90.7%). The proportion of patients achieving an HBV DNA level of < 29 IU/mL was lower in Study 110 but was again similar between TAF and TDF groups at both 48 weeks (63.9% versus 66.8%) and 96 weeks (72.8% versus 74.7%). There was no statistically significant difference between TAF and TDF groups after 48 weeks in either Study 108 (difference in proportions between groups of 1.8%; 95% CI, −3.6% to 7.2%) or Study 110 (–3.6%; 95% CI, -9.8% to 2.6%]). Criteria for noninferiority were met in both studies, as the lower boundary of the 95% CI of the difference in proportions between groups was greater than –10%. The primary analysis was performed on the full analysis set population and was supported by an analysis in the per-protocol population. The mean change from baseline in HBV DNA was similar between TAF and TDF groups at both 48 weeks and 96 weeks in both studies. Subgroup analyses were presented for treatment-experienced or treatment-naive patients or for various measures of disease severity (baseline viral load, ALT, FibroTest score). There were no statistically significant differences between TAF and TDF in any of these subgroups for the primary outcome after 96 weeks of follow-up.

A higher proportion of patients treated with TAF achieved normalized ALT at 96 weeks (80.9% versus 71.1%) in Study 108, and this difference was statistically significant

(difference between groups 9.8%; 95% CI, 0.2% to 19.3%). In Study 110, a high proportion of patients treated with TAF versus TDF achieved ALT normalization (75.4% versus 67.5% of patients), and this difference was statistically significant (8.0%; 95% CI, 1.2% to 14.7%). No adjustments were made for multiple statistical testing for these outcomes, and, thus, they are at elevated risk of type I error. Mean change from baseline in ALT values did not differ between treatment groups at week 48 and at week 96 in both studies.

There were very few patients who experienced hepatitis B surface antigen (HBsAg) loss or seroconversion in either study, and there were no statistically significant differences between groups. In Study 110, there were more patients in the TAF group than in the TDF group who experienced HBeAg loss (difference in proportions between groups 3.7%; 95% CI, –1.9% to 9.4%, *P* = 0.20) and seroconversion (5.1%; 95% CI 0.2% to 10.1%, *P* = 0.050) at 96 weeks. No patients would be expected to achieve HBeAg loss/seroconversion in Study 108, as these patients were already HBeAg-negative.

Fibrosis was assessed using FibroTest. In all groups, FibroTest scores decreased (improved) from baseline, with a greater reduction in scores in the TAF group than in the TDF group in both studies, [redacted], and no adjustments were made for multiple comparisons. There is no established minimal clinically important difference for FibroTest; therefore, the clinical significance of this difference in unknown.

Harms

There were [redacted]. Other common adverse events in both groups included nasopharyngitis and upper respiratory tract infection.

[redacted]

[redacted]

Notable harms included those related to bone health and renal events. There were no notable or consistent differences between TAF and TDF for patients experiencing fractures, “bone events,” osteopenia, osteoporosis, or decreased bone mineral density. Bone mineral density was assessed in terms of its change from baseline and compared between TAF and TDF groups as part of the formal hierarchy in the statistical analysis plan. There were smaller per cent reductions in bone mineral density after 48 weeks in the TAF group than in the TDF group, both in spine and hip, in both Study 108 ([redacted]. Similar differences between groups were reported for hip and spine at the 96-week time point as well.

There were no statistical differences between groups in the number of patients experiencing renal events, including proteinuria. Renal injury was also assessed using

change from baseline in serum creatinine. In Study 110, there was a smaller increase in serum creatinine in the TAF than in the TDF groups after 48 weeks ([redacted]), and these differences persisted at 96 weeks. There was no difference in the increase in serum creatinine between TAF and TDF groups in Study 108.

Additional notable harms included events involving increased cholesterol, and the proportion of patients with grade 3 events of elevated fasting low-density lipoprotein cholesterol (LDL-C). There was a numerically higher proportion of TAF patients with this event compared with TDF patients in [redacted]. Patients in the TAF group had an increase from baseline in median fasting LDL-C, while patients in the TDF group had a decrease from baseline ([redacted]).

Potential Place in Therapy[1]

Given the bone and renal safety concerns associated with long-term therapy with TDF, the more favourable pharmacological profile of TAF permits a marked (one-tenth) reduction in dosage, reducing systemic exposure (compared with TDF) and potentially improving bone and renal safety. However, TAF has been shown to increase urine glucose levels (in 5% of patients receiving TAF versus 1% of those receiving TDF), although the majority of these patients with elevated urine glucose had pre-existing glycosuria at baseline or had risk factors that might contribute to urine glucose elevations. TAF has also been shown to lead to LDL-C levels greater than 300 mg/dL (in 4% of patients receiving TAF versus none of patients receiving TDF), which have not been seen with TDF. Given that HBV patients are on these medications lifelong, the LDL-C increase can be a concern with long-term use of TAF. As well, the long-term clinical significance of renal and bone mineral density changes between TAF and TDF is not known.

With evidence from two DB RCTs showing that TAF is safe, tolerable, and noninferior to TDF, according to the clinical expert consulted for this review, its use as a first-line therapy is appropriate. Longer-term follow-up will be required to determine whether the differences in bone and renal changes seen with TAF will be clinically relevant and whether this benefit is outweighed by the increase in LDL-C levels. TAF is likely appropriate for patients with developing and/or established renal and bone disease, to hasten progress in HBV treatment that may be seen with TDF therapy.

1 This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Conclusions

Two manufacturer-sponsored multi-centre DB RCTs were included in the systematic review. Both studies are ongoing, with follow-up data available to 96 weeks. Study 108 included patients who were HBeAg-negative, and Study 110 included patients who were HBeAg-positive. The primary outcome of both studies was the proportion of patients who achieved undetectable HBV DNA at 48 weeks. In this regard, TAF was noninferior to TDF in both studies at the 48-week time point, and this was also observed at 96 weeks. There were no statistically significant differences between TAF and TDF groups for other efficacy outcomes, including change from baseline in HBV DNA and ALT, or in the proportion of patients who experienced HBsAg loss/seroconversion. Fibrosis scores, assessed by FibroTest, were improved with TAF therapy versus TDF; however, this difference was only statistically significant in Study 110 and not in Study 108, and no adjustment was made for multiple statistical comparisons. There were no deaths in either study, and clinical outcomes such as morbidity, health-related quality of life, and symptoms, were not assessed. There were no notable differences in the proportion of patients experiencing an adverse event or a serious adverse event or withdrawing due to an adverse event. Notable harms such as bone-related adverse events (e.g., fractures) and renal events were infrequent, with no notable differences between groups. Bone health was also formally assessed as a secondary outcome using bone mineral density, and there was a statistically significant improvement in scores (hip and spine) for TAF compared with TDF in both studies. Renal function, formally assessed by serum creatinine, declined less for patients receiving TAF than for those receiving TDF; however, these differences were statistically significant only in one of the two studies.

Table 1: Summary of Results

	Study 108		Study 110	
	TAF 25 mg (N = 285)	**TDF 300 mg (N = 140)**	**TAF 25 mg (N = 581)**	**TDF 300 mg (N = 292)**
Virology				
HBV DNA of < 29 IU/mL at week 48, n (%) Primary analysis	268 (94.0)	130 (92.9)	371 (63.9)	195 (66.8)
Difference in proportions (95% CI)	1.8% (−3.6% to 7.2%) Noninferiority met[a,b]		–3.6% (–9.8% to 2.6%) Noninferiority met[a,b]	
HBV DNA < 29 IU/mL, week 96, n (%)	257 (90.2)	127 (90.7)	423 (72.8)	218 (74.7)
Difference in proportions (95% CI)[b]	−0.6% (−7.0% to 5.8%) *P* = 0.84		–2.2% (–8.3% to 3.9%) *P* = 0.47	
Mortality				
Deaths, n	0	0	0	0
Morbidity				
Patients with HCC (reported as AE), n (%)	[redacted]	[redacted]	[redacted]	[redacted]
HRQoL	NR	NR	NR	NR
CHB-related symptoms	NR	NR	NR	NR
Harms				
Patients with > 0 AEs, week 96 N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with > 0 SAEs, week 96 N (%)	[redacted]	[redacted]	[redacted]	[redacted]

	Study 108		Study 110	
	TAF 25 mg (N = 285)	**TDF 300 mg (N = 140)**	**TAF 25 mg (N = 581)**	**TDF 300 mg (N = 292)**
WDAEs, week 96 N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Notable Harms				
Hip BMD mean (SD) baseline, g/cm^2	0.953 (0.1555)	0.938 (0.1438)	0.957 (0.1448)	0.960 (0.1402)
% change at week 48	[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM (95% CI) [c]	[redacted]		[redacted]	
Spine BMD **m**ean (SD) baseline, g/cm^2	1.050 (0.190)	1.033 (0.184)	1.059 (0.1631)	1.061 (0.1636)
% change at week 48	[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM (95% CI)[c]	[redacted]		[redacted]	
Serum creatinine, mean (SD) baseline, µmol/L[d]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline, 48 weeks	[redacted] *P* = 0.32[e]	[redacted]	[redacted] *P* = 0.020 [e]	[redacted]
Proteinuria grade 1, week 48, n (%)	51 (18.1)	23 (16.4)	138 (23.9)	51 (17.8)
Proteinuria grade 2, week 48, n (%)	3 (1.1)	3 (2.1)	20 (3.5)	13 (4.5)
Proteinuria grade 3, week 48, n (%)	0	0	0	1 (0.3)
Between-group comparison, *P* value (all grades)[f]	[redacted]		*P* = 0.21	

AE = adverse event; BMD = bone mineral density; CHB = chronic hepatitis B; CI = confidence interval; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HRQoL = health-related quality of life; LSM = least squares mean; NR = not reported; SAE = serious adverse event; SD = standard deviation; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; WDAE = withdrawal due to adverse event.

[a] Primary outcome: Because the lower bound of the two-sided 95% CI of the difference (TAF – TDF) in the response rate was greater than the pre-specified −10% margin, the TAF group met the primary end point of noninferiority to the TDF group.

[b] Difference in the proportion between treatment groups and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HBV DNA categories and oral antiviral treatment status strata.

[c] *P* values, difference in least squares means and its 95% CI were from the analysis of variance (ANOVA) model including treatment as a fixed effect.

[d] Converted from mg/dL by CADTH Common Drug Review (CDR).

[e] *P* value was from the analysis of covariance (ANCOVA) model on observed data with treatment as a fixed effect and baseline serum creatinine as a covariate.

[f] *P* value was from the rank ANCOVA effect model on observed data with treatment as a fixed effect and adjusting for baseline toxicity grade.

Source: Clinical Study Reports for Studies 108[10] and 110.[11]

Introduction

Disease Prevalence and Incidence

Hepatitis B virus (HBV) belongs to the Hepadnaviridae family of small, enveloped, primarily hepatotropic DNA viruses. HBV has nine genotypes, A to J, with different prevalence in geographic regions, i.e., genotype A is seen mainly in northwest Europe, North America, India, and Africa.[1,2] In low-endemic regions, transmission is primarily through high-risk sexual behaviour and intravenous drug use, and, therefore, the infection is found predominantly in adolescents and adults.[1] Globally, approximately 2 billion people have serological evidence of HBV, and 250 million are chronically infected.[2] Approximately one-third of all cases of liver cirrhosis and half of all cases of hepatocellular carcinoma are attributable to chronic hepatitis B (CHB).[3] There do not appear to be any reliable estimates of prevalence and incidence of CHB in Canada; however, the estimated combined prevalence of CHB and chronic hepatitis C is approximately 600,000.[4-6]

Standards of Therapy

The Canadian Association for the Study of the Liver consensus guidelines recommend antiretroviral treatment for CHB patients with the following clinical characteristics: hepatitis B e antigen (HBeAg)-positive patients with high levels of HBV DNA (> 20,000 IU/mL) with elevated alanine aminotransferase (ALT) greater than the upper limit of normal (ULN) for three to six months;

HBeAg-negative patients with lower levels of HBV DNA (> 2,000 IU/mL) and ALT greater than the ULN for three to six months; and patients with either HBeAg-positive or HBeAg-negative status who have significant liver inflammation and fibrosis.[7] These recommendations are in agreement with those of other major organizations such as the European Association for the Study of the Liver (EASL)[8] and the American Association for the Study of the Liver Disease (AASLD).[9] A summary of the natural history of disease, diagnosis, management, and prognosis of HBV can be found in Appendix 7. The preferred first-line antiretroviral treatments for CHB patients in Canada have been tenofovir disoproxil fumarate (TDF), entecavir, and pegylated interferon, according to the clinical expert consulted by CDR for this review.

Drug

Tenofovir alafenamide (TAF) is a prodrug of tenofovir. The antiviral properties of tenofovir are due to its inhibition of HBV polymerase, which, in turn, inhibits DNA synthesis and viral replication. TAF is indicated for the treatment of chronic hepatitis B in adults with compensated liver disease. The Health Canada–recommended dose for TAF is one 25 mg tablet once daily, taken with or without food.

Table 2: Key Characteristics of Tenofovir Alafenamide, Tenofovir Disoproxil Fumarate, Entecavir, Lamivudine, Telbivudine, Pegylated Interferon, and Adefovir Dipivoxil

	Tenofovir Alafenamide	Tenofovir Disoproxil Fumarate	Entecavir
Mechanism of Action	Inhibits HBV polymerase, causes chain termination, inhibiting HBV DNA synthesis	Inhibits HBV polymerase, causes chain termination, inhibiting HBV DNA synthesis	Inhibits HBV polymerase, inhibiting HBV DNA synthesis
Indication[a]	Treatment of CHB in adults with compensated liver disease	Treatment of CHB infection in patients 18 years of age and older, with: • compensated liver disease, with evidence of active viral replication, with elevated serum ALT levels or evidence of fibrosis (based on liver biopsy or a noninvasive procedure) • evidence of lamivudine-resistant HBV • decompensated liver disease. Also: HIV-1	Treatment of CHB virus infection in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease
Route of Administration	Oral	Oral	Oral
Recommended Dose	25 mg once daily	300 mg once daily	0.5 mg once daily
Serious Side Effects / Safety Issues	• Lactic acidosis and severe hepatomegaly with steatosis • Post-treatment exacerbation of hepatitis	• Lactic acidosis and severe hepatomegaly with steatosis • Post-treatment exacerbation of hepatitis • Nephrotoxicity • Reduced BMD	• Acute exacerbations of hepatitis B • Lactic acidosis and severe hepatomegaly with steatosis • Resistance to HIV nucleoside reverse transcriptase inhibitors if used to treat HBV infection in patients with HIV infection that is not being treated

	Lamivudine	Telbivudine	Pegylated Interferon Alfa-2a
Mechanism of Action	Inhibits HBV viral polymerase	Inhibits HBV viral polymerase	Immune modulator
Indication[a]	Treatment of patients with CHB and evidence of HBV replication Due to high rates of resistance that developed in treated patients, lamivudine treatment should be considered only when the use of an alternative antiviral agent with a higher genetic barrier to resistance is not available or appropriate.	Treatment of chronic CHB in adults of 16 years and older with compensated liver disease with evidence of viral replication and active liver inflammation Points to be considered when initiating therapy: For HBeAg-positive patients, treatment **should** be initiated **only** in patients with baseline HBV DNA < 9 $\log_{10}$ copies/mL and baseline ALT > 2 × ULN. For HBeAg-negative patients, treatment **should** be initiated **only** in patients with baseline HBV DNA < 7 $\log_{10}$ copies/mL. On-treatment response should guide continued therapy.	For the treatment of both HBeAg-positive and HBeAg-negative chronic hepatitis B in patients with compensated liver disease, liver inflammation, and evidence of viral replication (both cirrhotic and non-cirrhotic disease)
Route of Administration	Oral	Oral	Injection (subcutaneous)
Recommended Dose	100 mg once daily	600 mg once daily	180 mcg once weekly
Serious Side Effects / Safety Issues	• Lactic acidosis and severe hepatomegaly with steatosis • Post-treatment exacerbation of hepatitis • HIV resistance may emerge in CHB patients with unrecognized or untreated HIV infection	• Lactic acidosis and severe hepatomegaly with steatosis • Post-treatment exacerbation of hepatitis	• May cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders

	Adefovir Dipivoxil		
Mechanism of Action	Inhibits viral polymerases by direct binding competition with the natural substrate (deoxyadenosine triphosphate) and, after incorporation into viral DNA, results in DNA chain termination		
Indication[a]	Treatment of CHB in adults with compensated and decompensated liver disease with evidence of active viral replication and evidence of either histologically active disease or elevation in serum aminotransferases (ALT or AST)		
Route of Administration	Oral		
Recommended Dose	10 mg once daily		
Serious Side Effects / Safety Issues	• Lactic acidosis and severe hepatomegaly with steatosis • Post-treatment exacerbation of hepatitis • Nephrotoxicity • HIV resistance may emerge in CHB patients with unrecognized or untreated HIV		

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMD = bone mineral density; CHB = chronic hepatitis B; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; ULN = upper limit of normal.

[a] Health Canada indication.

Source: Product monographs from e-CPS.[12]

Objective and Methods

Objective

To perform a systematic review of the beneficial and harmful effects of tenofovir alafenamide for the treatment of adults with chronic hepatitis B and compensated liver disease.

Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Adults with chronic hepatitis B and compensated liver disease **Subgroups:** Severity of disease (less severe versus more severe) HBeAg-positive versus -negative Prior treatment for hepatitis B	
Intervention	Tenofovir alafenamide 25 mg orally once daily	
Comparators	Tenofovir disoproxil fumarate Entecavir Lamivudine	Adefovir Telbivudine Interferons (pegylated)
Outcomes	**Key efficacy outcomes:** Mortality[a] Hepatic-related morbidity (or other manifestations of decompensated cirrhosis, HCC)[a] Health-related quality of life (measured by a validated scale)[a] Symptoms (e.g., skin itch, fatigue, poor appetite)[a] **Other efficacy outcomes:** Disease regression (i.e., fibrosis)[a] Resistance[a] Change in HBV DNA levels[a] (including viral blipping and viral breakthrough) Change in ALT levels Serologic response (loss of HBsAg with seroconversion to anti-HBs, rate of HBeAg seroconversion) Change in serum HBsAg level **Harms outcomes:** • adverse events • serious adverse events • withdrawals due to adverse events Notable harms: lactic acidosis, hepatomegaly with steatosis, hypercholesterolemia, renal injury,[a] reduced bone mineral density[a]	
Study Design	Published and unpublished phase III RCTs	

ALT = alanine aminotransferase; HBe = hepatitis B e; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; RCT = randomized controlled trial.

[a] These were outcomes that were identified to be of importance to patients in their input to CDR.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records & daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Vemlidy (tenofovir alafenamide) and chronic hepatitis B.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on October 27, 2017. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on February 21, 2018. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, databases (free). Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in Table 4.

Results

Findings From the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and described in Section 3.2. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

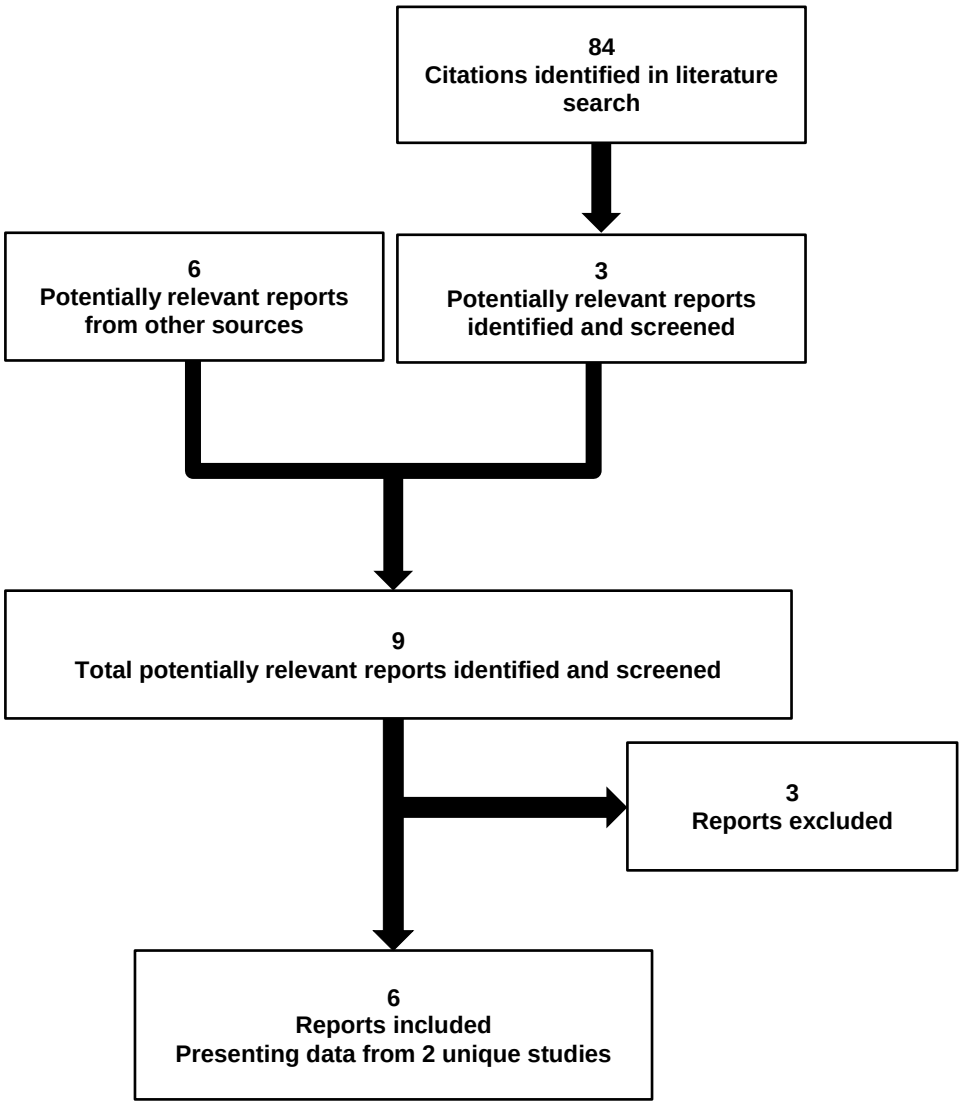


Table 4: Details of Included Studies

		Study 108	Study 110
Designs & Populations	**Study Design**	DB RCT (noninferiority)	DB RCT (noninferiority)
	Locations	105 sites: North America (Canada), Europe, Asia, Australia, New Zealand	161 sites: North America (Canada), Europe, Asia, Australia, New Zealand
	Randomized (N)	426	875
	Inclusion Criteria	Male and nonpregnant, nonlactating female patients, 18 years of age and older Documented CHB infection (e.g., HBsAg-positive for more than 6 months) HBeAg-positive at screening (Study 110) HBeAg-negative CHB (Study 108) with all of the following: • HBeAg-negative and hepatitis B e antibody (anti-HBe) positive at screening • Screening HBV DNA ≥ 2×10^4 IU/mL • Screening serum ALT level > 60 U/L (males) or > 38 U/L (females) and ≤ 10 × ULN (by central laboratory range) Treatment-naive patients (defined as < 12 weeks of OAV treatment with any nucleoside or nucleotide analogue) or treatment-experienced patients (defined as patients meeting all entry criteria [including HBV DNA and serum ALT criteria] and with > 12 weeks of previous treatment with any nucleoside or nucleotide analogue) Treatment-experienced patients receiving OAV treatment at screening must have continued their treatment regimen until the time of randomization, when it was discontinued. Estimated glomerular filtration rate ≥ 50 mL/min (using the Cockcroft-Gault method) Normal electrocardiogram (ECG; or if abnormal, determined by the investigator not to be clinically significant)	
	Exclusion Criteria	Coinfection with hepatitis C virus (HCV), HIV, or hepatitis D virus (HDV) Evidence of HCC (e.g., as evidenced by recent imaging) Any history of, or current evidence of, clinical hepatic decompensation Abnormal hematological and biochemical parameters (e.g., hemoglobin < 10 g/dL, absolute neutrophil count < $750/mm^3$, platelets ≤ $50{,}000/mm^3$, aspartate aminotransferase (AST) or ALT > 10 × ULN, total bilirubin > 2.5 × ULN, albumin < 3.0 g/dL, international normalized ratio (INR) > 1.5 × ULN (unless stable on anticoagulant regimen) Received solid organ or bone marrow transplant Significant renal, cardiovascular, pulmonary, or neurological disease in the opinion of the investigator Significant bone disease or multiple bone fractures Malignancy within the 5 years prior to screening, with the exception of specific cancers that were cured by surgical resection (basal cell skin cancer, etc.). Patients under evaluation for possible malignancy were not eligible. At the time of screening, receiving therapy with immunomodulators (e.g., corticosteroids), investigational agents, nephrotoxic agents, or agents capable of modifying renal excretion Alcohol or substance abuse judged by the investigator to potentially interfere with patient compliance	
Drugs	**Intervention**	TAF 25 mg once daily and matched placebo of TDF 300 mg once daily	
	Comparator(s)	TDF 300 mg once daily and matched placebo of TAF 25 mg once daily	
Duration	**Phase**		
	Screening	45 days	
	Double-blind	144 weeks (DB phase was initially planned for 48 weeks but was revised under amendments 1 [extension to 96 weeks] and 2 [extension to 144 weeks])	
	Follow-up	24 weeks or initiation of alternative HBV treatment	

		Study 108	Study 110
Outcomes	**Primary End Point**	Patients with HBV DNA < 29 IU/mL at week 48	
	Other End Points	Patients with plasma HBV DNA < 29 IU/mL at weeks 96, 144, 240, and 384 At weeks 48, 96, 144, 240, and 384: Patients with plasma HBV DNA < 29 IU/mL (target not detected) Patients with ALT normalization Patients with HBsAg loss Patients with HBsAg seroconversion to anti-HBs Change from baseline in fibrosis by FibroTest Incidence of drug resistant mutations Change from baseline in hip and spine BMD at week 48 (or up to week 384) Change from baseline in serum creatinine at week 48 **Safety** Treatment-emergent adverse events Hip and spine BMD using dual-energy X-ray absorptiometry (DXA) ECG Physical exams, vital signs, fundoscopic examination (for a subgroup of patients), and clinical laboratory tests (chemistry, hematology, urinalysis, and pregnancy testing)	**Key secondary efficacy end point:** Patients with HBeAg loss and seroconversion to anti-HBe at week 48 **Other secondary efficacy end points:** Patients with plasma HBV DNA < 29 IU/mL at weeks 96, 144, 240, and 384 Patients with HBeAg seroconversion to anti-HBs at weeks 96, 144, 240, and 384 At weeks 48, 96, 144, 240, and 384: Patients with plasma HBV DNA < 29 IU/mL (target not detected) Patients with ALT normalization Patients with HBsAg loss Patients with HBeAg loss Patients with HBsAg seroconversion Change from baseline in fibrosis by FibroTest Incidence of drug-resistant mutations Change from baseline in log10 (HBV DNA) (IU/mL) Change from baseline in log10 (HBsAg) (IU/mL) Change from baseline in ALT **Safety** Adverse events Potential uveitis events Potential cardiovascular events Laboratory evaluations Bone safety analysis (fractures, bone events, BMD) Renal safety analyses (creatinine, eGFR, protein)
Notes	**Publications**	Buti et al. 2016[13]	Chan et al. 2016[14]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMD = bone mineral density; CHB = chronic hepatitis B; DB = double-blind; DXA = dual X-ray absorptiometry; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HBe = hepatitis B e; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HDV = hepatitis D virus; INR = international normalized ratio; OAV = oral antivirals; RCT = randomized controlled trial; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ULN = upper limit of normal.

Note: Six additional reports were included (manufacturer's submission,[15] Health Canada Reviewer's report,[16] FDA clinical and statistical review[17,18]).
Source: Clinical Study Reports for Studies 108[10] and 110.[11]

Included Studies

Description of Studies

Two manufacturer-sponsored noninferiority double-blind (DB) randomized controlled trials (RCTs), Study 108 (N = 426) and Study 110 (N = 875), were included in this systematic review. Both studies randomized patients with CHB in a 2:1 ratio to either TAF or TDF. Both studies were multinational: Study 108 had 105 sites spread across 17 countries (including Canada), and Study 110 had 161 sites spread across 19 countries (including Canada). The designs of both studies were similar, the major difference being that Study 108 included patients who were HBeAg-negative and Study 110 included patients who were HBeAg-positive. Both studies were initially planned for a DB treatment phase of 48 weeks; however, this was extended, first, to 96 weeks and then to 144 weeks, under two protocol amendments. These amendments were in response to an FDA request for longer-term data for assessment of safety and efficacy. The clinical study report (CSR) available to CADTH Common Drug Review (CDR) at the time of this report has complete follow-up to 96 weeks. The week 48 analysis was conducted after the last patient completed the week 48 visit or prematurely discontinued the study drug. Results from this analysis were reported in the interim week 48 CSRs. The week 96 analysis was conducted after the last patient completed the week 96 visit or prematurely discontinued study drug. The results of this analysis are the subject of these interim CSRs. The week 144 analysis will be conducted after the last subject completes the week 144 visit or prematurely discontinues study drug. This 144-week analysis is expected to be available in the first quarter of 2018.

Randomization was stratified by plasma HBV DNA level (Study 108: < 7 $\log_{10}$ IU/mL, ≥ 7 to < 8 $\log_{10}$ IU/mL, ≥ 8 $\log_{10}$ IU/mL; Study 110: ≥ 8 $\log_{10}$ IU/mL, < 8 $\log_{10}$ IU/mL) and oral antiviral treatment status (treatment-naive versus treatment-experienced) at screening. Randomization was conducted through use of an interactive Web response system.

Populations

Inclusion and Exclusion Criteria

Study 108 included patients with a diagnosis of CHB who were HBeAg-negative, and Study 110 included patients with a diagnosis of CHB who were HBeAg-positive, for at least six months. Patients in both studies could be either treatment-naive or treatment-experienced. Treatment-experienced patients were required to have continued their therapy up until the time of randomization, before switching to study drug. Patients were required to have an estimated glomerular filtration rate of at least 50 mL/min (Cockcroft-Gault). Patients were excluded if they had a coinfection with hepatitis C virus (HCV) or HIV (Table 4).

Baseline Characteristics

Patients in Study 108 were older, on average, than patients in Study 110 (approximately 46 years old versus 38 years old) and included a higher proportion of white patients and a lower proportion of Asian patients. Baseline HBV DNA levels were lower in Study 108 (Study 108: mean 5.7 $\log_{10}$ IU/mL, standard deviation [SD] 1.3 versus Study 110: mean 7.6 $\log_{10}$ IU/mL, SD 1.4), as were baseline ALT levels (Study 108: mean 94 U/L versus Study 110: mean 120 U/L). The mean FibroTest score was higher in Study 108 than in Study 110 (0.43 versus 0.34) (Table 5). There were fewer patients in Study 108 who were treatment-experienced than in Study 110 (approximately 21% versus 26%).

With respect to differences between groups within studies, in Study 108, patients in the TAF group had a shorter duration of HBV than those in the TDF group (mean of 8.5 versus 9.3 years). In Study 110, participants in the TAF group had lower baseline ALT levels than those in TDF group (117 U/L versus 125 U/L).

Table 5: Summary of Baseline Characteristics

	Study 108		Study 110	
	TAF (N = 285)	**TDF (N = 140)**	**TAF (N = 581)**	**TDF (N = 292)**
Mean (SD) age, years	45 (11.6)	48 (10.4)	38 (11.0)	38 (11.7)
Male, n (%)	173 (60.7)	86 (61.4)	371 (63.9)	189 (64.7)
Race, n (%)				
Asian	205 (71.9)	101 (72.1)	482 (83.0)	232 (79.5)
White	71 (24.9)	35 (25.0)	96 (16.5)	52 (17.8)
Black or African-American	5 (1.8)	3 (2.1)	2 (0.3)	3 (1.0)
Native Hawaiian or Pacific Islander	2 (0.7)	0	1 (0.2)	3 (1.0)
Other	2 (0.7)	1 (0.7)	0	2 (0.7)
Mean (SD) HBV DNA, log_{10} IU/mL	5.7 (1.34)	5.8 (1.32)	7.6 (1.34)	7.6 (1.41)
Mean (SD) ALT, U/L	94 (88.3)	94 (80.8)	117 (105.1)	125 (128.2)
ALT level, central lab normal range, n (%)				
≤ ULN	49 (17.2)	19 (13.6)	44 (7.6)	24 (8.2)
> ULN to 5 × ULN	209 (73.3)	109 (77.9)	470 (80.9)	225 (77.1)
> 5 × ULN to 10 × ULN	22 (7.7)	10 (7.1)	56 (9.6)	30 (10.3)
> 10 × ULN	5 (1.8)	2 (1.4)	11 (1.9)	13 (4.5)
HBeAg status, n (%)				
Positive	2 (0.7)	2 (1.4)	567 (97.6)	288 (98.6)
Negative	283 (99.3)	138 (98.6)	14 (2.4)	4 (1.4)
HBV genotype group, n (%)				
A	15 (5.3)	6 (4.3)	39 (6.7)	25 (8.6)
B	60 (21.1)	40 (28.6)	100 (17.2)	48 (16.4)
C	115 (40.4)	47 (33.6)	303 (52.2)	153 (52.4)
D	90 (31.6)	42 (30.0)	134 (23.1)	63 (21.6)
E	5 (1.8)	2 (1.4)	2 (0.3)	1 (0.3)
F	0	0	3 (0.5)	2 (0.7)
H	0	2 (1.4)	0	0
Unknown	0	1 (0.7)	0	0
Years positive for HBV, mean (SD)	8.5 (7.85)	9.3 (8.72)	6.3 (6.24)	6.3 (6.33)
Previous oral nucleoside/nucleotide,[a] n (%)				
Yes	60 (21.1)	31 (22.1)	151 (26.0)	77 (26.4)
No	225 (78.9)	109 (77.9)	430 (74.0)	215 (73.6)
Cirrhosis history, n (%)				
Yes	24 (11.0)	14 (12.4)	41 (9.8)	24 (11.3)
No	195 (89.0)	99 (87.6)	376 (90.2)	189 (88.7)

	Study 108		Study 110	
FibroTest score, mean (SD)	0.43 (0.223)	0.45 (0.229)	0.34 (0.227)	0.32 (0.225)
eGFR by CG (mL/min), mean (SD)	104.7 (27.83)	100.3 (24.23)	113.7 (27.78)	112.5 (29.33)
Diabetes mellitus, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Cardiovascular disease, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hyperlipidemia, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

ALT = alanine aminotransferase; CG = Cockcroft-Gault; eGFR = estimated glomerular filtration rate; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; SD = standard deviation; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ULN = upper limit of normal.

[a] Previous oral nucleoside/nucleotide treatment status was categorized as "Yes" or "No" regardless of treatment duration.

Source: Clinical Study Reports for Studies 108[10] and 110.[11]

Interventions

TAF and TDF were both administered orally, once daily in each study. The original DB comparative phase of both studies was planned for 48 weeks; however, this was increased, first, to 96 weeks and then to 144 weeks under two subsequent protocol amendments. Enrolled patients who were treatment-experienced continued therapy with their current regimen until the time of randomization, when they discontinued therapy and began their new regimen. Blinding was conducted using a matching placebo tablet of each study drug.

Outcomes

The primary outcome of both studies was the proportion of patients who achieved undetectable HBV DNA by week 48. Secondary outcomes included bone mineral density (hip and spine) and assessment of renal function (serum creatinine and proteinuria events), as well as HBeAg seroconversion (Study 110 only).

The Roche COBAS TaqMan HBV test for use with the High Pure System was used to measure plasma HBV DNA. According to the manufacturer, this is the same assay used in the phase III studies leading to approval of TDF for treatment of CHB infection. The lower limit of quantification in plasma for the assay is 29 IU/mL, and that was the primary end point cut-off for viral suppression in both studies. Levels of HBsAg were quantified in serum by the Abbott Architect assay, with a lower limit of quantification of ≤ 0.05 IU/mL. An HBsAg loss was defined as a change in HBsAg result from HBsAg-positive at baseline to HBsAg-negative at a post-baseline visit, with baseline anti-HBs negative or missing. The manufacturer defined HBsAg seroconversion as HBsAg loss and a change in anti-HBs test from anti-HBs–negative or missing at baseline to anti-HBs–positive at a post-baseline visit. Similarly, patients were considered to have experienced HBeAg loss if their HBeAg changed from HBeAg-positive at baseline to HBeAg-negative at a post-baseline visit, with baseline anti-HBe–negative or missing. Patients were considered to have seroconverted if they had an HBeAg loss and a change in anti-HBe result from anti-HBe–negative or missing at baseline to anti-HBe–positive at a post-baseline visit.

Fibrosis of the liver was assessed by FibroTest at each visit. FibroTest is a composite of five serum biochemical parameters:
alpha-2-macroglobulin, apolipoprotein A1, haptoglobin, gamma-glutamyltranspeptidase, and bilirubin. It also takes into account patients' age and sex Values of FibroTest range from 0 to 1, and the manufacturer-recommended cut-off values for assessing fibrosis are < 0.31, no or minimal fibrosis; 0.32 to 0.58, moderate fibrosis; > 0.58, advanced or severe

fibrosis (cirrhosis).[19,20] The manufacturer also provided cut-offs for FibroTest that corresponded to the METAVIR histological score (minimal, F0 to F1; significant ≥ F2 to < F3; and advanced, ≥ F3 to F4) based on biopsy; 0.27 for F1, 0.48 for F2, 0.58 for F3, and 0.74 for F4.[21] The FibroTest cut-off ranges to determine fibrosis stage selected in the two studies reviewed here were slightly different than the manufacturer-recommended ones: 0 to 0.48, 0.49 to 0.74, 0.75 to 1. See Appendix 5 for further details about the validity of the FibroTest. No minimal clinically important difference was found in a search of the literature by CDR.

Bone health was assessed as a secondary safety outcome using hip and spine bone mass density (BMD) measured by dual-energy X-ray absorptiometry (DXA). The initial baseline DXA was performed during screening and was completed at least 14 days before the first dose of study drug. DXA was also assessed at week 48, within a window of 14 days. The change from baseline in fracture probabilities were assessed using the FRAX algorithm.

Renal laboratory abnormalities were assessed using serum creatinine, estimated glomerular filtration rate (three different formulas: Cockcroft-Gault, Chronic Kidney Disease Epidemiology Collaboration creatinine, and cystatin-C equations), protein, retinol-binding protein, and beta-2 microglobulin.

Serum chemistry and liver function tests were performed at screening, baseline, and every four weeks through week 48, then every eight weeks to week 96. ALT normalization was defined as ALT greater than ULN (by central laboratory normal range or AASLD normal range) at baseline but within normal range at a post-baseline visit. Laboratory results, such as ALT and various lipid measures, were graded as grade 0, grade 1 (mild), grade 2 (moderate), grade 3 (severe), or grade 4 (life-threatening) using criteria specified in the protocol. Treatment-emergent laboratory abnormalities in the DB phase were defined as values that increased at least one toxicity grade from baseline at any post-baseline visit for those who had not discontinued study drug permanently, or up to and including the last dose date of the blinded study drugs for those who discontinued study drug permanently. If the relevant baseline laboratory data were missing, any laboratory abnormality of at least grade 1 was considered treatment-emergent. For the lipid and glucose measurements, only those measurements assessed under fasting status were summarized. Various bone events were also captured as adverse events/serious adverse events under terms such as “fracture,” “osteoporosis,” and “osteopenia.”

Statistical Analysis

The calculated sample sizes for TAF (N = 260) and TDF (N = 130) patients in Study 108 and for TAF (N = 576) and TDF (N = 288) patients in Study 110 were planned to provide 90% power in Study 108 and 84% power in Study 110 to rule out the noninferiority margin of 10% at a one-sided significance level of 0.025. These sample sizes were based on the assumption that the expected difference between TAF and TDF in the proportion of patients achieving the primary outcome would be zero, and that response rates for patients achieving the primary outcome would 91% in Study 108 and 69% in Study 110. These estimates were similar to response rates seen for the same outcome in the pivotal trials of TDF.

The primary efficacy analysis was a noninferiority analysis, conducted after the last randomized patient reached week 48 or discontinued study drug prematurely. Noninferiority was assessed using a 95% confidence interval (CI) approach, with a noninferiority margin of 10%. Noninferiority was concluded if the lower bound of the two-sided 95% CI of the

difference between TAF and TDF groups in the proportion of patients who achieved HBV DNA < 29 IU/mL at week 48 was greater than –10%.

If noninferiority of TAF versus TDF was established, superiority of TAF over TDF was tested as a secondary assessment of the primary outcome. The baseline HBV DNA level and oral antiviral treatment status stratum-stratified, two-sided Cochran–Mantel–Haenszel test was also used to assess superiority.

For all the secondary efficacy end points involving proportions, *P* values were calculated using the Cochran–Mantel–Haenszel test, stratified by baseline HBV DNA and oral antiviral treatment status, and the proportion difference between the two treatment groups. The associated 95% CI was calculated based on stratum-adjusted Mantel-Haenszel proportion. For continuous end points, such as change from baseline in HBV DNA, ALT, and fibrosis scores, the *P* values and differences in change from baseline were constructed using ANOVA models (including treatment group), baseline HBV DNA, and oral antiviral treatment status as fixed effects in the model.

Adjustments for multiplicity were performed for the primary efficacy end point and the four key secondary safety end points presented in the interim week 48 CSR in both studies. No such adjustments were made for week 96 analyses. A sequential gatekeeping procedure was employed. If noninferiority was achieved for the primary efficacy end point, then subsequent secondary end points were tested in the following order: change from baseline in BMD (hip), change from baseline in BMD (spine), change from baseline in serum creatinine, and treatment-emergent proteinuria. Additionally, in Study 110, the proportion of patients with HBeAg loss and seroconversion was also tested as part of the hierarchy.

For the primary end point and for the secondary efficacy end points involving proportions, missing data were handled using a missing-equals-failure approach in both studies. For key secondary end points, missing data were handled via a mixed-model for repeated measures approach. Sensitivity analyses were performed, and these included an analysis excluding all missing data. For per cent change from baseline in hip and spine BMD, as well as change from baseline in serum creatinine, analyses were performed using last observation carried forward (LOCF) up to week 96 to impute missing data. For the remaining end points, values for missing data were not imputed, unless specified otherwise.

Analysis Populations

The analysis populations for both studies were as follows:

Randomized Analysis Set

The randomized analysis set included all patients randomized to the study. This was the primary analysis set for by-patient listings.

Safety Analysis Set

The safety analysis set included all randomized patients who received at least one dose of study drug. Patients were analyzed according to the treatment they actually received. The safety analysis set was the primary analysis set for safety analyses.

Full Analysis Set

The full analysis set (FAS) included all randomized patients who received at least one dose of study drug. Patients were analyzed according to the treatment to which they were randomized. This was the primary analysis set for efficacy analyses.

Per-Protocol Analysis Set

The week 96 per-protocol (PP) analysis set included all randomized patients who received at least one dose of study drug and had not been excluded based on the following criteria: lacking an on-treatment HBV DNA sample within the 96-week analysis window (except those who withdrew due to lack of efficacy), those receiving ongoing therapy with a prohibited drug, and adherence below the 2.5th percentile. Patients were analyzed according to the treatment they actually received. The PP analysis set was the secondary analysis set for efficacy analysis.

Patient Disposition

Both Study 108 and Study 110 are ongoing, with approximately half of the patients in each study having completed the DB phase. At this 96-week time point, there were no notable differences in the proportion of patients withdrawing between groups (Table 6).

Table 6: Patient Disposition

	Study 108		Study 110	
	TAF	TDF	TAF	TDF
Screened, N	914		1473	
Screen failure	470		546	
Screen success, not randomized	18		52	
Randomized, N (%)	285	141	582	293
Randomized and treated, N (%)	285	140	581	292
Discontinued, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]
Investigator's discretion	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Withdrew consent	[redacted]	[redacted]	[redacted]	[redacted]
Noncompliance	[redacted]	[redacted]	[redacted]	[redacted]
Protocol criteria for withdrawal	[redacted]	[redacted]	[redacted]	[redacted]
Pregnancy	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]
HBsAg seroconversion	[redacted]	[redacted]	[redacted]	[redacted]
Protocol violation	[redacted]	[redacted]	[redacted]	[redacted]
Ongoing	[redacted]	[redacted]	[redacted]	[redacted]
Completed double-blind phase	[redacted]	[redacted]	[redacted]	[redacted]
Entered open-label phase	[redacted]	[redacted]	[redacted]	[redacted]
Full analysis set, N	285	140	581	292
Safety, N	285	140	581	292

HBsAg = hepatitis B surface antigen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

[redacted]

Source: Clinical Study Reports for Studies 108[10] and 110.[11]

Exposure to Study Treatments

[redacted]

Critical Appraisal

Internal Validity

Both Study 108 and Study 110 were DB, and blinding was facilitated through the use of a matching placebo. Randomization was carried out using an interactive Web response system.

Missing data for dichotomous end points were accounted for by using a missing-equals-failure approach. This approach has the potential to bias results, particularly in the case of differential rates of withdrawals between comparison groups, although this was not seen in either Study 108 or Study 110. Less than 10% of the population withdrew from the studies, as of 96 weeks of follow-up. The included studies typically accounted for missing data for continuous outcomes using an LOCF approach. Sensitivity analyses were also performed and appeared to support the results of the primary analysis. The LOCF approach can introduce bias in the results, particularly for outcomes such as BMD that show a natural deterioration over time. The risk of bias would be expected to increase when there are high proportions of withdrawals and differential withdrawals between groups within studies, and neither were the case among the included studies. The manufacturer noted that, for outcomes aside from the key secondary outcomes, there was no accounting for missing data.

Both Studies 108 and 110 employed a noninferiority analysis for the primary outcome, both using the same threshold, based on findings from the original clinical studies of TDF. Since TDF was the comparator in this study and the designs were similar, it seems reasonable to base the noninferiority margin on these studies, according to the FDA.[17,18] PP analyses were also reported, but only in Study 108 to support the findings of the primary analysis. Reporting the data from the PP population is recommended when a noninferiority design is employed.

The manufacturer performed power calculations before the study and provided a rationale for the numbers used in the calculations. In both studies, the manufacturer met the minimum sample size required.

There were two protocol amendments that extended the length of the DB phase, first, from 48 weeks to 96 weeks, then to 144 weeks. The second amendment was made while the studies were ongoing and after approximately half of the patients had completed the DB phase at 96 weeks. As a result, when the final CSR is available, half of the participants will have a 96-week DB treatment phase, and half will have a 144-week treatment phase. The main issue with these amendments is that results from an interim analysis at 48 weeks were reported while participants were continuing in the DB phase. These results may have

biased the results of these ongoing studies. However, the manufacturer does not appear to have used the results from the interim analyses to modify the design of the ongoing studies.

The manufacturer accounted for multiplicity for only the primary and four key secondary safety outcomes (and for HBeAg in Study 110), and only for the 48-week analyses. No adjustments for multiple comparisons were made for the 96-week data. Additionally, subgroup analyses were reported, but no adjustments were made for these analyses, and they may have been underpowered. Lack of adjustment for multiple comparisons increases the risk of type I error for the subgroup analyses.

The manufacturer did not employ a true intention-to-treat (ITT) analysis. The FAS, which was used for efficacy analyses, included only patients who were randomized and treated, while a true ITT analysis would have included all participants, regardless of whether they were treated.

External Validity

The primary outcome of both studies was the reduction in HBV DNA to undetectable levels. Other important clinical outcomes from the review protocol, such as mortality and morbidity, were not pre-defined outcomes of these studies, and the studies were not of sufficient size or duration to assess these outcomes. A relatively small proportion of patients infected with CHB develop serious complications of the disease; however, these are the outcomes of most importance to patients.

Fibrosis scores were assessed using FibroTest, which employs a combination of liver enzyme assays, rather than imaging. The clinical expert noted that FibroTest was not necessarily the most reliable means for assessing fibrosis. However, with respect to the other options, FibroScan is likely to be less readily available, and biopsies are considered too invasive, particularly for a clinical trial. The clinical expert questioned whether FibroTest was a sensitive and reliable enough assay to assess fibrosis after only 96 weeks of follow-up, noting that the changes from baseline to 96 weeks, in either group, were small and of questionable clinical significance. Additionally, CDR was unable to find an minimal clinically important difference for the FibroTest.

Participants in both Study 108 and Study 110 appeared to represent a typical population one would expect to see with chronic hepatitis B, albeit a healthy population, according to the clinical expert. Both trials had Canadian sites. More than half of the enrolled population in Study 108 and approximately one-third of patients in Study 110 were screen failures, and no reasons were reported why these patients were not included in the study. This might suggest a highly selected population, which can affect generalizability.

The comparator in both included studies was TDF. Therefore, there is no information regarding the relative efficacy and harms of TAF versus entecavir or less expensive alternatives, such as lamivudine or interferons.

The maximum DB follow-up period available as of the most current CSR is 96 weeks, although, under a protocol amendment, approximately half of the original randomized population will continue to 144 weeks of follow-up in the DB phase. Given the small number of clinical outcomes (no deaths, very few hepatocellular carcinoma [HCC] events), it is unlikely that this follow-up was long enough to assess longer-term outcomes such as mortality and morbidity. The open-label phase of both studies is planned to continue for 384 weeks; however, these will no longer be comparative trials at this point. The studies also assessed the safety of TAF relative to TDF specifically with respect to osteoporosis and

adverse renal outcomes. However, the included studies were unlikely to be of sufficient duration to assess these outcomes, particularly risk of fractures. Assessment of osteoporosis relied on BMD, and there were very few fractures across the studies. Use of BMD alone as a predictor of fracture risk fails to acknowledge other contributors to risk, including age and prior fractures.

Health-related quality of life was not assessed in the included trials. Quality of life was identified as an issue for patients in the input received from patient groups for this review. However, the concerns raised tend to be related to the stigma associated with the disease.

Approximately 20% of the participants in both studies had received anti-HBV therapy in the past. Participants were required to continue their prior anti-HBV therapy until randomization, and this raises concern about a potential carryover effect from this prior therapy. This concern is mitigated somewhat by the subgroup analyses that showed no difference in response for the primary outcome based on prior anti-HBV therapy.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 4). See Table 7 for detailed efficacy data.

Mortality

There were no deaths in either study after 96 weeks of follow-up.

Morbidity

Hepatitis-related morbidity was not specifically assessed as an outcome. However, serious adverse events of HCC were reported, and [redacted]).

Health-Related Quality of Life

Health-related quality of life was not assessed in either included study.

CHB-Related Symptoms

Symptoms related to CHB were not specifically assessed in the included studies.

Other Efficacy Outcomes

Virology

The proportion of patients achieving a HBV DNA level of < 29 IU/mL at 48 weeks was the primary outcome in both studies. In Study 108, the proportion of patients achieving the primary outcome was similar between TAF and TDF groups, at both week 48 (94.0% versus 92.9%, respectively) and week 96 (90.2% versus 90.7%, respectively) (Table 7). In Study 110, the proportion of patients achieving a HBV DNA of < 29 IU/mL was lower, but was again similar between TAF and TDF groups at both 48 weeks (63.9% versus 66.8%, respectively) and 96 weeks (72.8% versus 74.7%, respectively). There was no statistically significant difference between TAF and TDF groups after 48 weeks in either Study 108 (difference in proportions between groups of 1.8%, 95% CI, −3.6% to 7.2%) or Study 110 (–3.6%, 95% CI, –9.8% to 2.6%). Criteria for noninferiority was met in both studies, as the

lower boundary of the 95% CI of the difference in proportions between groups was greater than –10%. [redacted]

In both studies, the mean change from baseline in HBV DNA was similar between TAF and TDF groups at both 48 weeks and 96 weeks.

Subgroup analyses were conducted for treatment-experienced or treatment-naive patients or for various measures of disease severity (baseline viral load, ALT, FibroTest score) (Table 10). In the 48-week analysis, numerically fewer patients treated with TAF versus TDF achieved undetectable HBV DNA in the subgroup of patients with higher baseline viral load in both studies. However, these differences were no longer evident at 96 weeks of follow-up. It should also be noted that no adjustments were made for multiple comparisons in the subgroup analyses. There were no statistically significant treatment interactions in any of the other subgroups for the primary outcome.

Serologic Response

Very few patients experienced HBsAg loss or seroconversion in either study, and there were no statistically significant differences between groups (Table 9). In Study 110, there were more patients in the TAF group than in the TDF group who experienced HBeAg loss (difference in proportions between groups of 3.7%; 95% CI, –1.9% to 9.4%, *P* = 0.20) and seroconversion (5.1%; 95% CI, 0.2% to 10.1%, *P* = 0.050) at 96 weeks. No patients would be expected to achieve HBeAg loss/seroconversion in Study 108, as these patients were already HBeAg-negative.

Liver Enzymes

A higher proportion of patients treated with TAF achieved normalized ALT (central laboratory analysis) at 96 weeks (80.9% versus 71.1% treated with TDF) in Study 108, and this difference was statistically significant (difference between groups of 9.8%; 95% CI, 0.2% to 19.3%). In Study 110, a higher proportion of patients treated with TAF versus TDF achieved ALT normalization (75.4% versus 67.5% of patients), and this difference was statistically significant (8.0%; 95% CI, 1.2% to 14.7%). Similar results were seen when ALT was analyzed using AASLD criteria (Table 9). However, it should be noted that no adjustments were made for multiple comparisons. Mean change from baseline ALT values were similar between treatment groups at week 48 and week 96 in both studies.

Fibrosis

Fibrosis was assessed using FibroTest. In all groups, FibroTest scores decreased (improved) from baseline, with a greater reduction in scores in the TAF group versus the TDF group in both studies, [redacted](Table 9). There is no established minimal clinically important difference for FibroTest. Therefore, the clinical significance of this difference in unknown.

Table 7: Key Efficacy Outcomes

	Study 108		Study 110	
	TAF 25 mg (N = 285)	**TDF 300 mg (N = 140)**	**TAF 25 mg (N = 581)**	**TDF 300 mg (N = 292)**
Virology				
HBV DNA of < 29 IU/mL at week 48, n (%) Primary outcome (full analysis set)	268 (94.0)	130 (92.9)	371 (63.9)	195 (66.8)
Difference in proportions (95% CI)	1.8% (−3.6% to 7.2%) Noninferiority met[a,b]		–3.6% (–9.8% to 2.6%) Noninferiority met[a,b]	
Per-protocol set, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference in proportions (95% CI)[b]	[redacted]		[redacted]	
HBV DNA < 29 IU/mL, week 96, n (%)	257 (90.2)	127 (90.7)	423 (72.8)	218 (74.7)
Difference in proportions (95% CI)[b]	−0.6% (−7.0% to 5.8%) *P* = 0.84		–2.2% (–8.3% to 3.9%) *P* = 0.47	
Mortality				
Deaths, n	0	0	0	0
Morbidity				
Patients with HCC (reported as AE), n (%)	[redacted]	[redacted]	[redacted]	[redacted]
HRQoL	NR	NR	NR	NR
Symptoms	NR	NR	NR	NR

AE = adverse event; CI = confidence interval; HCC = hepatocellular carcinoma; HBV = hepatitis B virus; HRQoL = health-related quality of life; NR = not reported; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

[a] Primary outcome: Because the lower bound of the two-sided 95% CI of the difference (TAF – TDF) in the response rate was greater than the pre-specified –10% margin, the TAF group met the primary end point of noninferiority to the TDF group.

[b] Difference in the proportion between treatment groups and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HBV DNA categories and oral antiviral treatment status strata.

Source: Clinical Study Reports for Studies 108[10] and 110.[11]

Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See Table 8 for detailed harms data.

Adverse Events

There were [redacted] (Table 8). [redacted]. Other common AEs occurring in both groups included nasopharyngitis and upper respiratory tract infection.

Serious Adverse Events

[redacted] (Table 8).

Withdrawal Due to Adverse Events

[redacted] (Table 8).

Notable Harms

Notable harms included those related to bone health and renal events. There were no notable or consistent differences between TAF and TDF for patients experiencing fractures, “bone events,” osteopenia, osteoporosis, or decreased BMD. BMD was also assessed as a secondary safety end point, measured in terms of change from baseline, and formally compared between TAF and TDF groups. There were smaller per cent reductions in BMD after 48 weeks in the TAF group versus the TDF group, both in spine and hip, in both Study 108 ([redacted]) and Study 110 ([redacted]). Similar differences between groups were reported for hip and spine at the 96-week time point as well.

There were few renal events — no more than one in any group in either study. Renal injury was also assessed as a secondary safety end point using change from baseline in serum creatinine and events of treatment-emergent proteinuria. In Study 110, there was a smaller increase in serum creatinine in the TAF versus TDF group after 48 weeks ([redacted], respectively). [redacted]. There was no difference in the increase in serum creatinine between TAF and TDF groups in Study 108 (Table 8). There was no statistically significant difference between groups in the proportion of patients with proteinuria events at 48 weeks in either study.

Additional notable harms included events involving increased cholesterol and the proportion of patients with grade 3 events of elevated fasting low-density lipoprotein cholesterol (LDL-C). There was a numerically higher proportion of TAF patients with this event compared with TDF patients in [redacted]. Patients in the TAF group had an increase from baseline in median fasting LDL-C, while patients in the TDF group had a decrease from baseline ([redacted]). [redacted]) (Table 8).

Table 8: Harms

	Study 108		Study 110	
	TAF 25 mg (N = 285)	TDF 300 mg (N = 140)	TAF 25 mg (N = 581)	TDF 300 mg (N = 292)
Adverse Events				
Patients with > 0 AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Most common AE (≥ 5% in any group)				
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]	[redacted]	[redacted]
Serious Adverse Events				
Patients with > 0 SAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Most common SAEs				
Renal stones	[redacted]	[redacted]	[redacted]	[redacted]
HCC	[redacted]	[redacted]	[redacted]	[redacted]
WDAE				
WDAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Most common reasons	[redacted]		[redacted]	
Deaths				
Number of deaths, n (%)	0	0	0	0
Notable Harms				
Bone health				
Fractures, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Bone events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Osteopenia, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Osteoporosis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Decreased bone density, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hip BMD mean (SD) baseline	[redacted]	[redacted]	[redacted]	[redacted]
% change at week 48	[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM (95% CI) [a]	[redacted]		[redacted]	
% change at week 96	[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM (95% CI) [a]	[redacted]		[redacted]	
Spine BMD **m**ean (SD) baseline	[redacted]	[redacted]	[redacted]	[redacted]

	Study 108		Study 110	
% change at week 48	[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM (95% CI) [a]	[redacted]		[redacted]	
% change at week 96	[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM (95% CI) [a]	[redacted]		[redacted]	
Renal events				
Renal impairment, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Renal failure, n (%)	0	0	0	0
Proximal tubulopathy, n (%)	0	0	0	0
Serum creatinine, mean (SD) baseline, µmol/L	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline, 48 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline, 96 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Median eGFR, CG (mL/min)	[redacted]	[redacted]	[redacted]	[redacted]
Change at week 96	[redacted]	[redacted]	[redacted]	[redacted]
Proteinuria grade 1, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Proteinuria grade 2, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Proteinuria grade 3, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Between-group comparison, *P* value (across all grades)[c]	[redacted]		[redacted]	
Lipids				
Fasting cholesterol, grade 3, n (%)	3 (1.1)	0	7 (1.2)	0
Fasting LDL-C grade 3, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median change from baseline to week 96, direct LDL-C, mmol/L[d]	[redacted]	[redacted]	[redacted]	[redacted]
Median change from baseline to week 96, fasting HDL-C, mmol/L[d]	[redacted]	[redacted]	[redacted]	[redacted]
Hepatic steatosis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; BMD = bone mineral density; CI = confidence interval; CG = Cockcroft-Gault; eGFR= estimated glomerular filtration rate; HCC = hepatocellular carcinoma; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LSM = least squares mean; SAE = serious adverse event; SD = standard deviation; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

[a] *P* values, difference in least squares means and 95% CI were from the analysis of variance (ANOVA) model including treatment as a fixed effect.

[redacted]

[c] *P* value was from the rank ANCOVA effect model on observed data with treatment as a fixed effect and adjusting for baseline toxicity grade.

[d] Converted from mg/dL by CDR.

Source: Clinical Study Reports for Studies 108[10] and 110.[11]

Discussion

Summary of Available Evidence

Two manufacturer-sponsored, multi-centre DB RCTs, Study 108 and Study 110, met the inclusion criteria for this systematic review. Both trials compared TAF with TDF. The DB phase of the trials was initially designed to last 48 weeks, but protocol amendments made while the trial was ongoing extended the DB phase, first, to 96 weeks and then to 144 weeks. This resulted in approximately half of the patients having a DB treatment exposure of 96 weeks, while the remainder will be exposed to therapy for 144 weeks in the DB phase. The protocol amendments were in response to a request from the FDA to have longer-term efficacy and safety data. The study is ongoing, and, as of this review, only data for the 96-week follow-up are available. The primary outcome of Studies 108 and 110 was the proportion of patients who achieved undetectable levels of HBV DNA (< 29 IU/mL) at 48 weeks. Key secondary outcomes included the proportion of patients achieving undetectable HBV DNA at 96 weeks, patients with ALT normalization, HBsAg loss (as well as HBeAg loss in Study 110), seroconversion, and change from baseline in fibrosis, as well as safety outcomes such as assessment of BMD and renal impairment. Key critical appraisal issues included the lack of emphasis on key clinical outcomes specified in the review protocol, such as mortality and morbidity, as well as reliance on surrogate outcomes for assessment of key safety issues such as bone health. The manufacturer also did not account for multiplicity for any of the 96-week data, or for important secondary outcomes such as ALT and fibrosis.

Interpretation of Results

Efficacy

Unlike HCV, for which treatments are largely curative, HBV necessitates therapy on a long-term basis — often lifelong. This makes it important to understand the natural history of HBV. Like HCV, HBV causes serious complications in only a fraction of patients infected. The complications tend to mirror those seen with HCV, namely, cirrhosis and HCC, although these may occur at a lower rate than with HCV (reviewed in Appendix 6). Viral load is a key predictor of development of complications, and this explains why reduction in HBV DNA to undetectable levels was the primary outcome of both Studies 108 and 110. Demographic factors associated with progression of CHB to cirrhosis include older age and male sex. The decision to initiate therapy is typically based on patient age and various HBV markers, including HBV DNA, ALT levels, and stage of liver disease. In the World Health Organization (WHO) guidelines (Figure 3 in Appendix 7), the first consideration for whether to initiate treatment is the presence of cirrhosis.

Health-related quality of life and symptoms were not assessed in the included studies. Patient input to CDR suggests that the stigma associated with HBV infection and the complications associated with CHB are of primary concern to patients. Therefore, the primary outcome, reduction of virus to undetectable levels, will be of importance to patients. TAF was noninferior to TDF for this outcome, assessed at 48 weeks, and these results persisted to 96 weeks, the longest follow-up in the DB phase for both studies. Therefore, with the ability to clear virus in similar proportions of patients to TDF, TAF demonstrates efficacy in outcomes that are important to patients.

When comparing responses between HBeAg-positive (Study 110) and HBeAg-negative (Study 108) populations across the two studies, virologic response rates (reduction of HBV DNA to undetectable levels) were lower in the HBeAg-positive population; however, they also had larger reductions in HBV DNA from baseline. The different stages of CHB and the significance of the various proteins encoded by HBV are reviewed in Appendix 7. Patients who are HBeAg-positive tend to have higher levels of HBV DNA, as this disease phase is characterized by high rates of viral replication. Both HBeAg-positive and HBeAg-negative patients may have moderate to severe fibrosis. However, in the included studies, baseline fibrosis, assessed by FibroTest, was slightly lower in HBeAg-negative patients. It should be noted that TAF is currently indicated only for patients with compensated liver disease, while TDF is indicated for patients with either compensated or decompensated liver disease. According to the FDA, this is because TAF has not been studied in patients with decompensated CHB.[17,18]

Harms

Both TAF and TDF are prodrugs of tenofovir. However, TAF requires a much lower dose in order to achieve therapeutic levels of tenofovir, which implies that TAF may have less impact on notable harms associated with TDF, namely, bone-related disorders (fractures) and adverse renal outcomes. The mechanism behind the bone toxicity associated with TDF is not entirely clear. However, there are a few theories, many based on studies in patients with HIV. The renal effects of TDF may contribute to loss of BMD, as proximal tubulopathy due to the effects on TDF on mitochondrial DNA could promote loss of bicarbonate and phosphate.[22] TDF may have a direct effect on vitamin D absorption, which could contribute to hyperparathyroidism and increased bone turnover.[23] There were very few events related to either of these safety outcomes in Studies 108 or 110, and no clear differences in risk between groups. Assessment of these outcomes relied on surrogate markers, most notably BMD, which was statistically improved for patients receiving TAF compared with TDF. Therefore, TAF appears to have a lower risk of reducing BMD versus TDF. However, the follow-up of these studies was not long enough to ascertain whether this translated into a reduced risk of fractures.

There was a numerical increase in the risk of hypercholesterolemia in patients treated with TAF compared with patients treated with TDF in both studies. Although limited data are available from the extension periods, this trend appears to continue, as the most common notable harm was cholesterol-related events such as grade 3 elevations in LDL-C and total cholesterol. It is not entirely clear whether this numerical difference represents an increased risk of cholesterol-related events from baseline (i.e., compared with no treatment) or whether TDF has lipid-lowering properties that TAF does not possess. There is some evidence of a lipid-lowering effect of TDF according to the literature related to its use in HIV,[24] and the manufacturer attributes these differences in lipid results in the included studies to the fact that TDF has lipid-lowering properties. However, when looking at the change from baseline in LDL-C in the included studies, there is an increase from baseline with TAF and decrease from baseline in TDF, and the magnitude of the change from baseline is similar between the groups. Thus, although TDF may lower LDL-C, it is also possible that TAF raises LDL-C. The mechanism for the LDL-lowering ability of TDF has not been elucidated, but it does appear to have an effect on lipids. Either way, antiviral therapy for CHB is considered to be lifelong therapy in almost all patients; therefore, an increased risk of developing high cholesterol compared with TDF could be a limitation to the use of TAF. The clinical expert noted that improved BMD is not a good trade-off for elevated cholesterol and the increased risk of cardiovascular disease.

Potential Place in Therapy[2]

Given the bone and renal safety concerns associated with long-term TDF therapy, the more favourable pharmacological profile of TAF permits a marked (one-tenth) reduction in dosage and thus reduces systemic exposure, potentially improving bone and renal safety. However, TAF has been shown to increase urine glucose levels (in 5% of TAF patients versus 1% of TDF patients) and LDL-C levels > 300 mg/dL (in 4% of TAF patients versus no TDF patients) — effects that have not been seen with TDF — although the majority of these patients with elevated urine glucose had pre-existing glycosuria at baseline or had risk factors that might contribute to elevated urine glucose levels. Given that HBV patients are on these medications lifelong, the LDL increase can be a concern with long-term users of TAF. As well, the long-term clinical significance of differences in both renal and BMD changes between TAF and TDF is not known.

With evidence from two DB RCTs showing that TAF is safe, tolerable, and noninferior to TDF, its use as a first-line therapy is appropriate, according to the clinical expert consulted for this review. Longer-term follow-up is required to determine whether the differences in bone and renal changes seen with TAF are clinically relevant and whether this benefit is outweighed by the negative effect of the increase in LDL-C levels. It is likely appropriate for TAF be used in patients with developing and/or established renal and bone disease to hasten progress in HBV treatment that may be seen with TDF therapy.

Conclusions

Two manufacturer-sponsored multi-centre DB RCTs were included in the systematic review. Both studies are ongoing, with follow-up data available to 96 weeks. Study 108 included patients who were HBeAg-negative, and Study 110 included patients who were HBeAg-positive. The primary outcome of both studies was the proportion of patients who achieved undetectable HBV DNA at 48 weeks. TAF was noninferior to TDF in both studies, and this was also observed at 96 weeks. There were no statistically significant differences between TAF and TDF groups for other efficacy outcomes, including change from baseline in HBV DNA and ALT, and in the proportion of patients with HBsAg loss/seroconversion. Fibrosis scores, assessed by FibroTest, were improved with TAF therapy versus TDF, [redacted], and no adjustment was made for multiple statistical comparisons. There were no deaths in either study, and clinical outcomes such as morbidity, as well as health-related quality of life and symptoms, were not assessed. There were no notable differences in the proportion of patients experiencing an adverse event or a serious adverse event or withdrawing due to an adverse event. Notable harms such as bone-related adverse events (e.g., fractures) and renal events were infrequent, with no notable differences between groups. Bone health was also formally assessed as a secondary outcome using BMD, and there was a statistically significant improvement in scores (hip and spine) for TAF compared with TDF in both studies. Renal function, formally assessed by serum creatinine, declined less for TAF versus TDF. However, these differences were statistically significant only in one of the two studies.

2 This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

Two patient groups, the Canadian Liver Foundation (CLF) and the Hepatitis C Education and Prevention Society (HepCBC), provided input for this submission. The CLF, founded in 1969, is the only national health charity as well as the first organization in the world of its kind dedicated to directing funds for research into causes, preventive measures, and potential treatments for all forms of liver disease. HepCBC, founded in 1996, is a non-profit organization, run by people infected with, or affected by, viral hepatitis. Both the CLF and HepCBC are involved in a number of health education and prevention programs, peer support programs, and outreach activities. HepCBC disseminates hepatitis-related information through a variety of channels and among different population segments; it also provides support and encourages screening for hepatitis among groups considered at risk, either because of a history of exposure to the virus or because of coinfection with other viral diseases (e.g., HIV).

The CLF receives funding from pharmaceutical companies and donations from individuals to support its programs and activities. Grants of more than $50,000 from Gilead Sciences and Bristol-Myers Squibb Canada were reported by the CLF; however, these were not related to hepatitis B, and the grant agreements prohibit the funders from influencing the program objectives and deliverables. HepCBC receives funding for various viral hepatitis–oriented educational and awareness programs, including the costs incurred by the authors for attendance at educational conferences and meetings, from the following pharmaceutical companies: Merck Pharmaceuticals, Lupin Pharmaceuticals, Gilead Sciences, Janssen Pharmaceuticals, Bristol-Myers Squibb, and AbbVie, as well as from Innovative Medicines Canada, an association representing Canada's research-based pharmaceutical companies.

2. Condition-Related Information

The information for the CLF submission was collected from five patients and three caregivers and health care professionals through an online questionnaire modelled after the CADTH program submissions template. The online survey was available in three languages (English, French, and Chinese) and was made available both online and to CLF contacts across Canada at the beginning of October 2017. In contrast, two authors contributed to the HepCBC submission, after unsuccessful efforts to collect first-person data from patient and caregiver surveys from online sources and from patients of a local physician who treats patients with hepatitis B virus (HBV). One author was a researcher and a patient advocate, and was familiar with general patient concerns, research, and treatments in HBV. The other author was living with hepatitis C virus (HCV) and was familiar with health concerns of patients and caregivers of liver disease and viral hepatitis through working on HepCBC's support lines and outreach activities for patients.

Estimates of the prevalence of patients living with chronic hepatitis B (CHB) infection in Canada reported by the two patient groups ranged from approximately 420,000 to 600,000. Populations considered to be at high risk of HBV are immigrants, particularly from HBV-endemic countries; their spouses and children; aboriginal people; intravenous drug users; sex workers; prisoners; and men who have sex with men.

Infection with HBV may remain silent for decades, and a large proportion of infected individuals are asymptomatic. These people can therefore pass the disease on to others

unknowingly, a problem facilitated by lack of awareness of the risk factors for HBV infection. Among those with symptoms, symptom onset may indicate early signs of the disease or a late stage of infection and complications resulting from substantial liver damage. The symptoms negatively impact the physical, financial, psychological, and social aspects of an affected individual. Commonly reported symptoms among people with CHB infection and liver damage include fatigue, muscle weakness, poor appetite, weight loss, itchy skin, and jaundice. Over time, the risk of cirrhosis increases, which can be manifested as varices, ascites, edema, and hepatic encephalopathy. Progressive liver damage may also result in hepatocellular carcinoma (even before decompensation), decompensated liver disease, and premature death. In addition, patients with chronic liver damage are known to suffer from a number of comorbidities, including diabetes, hypertension, hyperlipidemia, chronic kidney disease, and osteoporosis. Early diagnosis is therefore critical in slowing the progression of the disease through lifestyle modifications and medications.

“I feel internal tremors in my body and spasm in my extremities. I also feel pain on the right upper quadrant and back.” – Patient

“Most are asymptomatic until they develop decompensated cirrhosis and need a liver transplant or have advanced cancer, in which case, there are no curative options, only palliative options, including sorafenib.” – Health Professional

CHB infection and the resulting liver damage are associated with a strong social stigma, which limits an individual’s life opportunities such as employment prospects, relationships, plans for immigration, and even eligibility for loans and life insurance. This often discourages patients from disclosing their status, or from undergoing testing or treatments for HBV out of fear of social stigma and prejudice, affecting both themselves and family members. The fear of disclosing can go to the extent that patients indicate alcoholism as the cause of cirrhosis rather than CHB infection. Caregivers may also face significant burden resulting from a loss of employment particularly if they are also infected, and social stigma. Due to a general ignorance about HBV risk factors, people tend to avoid casual contact with the infected individuals or their caregivers, thus resulting in social isolation which may lead to stress, mental illness, and divorce. When a child has contracted HBV from his/her mother while in the womb, the mother may feel guilty or the child may feel resentment, leading to emotional distress.

3. Current Therapy-Related Information

The information for this section was obtained from the CLF’s online questionnaire and from the HepCBC authors’ experience working with high-risk groups and health professionals.

The treatments for CHB infection are aimed at improving quality of life, preventing or reversing progression of liver disease to liver failure, minimizing the risk of developing liver cancer and of transmitting the virus to others. Currently available treatments in Canada are targeted to minimize the progression of liver damage by controlling viral load. These include interferon injections, lamivudine, adefovir, telbivudine, tenofovir, and entecavir. According to the Canadian Association for the Study of the Liver (CASL), tenofovir or entecavir should be used as the first-line treatment, particularly for treatment-naive patients, due to their high potency and relatively low or nonexistent rates of antivirus resistance. These two drugs suppress HBV virus replication; prevent or reverse fibrosis progression, cirrhosis, and decompensation; and reduce the risk of liver cancer.

Both patient groups indicated that entecavir and tenofovir are quite effective and well-tolerated; however, long-term use of these drugs may lead to resistance and weakening of

the kidney function and metabolic bone disease. Renal function should be monitored regularly with any antiviral treatment, due to excretion by the kidneys. Adjustment of dosage may be required to prevent serious kidney damage. Entecavir is often in short supply across Canada. Lamivudine is known to have a high risk of resistance. Interferons are rarely used today.

4. Expectations About the Drug Being Reviewed

The information for this section came from the online questionnaire by the CLF. Authors of the HepCBC report gathered information through research, manufacturer-provided product monographs, webinars, the CASL and Public Health Agency of Canada guidelines and information bulletins, and consultations with a local HBV specialist.

The CLF report indicated three characteristics expected from an improved CHB treatment: control of viral load, prevention of resistance, and avoidance of kidney and bone complications. Since CHB medications are taken for life, care should be taken to ensure safety for liver as well as other organs. Therefore, physicians would prefer customized treatment and lower doses to meet the efficacy and safety standards as well as patients' needs. The HepCBC report echoed similar expectations from the treatment. Patients with chronic liver disease expect the new treatment to prevent liver cancer, liver and kidney failure, and transmission of HBV to their children and spouse by suppressing the virulence and effects of the disease.

Although tenofovir alafenamide fumarate (TAF) had not been used by the respondents, patients were interested in taking or inquiring about TAF, and health care providers showed confidence in the drug following the Notice of Compliance by Health Canada and FDA approval in the US. They emphasized that findings from clinical trials spanning 96 weeks showed TAF to be generally equivalent to the older drug, tenofovir disoproxil fumarate (TDF) in viral suppression, risk of resistance, and safety. However, due to the differences in molecular structure, TAF requires approximately one-tenth of the dose needed with TDF (daily dosage 25 mg versus 300 mg, respectively). The lower dosage of tenofovir translates to a decreased potential for kidney and bone damage for longer periods, which was supported by clinical trials. Therefore, the need to reduce dosage because of renal impairments (creatinine clearance < 50 mL/minute) is less likely. In addition, TAF showed faster and greater normalization of alanine transaminase, a marker of liver damage, compared with TDF in trials. These two characteristics are a significant advantageous factor for TAF. However, physicians suspect that not all patients could afford the treatment for many years, given its high price, and therefore this drug may not be prescribed until damage to kidneys and bone is obvious.

"Tenofovir dipivoxil (Viread) is an efficacious antiviral agent, but the risk of nephrotoxicity after many years of use is very problematic, as is the risk of metabolic bone disease. Vemlidy is a safer option that has antiviral efficacy." – Health Professional

5. Additional Information

Both the CLF and the HepCBC expressed an interest in making TAF available in order to broaden the available treatment options. Authors of the HepCBC report recommended close monitoring of the following in regard to TAF use: fasting low-density lipoprotein cholesterol, fasting glucose, and urine glucose levels; resistance at individual and population levels; new contraindications; efficacy in high-risk populations; effect of genetic and environmental factors; and possible drug interactions.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present Ovid MEDLINE(R) ALL 1946 to present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of search:	October 27, 2017
Alerts:	Bi-Weekly search updates until (February 21, 2018)
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
medall	Ovid database code; Ovid MEDLINE(R) ALL 1946 to present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Searches**
1	(vemlidy* or (tenofovir* adj2 alafenamide*) or (GS adj2 "7340") or TAF or GS-7340).ti,ab,ot,kf,hw,rn,nm.
2	(379270-37-8 or 377091-31-1).rn,nm.
3	1 or 2
4	exp Hepatitis b/ or exp hepatitis b, chronic/ or exp liver/ or exp liver diseases/ or exp acute-on-chronic liver failure/ or exp liver cirrhosis/
5	(hepatitis b or hepatitisB or hbv or liver or livers or hepatic* or hepatitis or cirrhosis or cirrhotic*).ti,ab,ot,kf,hw.
6	4 or 5
7	3 and 6
8	7 use medall
9	*tenofovir alafenamide/
10	(vemlidy* or (tenofovir* adj2 alafenamide*) or (GS adj2 "7340") or TAF or GS-7340).ti,ab,ot,kw.
11	9 or 10
12	exp Hepatitis b/ or exp compensated liver cirrhosis/ or exp chronic liver disease/ or exp liver/
13	(hepatitis b or hepatitisB or hbv or liver or livers or hepatic* or hepatitis or cirrhosis or cirrhotic*).ti,ab,ot,kw.
14	12 or 13
15	11 and 14
16	15 use oemezd
17	conference abstract.pt.
18	16 not 17
19	8 or 18
20	remove duplicates from 19

OTHER DATABASES		
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.	

Grey Literature

Dates for Search:	October 23, 2017 – October 24, 2017
Keywords:	Vemlidy (tenofovir alafenamide), chronic hepatitis B
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

Appendix 3: Excluded Studies

Reference	Reason for Exclusion
Agarwal, J Hepatol 2015[25]	Doses not relevant

Appendix 4: Detailed Outcome Data

Table 9: Other Efficacy Outcomes

	Study 108		Study 110	
	TAF 25 mg (N = 285)	**TDF 300 mg (N = 140)**	**TAF 25 mg (N = 581)**	**TDF 300 mg (N = 292)**
Virology				
Mean (SD) baseline HBV DNA, log_{10} IU/mL	5.75 (1.341)	5.77 (1.321)	7.59 (1.338)	7.62 (1.408)
Mean (SD) change from baseline week 48, log_{10} IU/mL	−4.31 (1.296)	−4.33 (1.311)	–5.75 (1.310)	–5.83(1.427)
LSM difference between groups (95% CI)	[redacted]		[redacted]	
Mean (SD) change from baseline week 96, log_{10} IU/mL	[redacted]	[redacted]	[redacted]	[redacted]
LSM difference between groups (95% CI)	[redacted]		[redacted]	
ALT Normalization[c]				
Normalized ALT (central), week 48, n (%)	196 (83.1)	91 (75.2)	384/537 (71.5)	179/268 (66.8)
Difference in proportions (95% CI)[b]	8.0% (−1.3% to 17.2%) *P* = 0.076		4.6% (–2.3% to 11.4%) *P* = 0.18	
Normalized ALT (central), week 96, n (%)	191 (80.9)	86 (71.1)	405/537 (75.4)	181/268 (67.5)
Difference in proportions (95% CI)[b]	9.8% (0.2% to 19.3%) *P* = 0.038		8.0% (1.2% to 14.7%) *P* = 0.017	
Normalized ALT (AASLD), week 48, n (%)	137 (49.6)	44 (31.9)	257 (44.9)	105 (36.2)
Difference in proportions (95% CI)[b]	17.9% (8.0% to 27.7%) *P* < 0.001		8.7% (1.8% to 15.6%) *P* = 0.014	
Normalized ALT (AASLD), week 96, n (%)	139 (50.4)	55 (39.9)	299/572 (52.3)	121/290 (41.7)
Difference in proportions (95% CI)[b]	10.9% (0.8% to 21.0%) *P* = 0.035		10.6% (3.6% to 17.6%) *P* = 0.003	
Mean (SD) baseline ALT, U/L	94 (88.3)	94 (80.8)	117 (105.1)	125 (128.2)
Mean (SD) change in ALT from the baseline, U/L, week 48	−66.8 (90.58) *P* = 0.65	−62.0 (84.70)	–84.4 (110.17) *P* = 0.95	−84.2 (127.19)
Mean (SD) change in ALT from the baseline, U/L, week 96	[redacted]	[redacted]	[redacted]	[redacted]
HBsAg Loss/Seroconversion[d]				
HBsAg loss, week 48, n (%)	0	0	4 (0.7)	1 (0.3)
HBsAg seroconversion, week 48, n (%)	0	0	3	0
HBsAg loss, week 96, n (%)	1/281 (0.4)	0/138	7/576 (1.2)	4/288 (1.4)
Difference in proportions (95% CI)[b]	0.1% (–2.5% to 2.7%) *P* = 0.72		-0.1% (–2.0% to 1.8%) *P* = 0.88	
HBsAg seroconversion, week 96, n (%)	1/281 (0.4)	0/138	6 (1.0)	0
HBeAg Loss/ Seroconversion[e]				
HBeAg loss, week 96, n (%),	NR	NR	123/565 (21.8)	51/285 (17.9)
Difference in proportions (95% CI)[b]			3.7% (–1.9% to 9.4%), *p* = 0.20	
HBeAg seroconversion week 96, n (%)	NR	NR	99/565 (17.5)	35/285 (12.3)

	Study 108		Study 110	
Difference in proportions (95% CI)[b]			5.1% (0.2% to 10.1%), *P* = 0.050	
Fibrosis				
Mean (SD) baseline FibroTest	0.43 (0.223)	0.45 (0.229)	0.34 (0.227)	0.32 (0.225)
Mean (SD) change from baseline in FibroTest scores, week 96	[redacted]	[redacted]	[redacted]	[redacted]
Difference in LSM (95% CI)[f]	[redacted]		[redacted]	
Resistance[g]				
Viral resistance mutations detected, week 48, n	0	0	0	0

AASLD = American Association for the Study of Liver Disease; ALT = alanine aminotransferase; CI = confidence interval; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; SD = standard deviation; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

[redacted]

[b] Difference in the proportion between treatment groups and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HBV DNA categories and oral antiviral treatment status strata.

[c] ALT normalization was defined as ALT greater than ULN (by central laboratory normal range or AASLD normal range) at baseline but within normal range at a post-baseline visit.

[d] HBsAg loss was defined as a change in HBsAg result from HBsAg-positive at baseline to HBsAg-negative at a post-baseline visit, with baseline anti-HBs negative or missing. HBsAg seroconversion was defined as HBsAg loss and a change in anti-HBs test from anti-HBs negative or missing at baseline to anti-HBs positive at a post-baseline visit.

[e] HBeAg loss occurred if HBeAg went from HBeAg-positive at baseline to HBeAg-negative at a post-baseline visit, with baseline anti-HBe negative or missing. HBeAg seroconversion occurred if a patient had an HBeAg loss and a change in anti-HBe result from anti-HBe negative or missing at baseline to anti-HBe positive at a post-baseline visit.

[f] *P* value, difference in least squares means, and its 95% CI were from analysis of variance (ANOVA) model with baseline HBV DNA categories, oral antiviral treatment status, and treatment group as fixed effects in the model.

[g] Viral resistance: Sequence analyses were performed on all subjects who experienced virologic breakthrough at week 48, discontinued the study at or after week 24 with HBV DNA ≥ 69 IU/mL, or had HBV DNA ≥ 69 IU/mL at week 48 in the absence of virologic breakthrough (TAF, n = 7; TDF, n = 3).

Source: Clinical Study Reports for Studies 108[10] and 110.[11]

Table 10: Subgroup Data for Primary Outcome (Patients With Undetectable HBV DNA)

	Study 108		Study 110	
Virology Patients with HBV DNA <29 IU/mL, n (%)	**TAF 25 mg (N = 285)**	**TDF 300 mg (N = 140)**	**TAF 25 mg (N = 581)**	**TDF 300 mg (N = 292)**
By prior therapy				
Week 48 data				
Treatment-experienced	56/60 (93.3)	28/30 (93.3)	69/137 (50.4)	39/69 (56.5)
Difference between groups [95% CI][a]	[redacted]		[redacted]	
Treatment-naive	212/225 (94.2)	102/110 (92.7)	302/444 (68.0)	156/223 (70.0)
Difference between groups [95% CI][a]	[redacted]		[redacted]	
Test for homogeneity	*P* = 0.82		*P* = 0.68	
Week 96 data				
Treatment-experienced	54/60 (90.0)	26/30 (86.7)	92/137 (67.2)	50/69 (72.5)
Difference between groups [95% CI][a]	[redacted]		[redacted]	
Treatment-naive	203/225 (90.2)	101/110 (91.8)	331/444 (74.5)	168/223 (75.3)

	Study 108		Study 110	
Difference between groups [95% CI][a]	[redacted]		[redacted]	
Test for homogeneity	[redacted]		[redacted]	
By baseline HBV DNA				
Week 48 data				
Study 108: < 7 log_{10} IU/mL	221/230 (96.1)	108/116 (93.1)	-	-
Difference between groups [95% CI][a]	3.8% (−1.9% to 9.6%)			
Study 108: ≥ 7 to < 8 log_{10} IU/mL	38/42 (90.5)	20/20 (100.0)	–	–
Difference between groups [95% CI][a]	NR			
Study 108: ≥ 8 log_{10} IU/mL	8/13 (61.5)	3/4 (75.0)	–	–
Difference between groups [95% CI][a]	NR			
Study 108: < 7 log_{10} IU/mL	221/230 (96.1)	107/116 (92.2)	–	–
Difference between groups [95% CI][a]	3.8% (−1.9% to 9.6%)			
Study 108: ≥ 7 log_{10} IU/mL	47/55 (85.5)	23/24 (95.8)	–	–
Difference between groups [95% CI][a]	−10.4% (−25.2% to 4.5%)			
Test for homogeneity	*P* = 0.080			
Study 110: < 8 log_{10} IU/mL	–	–	254/309 (82.2)	123/150 (82.0)
Difference between groups [95% CI][a]			0.1% (–7.4% to 7.5%)	
Study 110: ≥ 8 to < 9 log_{10} IU/mL	–	–	111/225 (49.3)	68/113 (60.2)
Difference between groups [95% CI][a]			NR	
Study 110: ≥ 9 log_{10} IU/mL	–	–	6/47 (12.8)	4/29 (13.8)
Difference between groups [95% CI][a]			NR	
Test for homogeneity			NR	
Study 110: < 8 log_{10} IU/mL	–	–	254/309 (82.2)	123/150 (82.0)
Difference between groups [95% CI][a]			0.1% (–7.4% to 7.5%)	
Study 110: ≥ 8 log_{10} IU/mL	–	–	117/272 (43.0)	72/142 (50.7)
Difference between groups [95% CI][a]			–7.6% (–17.8% to 2.5%)	
Test for homogeneity	–	–	*P* = 0.34	
Week 96 data				
Study 108: < 7 log_{10} IU/mL	207/230 (90.0)	105/116 (90.5)	–	–
Difference between groups [95% CI][a]	[redacted]			
Study 108: ≥ 7 log_{10} IU/mL	50/55 (90.9)	22/24 (91.7)	–	–
Difference between groups [95% CI][a]	[redacted]			
Study 110: < 8 log_{10} IU/mL	–	–	260/309 (84.1)	121/150 (80.7)
Difference between groups [95% CI][a]			[redacted]	
Study 110: ≥ 8 log_{10} IU/mL	–	–	163/272	97/142 (68.3)

	Study 108		Study 110	
			(59.9)	
Difference between groups [95% CI][a]			[redacted]	
Test for homogeneity	[redacted]		[redacted]	
By baseline ALT (central lab normal range)				
Week 48 data				
≤ ULN	46/49 (93.9)	17/19 (89.5)	26/44 (59.1)	17/24 (70.8)
Difference between groups [95% CI][a]	5.5% (NC[b])		−3.2% (−25.4% to 19.0%)	
> ULN	222/236 (94.1)	113/121 (93.4)	345/537 (64.2)	178/268 (66.4)
Difference between groups [95% CI][a]	0.8% (−5.0% to 6.6%)		−3.5% (−10.0% to 3.1%)	
Test for homogeneity	*P* = 0.60		*P* = 0.82	
Week 96 data				
≤ ULN	[redacted]	[redacted]	[redacted]	[redacted]
Difference between groups [95% CI][a]	[redacted]		[redacted]	
> ULN	[redacted]	[redacted]	[redacted]	[redacted]
Difference between groups [95% CI][a]	[redacted]		[redacted]	
Test for homogeneity	*P* = 0.42		*P* = 0.36	
By baseline FibroTest score				
Week 48				
< 0.75	237/249 (95.2)	110/119 (92.4)	332/521 (63.7)	172/260 (66.2)
Difference between groups [95% CI][a]	3.2% (−2.6% to 9.1%)		0.84 (0.60 to 1.18)	
≥ 0.75	27/31 (87.1)	19/20 (95.0)	31/45 (68.9)	17/22 (77.3)
Difference between groups [95% CI][a]	−6.2% (−29.3% to 17.0%)		0.77 (0.21 to 2.78)	
Test for homogeneity	*P* = 0.13		*P* = 0.90	
Week 96				
< 0.75	[redacted]	[redacted]	[redacted]	[redacted]
Difference between groups [95% CI][a]	[redacted]		[redacted]	
≥ 0.75	[redacted]	[redacted]	[redacted]	[redacted]
Difference between groups [95% CI][a]	[redacted]		[redacted]	
Test for homogeneity	*P* = 0.76		*P* = 0.22	

ALT = alanine aminotransferase; CI = confidence interval; HBV = hepatitis B virus; NC = not calculated; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

[a] Difference in response rates and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HBV DNA categories and oral antiviral treatment status strata (if not the subgroup factor).

[b] Due to small sample sizes, the point estimate is not reliably calculated.

Source: Clinical Study Reports for Studies 108[10] and 110.[11]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- FibroTest

Findings

FibroTest

Mortality associated with chronic hepatitis B (CHB) infection is mostly the result of liver cirrhosis, which is the final stage of fibrosis, and its complications.[26] The extent of liver fibrosis is therefore an important factor to determine the progression of disease and the need for treatment. Liver biopsy used to be considered the "gold standard" to assess fibrosis. However, biopsy has limitations associated with invasiveness, a risk of complications (rate 0.57%) and mortality (rate ranging from 0.009% to 0.12%), and sample and interobserver variability. Because of these issues with biopsy, several noninvasive biomarkers have been used and validated, and these have variable diagnostic accuracy.[19]

FibroTest (FT, developed by Biopredictive, Paris, France; also known as FibroSURE developed by LabCorp, Burlington, North Carolina, USA) is a composite of five serum biochemical parameters — alpha-2-macroglobulin, apolipoprotein A1, haptoglobin, gamma-glutamyltranspeptidase, and bilirubin. It also takes into account patients' age and sex. Values of FT range from 0 to 1, and fibrosis worsens as the FT score increases.[19] The manufacturer-recommended cut-off values are < 0.31, no or minimal fibrosis; 0.32 to 0.58, moderate fibrosis; > 0.58, advanced or severe fibrosis (cirrhosis).[20] The manufacturer also provided cut-offs for FT that corresponded to the METAVIR histological score (minimal, F0 to F1; significant, ≥ F2 to < F3; and advanced, ≥ F3 to F4) based on biopsy; 0.27 for F1, 0.48 for F2, 0.58 for F3, and 0.74 for F4.[21] The FT cut-off ranges to determine fibrosis stage that were selected in the two studies being reviewed in by the CADTH Common Drug Review here were slightly different than the manufacturer-recommended ones: 0 to 0.48, 0.49 to 0.74, 0.75 to 1. This indicates that the degree of severity of fibrosis can be interpreted differently based on the cut-offs used. The cut-off for moderate fibrosis (0.49 to 0.74) used in the studies overlapped with that of severe fibrosis recommended by the manufacturer (0.58), a finding corroborated by the clinical expert.

A number of studies, including meta-analyses, have been conducted to assess the validity and diagnostic and prognostic accuracy of FT in the CHB population. The results from meta-analyses are summarized in Table 11. Only one meta-analysis, by Salkic et al.,[19] was designed to estimate an overall summary of the diagnostic accuracy of FT for predicting CHB-related fibrosis. In addition, the authors estimated the diagnostic accuracy using cut-offs similar to the ones recommended by the manufacturer. As can be seen in Table 11, FT showed a satisfactory diagnostic accuracy (area under the receiver operating curve [AUROC] 0.84) for fibrosis; however, the sensitivity of the test was suboptimal. When estimates were generated using manufacturer-recommended cut-offs to categorize fibrosis stage, any score below 0.48 was similar in diagnostic performance to the pooled estimate; however, the sensitivity of the test dropped to approximately 62% for an FT score of 0.48 (significant fibrosis). Overall diagnostic accuracy was similar for cirrhosis (AUROC 0.87),

with suboptimal sensitivity. When different cut-offs for cirrhosis were used, a score of 0.74 was associated with low sensitivity, approximately 61%. On the other hand, a score below 0.74 had a similar or improved diagnostic performance compared with the pooled estimates. These results indicate that FT has high specificity for fibrosis and cirrhosis, but its sensitivity is suboptimal for cut-offs greater than 0.48 and 0.74, respectively. The authors concluded that FT should be accompanied by other noninvasive modalities to improve accuracy of detection of liver fibrosis, particularly for significant fibrosis and cirrhosis.[19]

The developers of FT recommended that it be used as a continuous rather than binary variable; however, in clinical practice, making the distinction between different stages of liver disease is important for prescribing antiviral treatment. Therefore, the optimum FT thresholds for detection should be carefully chosen, balancing other parameters.[19] One group of researchers, for example, indicated that significant fibrosis should be identified with at least 85% sensitivity and specificity. Since a diagnosis of liver fibrosis can be confirmed by repeating noninvasive tests like this or by conducting additional tests, the relevant clinical consequences of false-positives or false-negatives above the 85% cut-off are minimal[27]

Xu et al.[28] conducted a meta-analysis by pooling results separately for studies validating FT for fibrosis and cirrhosis. Results showed a similar diagnostic accuracy, with standardized AUROCs (adjusted for spectrum of fibrosis stages) of 0.84 and 0.90 for significant fibrosis (F2 to F4) and cirrhosis (F4), respectively.

Another meta-analysis conducted by the developers of FT, Poynard et al.,[29] was a regular update of the previously published meta-analyses by the same group on the clinical validation of FT in CHB patients. The meta-analysis assessed the differentiation of nonadvanced fibrosis (F0 to F1) from advanced fibrosis (F2 to F4) using FT. Two separate meta-analyses were performed: one with data from all identified published studies, and the other using individual data included in an integrated database managed by the developers. The standardized AUROC for FT was 0.84 and 0.85 for the diagnosis of advanced fibrosis and cirrhosis, respectively. The performance of FT to differentiate fibrosis stages was evaluated using the Obuchowski measure, a multinomial version of the AUROC, which is interpreted as the probability that the index will accurately rank two randomly chosen patient samples from different fibrosis stages based on a weight, with a penalty for misclassifying patients. Results showed the overall mean accuracy of FT for different fibrosis stages was 0.844. The authors recommended using FT as a first-line diagnostic procedure, with a moratorium on liver biopsy, but advised using other procedures to make decisive diagnosis and staging.

Biomarkers for progressive liver disease should be validated with clinical end points in addition to validating their accuracy of diagnosing and distinguishing between stages of the disease. A meta-analysis was performed by the developers of FT to assess the five-year comparative prognostic value of this biomarker, along with several others, in patients with chronic liver disease.[30] Of the six included studies, only one study used FT measurement among patients with HBV. It found a high overall AUROC for prognostic value of 0.94. However, no information regarding minimal clinically important difference (MCID) or time to detect an MCID was available from any of the reviewed studies.

Table 11: Validity of FibroTest in Diagnosis and Prognosis of HBV Across Meta-Analyses

Ref	Disease or Stage	Cut Point	AUROC	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, %	NPV, %
Salkic et al. 2014 [19] 16 studies (N = 2494)	CHB-related fibrosis (F1 to F2)	Summary estimate	0.84 (0.78 to 0.88)	71.2 (64.6 to 77.1)	81.4 (74.8 to 86.6)	79.3	73.9
		0.31 (F1)	0.85	76.5 (65.1 to 85.0)	78.8 (62.7 to 89.2)	78.3	77.0
		0.31 to 0.48 (F1 to F2)	0.86	73.3 (64.6 to 80.6)	83.8 (73.9 to 90.4)	81.9	75.8
		0.48 (F2)	0.78	62.3 (46.8 to 75.6)	79.4 (69.0 to 86.9)	75.2	67.8
Salkic et al. 2014 [19] 13 studies (N = 1754)	CHB-related cirrhosis (F4)	Summary estimate	0.87 (0.85 to 0.90)	71.5 (62.1 to 79.3)	87.0 (83.8 to 89.6)	57.9	92.4
		0.74	0.87	61.5 (46.6 to 74.5)	90.8% (88.0 to 93.0%)	62.6	90.4
		< 0.74	0.88	79.9 (71.7 to 86.2)	83.5 (79.6 to 86.7)	54.5	94.3
Xu et al. 2014 [28] 11 studies (N = 1640)	CHB-related fibrosis (F2 to F4)	Summary estimate	0.84 (0.69 to 0.90)	NR	NR	NR	NR
Xu et al. 2014 [28] 9 studies (N = 1101)	CHB-related cirrhosis (F4)	Summary estimate	0.90 (0.68 to 0.92)	NR	NR	NR	NR
Poynard et al. 2011 [29] 8 studies (N = 1842)	CHB-related advanced fibrosis	Summary estimate	0.84 (0.79 to 0.86)	NR	NR	NR	NR
	CHB-related cirrhosis	Summary estimate	0.85 (0.80 to 0.90)	NR	NR	NR	NR
Poynard et al. 2011 [30] 1 study (N = 978)	HBV	Summary estimate	0.94	NR	NR	NR	NR

AUROC = area under the receiver operating curve; CHB = chronic hepatitis B; NPV = negative predictive value; NR = not reported; PPV = positive predictive value.

Table 12: Summary of MCID Findings for Fibrotest

Instrument	Type	Evidence of Validity	MCID	References
FibroTest	A combination of serum biomarkers (alpha-2-macroglobulin, apolipoprotein A1, haptoglobin, gamma glutamyltranspeptidase, and bilirubin)	Yes, but suboptimal sensitivity	Unknown	[19,28,30]

Conclusion

There have been several studies to determine the validity of FT in accurately diagnosing and determining the stage of liver disease among patients with HBV. A number of meta-analyses with varied methodologies, number of studies, and patient populations have compared the diagnostic and prognostic performance of FT with several noninvasive biomarkers as well as biopsy. While FT has shown to be a valid measure that is similar in diagnostic performance to noninvasive measures, it has suboptimal sensitivity in detecting significant (F2) and advanced/cirrhosis (F4) fibrosis. Therefore, it is recommended for use in combination with other biomarkers for conclusive diagnosis and prognosis. There was no information on the MCID of FT.

Appendix 6: Summary of Open-Label Studies

Objective

To provide a summary of efficacy and safety data from the open-label (OL) phase of Studies 108 and 110 in patients receiving TAF 25 mg once daily for the treatment of HBeAg-negative and HBeAg-positive chronic hepatitis B (CHB), respectively.

Methods

Patients who completed the 96- or 144-week double-blind phase were allowed to enter an OL extension period for up to an additional 48 and 240 weeks, respectively (i.e., a total of 144 and 340 weeks, respectively). No additional selection criteria were in place for patients to enter the OL period. The study is ongoing, and only interim data for patients randomized to receive double-blind treatment for 96 weeks and OL treatment for up to week 144 are available and discussed in this report. During the OL period, all patients, regardless of their treatment status during the double-blind phase, received 25 mg tenofovir alafenamide (TAF) once daily. As in the double-blind phase of the studies, HBV virology and serology, laboratory parameters, fibrosis, and adverse events (AEs) were monitored throughout the OL phase. Patients who permanently stopped TAF treatment either before week 96 or before the end of the study period (week 384) and who did not have HBsAg loss and confirmed seroconversion to anti-HBs, were followed every four weeks for 24 weeks after discontinuing treatment or starting alternative HBV therapy, whichever occurred first.

The OL safety analysis set was defined as all randomized patients who received at least one dose of the study drug during the OL phase. This was identical to OL full analysis set (FAS) and was the primary analysis set for the OL safety analyses. Patients were analyzed according to the treatment group they were in during the double-blind phase, although both groups received the same study drug.

For the efficacy parameters, only the proportion of patients with HBV DNA < 29 IU/mL were summarized for the OL phase without any formal statistical testing. All safety data were also summarized descriptively. Values of baseline characteristics during the OL phase were reset as the last non-missing value obtained on or before day 1 of the OL treatment (day 14 for spine and hip bone mineral density assessment only). All missing values for the efficacy end point were considered excluded from the OL phase.

Patient Disposition

As described in Table 6, a total of 200 (47.1%) and 341 (39.1%) patients in Studies 108 and 110, respectively, entered the OL phase following the 96-week double-blind period. In Study 108, 134 (47.0%) patients continued to receive TAF 25 mg once daily, and 66 (47.1%) patients switched from tenofovir disoproxil fumarate (TDF) 300 mg treatment during the double-blind phase. No patients in the first group and two patients (1.4%) in the second group prematurely discontinued the OL treatment. In Study 110, 227 (39.1%) received TAF in both double-blind and OL phases, and 114 (39.0%) switched from TDF to TAF during the OL treatment. Eleven (11.9%) and 4 (1.4%) patients in the first and second groups, respectively, discontinued the OL treatment.

Results

[redacted] The results are described in Table 13.

Table 13: Patients With HBV DNA < 29 IU/mL During the Open-Label Phase

	Study 108		Study 110	
	OL TAF (DB TAF) (N = 134)	OL TAF (DB TDF) (N = 66)	OL TAF (DB TAF) (N = 226)	OL TAF (DB TDF) (N = 114)
Virology				
HBV DNA of at baseline				
< 29 IU/mL	[redacted]	[redacted]	[redacted]	[redacted]
≥ 29 IU/mL	[redacted]	[redacted]	[redacted]	[redacted]
HBV DNA at week 108				
< 29 IU/mL	[redacted]	[redacted]	[redacted]	[redacted]
≥ 29 IU/mL	[redacted]	[redacted]	[redacted]	[redacted]
HBV DNA at week 120				
< 29 IU/mL	[redacted]	[redacted]	[redacted]	[redacted]
≥ 29 IU/mL	[redacted]	[redacted]	[redacted]	[redacted]
HBV DNA at week 132				
< 29 IU/mL	[redacted]	[redacted]	[redacted]	[redacted]
≥ 29 IU/mL	[redacted]	[redacted]	[redacted]	[redacted]
HBV DNA at week 144				
< 29 IU/mL	[redacted]	[redacted]	[redacted]	[redacted]
≥ 29 IU/mL	[redacted]	[redacted]	[redacted]	[redacted]

HBV = hepatitis B virus; DB = double-blind; OL = open-label; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.
Source: Clinical Study Reports for Studies 108[10] and 110.[11]

In terms of harms, [redacted]

[redacted]The results are described in Table 14.

Table 14: Harms During the Open-Label Phase

	Study 108		Study 110	
	OL TAF (DB TAF) (N = 134)	OL TAF (DB TDF) (N = 66)	OL TAF (DB TAF) (N = 226)	OL TAF (DB TDF) (N = 114)
Adverse Events				
Subjects with > 0 AEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Hepatic lesion	[redacted]	[redacted]	[redacted]	[redacted]
Hepatic cirrhosis	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Coronary artery disease	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial ischemia	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]	[redacted]	[redacted]
Serious Adverse Events				
Subjects with > 0 SAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Most common SAEs[a]				
HCC	[redacted]	[redacted]	[redacted]	[redacted]
WDAE				
WDAEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Deaths				
Number of deaths, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Notable Harms				
Fractures, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Bone events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Osteopenia, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Osteoporosis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

	Study 108		Study 110	
Decreased bone density, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Renal impairment, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Abnormal laboratory parameters (any grade)				
Creatinine, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
eGFRCG (≥ 25% mL/min)	[redacted]	[redacted]	[redacted]	[redacted]
Fasting cholesterol, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Fasting LDL-C, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hepatic steatosis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
ALT, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; ALT = alanine aminotransferase; DB = double-blind; eGFRCG = estimated glomerular filtration rate (Cockcroft-Gault); HCC = hepatocellular carcinoma; LDL-C = low-density lipoprotein cholesterol; OL = open-label; SAE = serious adverse event; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; WDAE = withdrawal due to adverse events.
Source: Clinical Study Reports for Studies 108[10] and 110.[11]

Limitations

The two extension studies were OL studies. The study results were descriptive in nature and no between-group analyses were conducted. Since all patients received the same study drug at the same dose, the design was essentially a single-arm trial, and therefore lacked a control group for comparison. Data for the serologic and biochemical efficacy parameters, which would provide information to assess long-term efficacy, are currently unavailable. Considering the lifelong nature of the disease, data on whether efficacy, safety and tolerability are sustained beyond the follow up currently available from these extension studies are needed. Therefore, the complete 384-week OL data will provide additional evidence to assess the long-term safety profile of TAF.

Conclusions

The extension period of Studies 108 and 110 provided additional OL data to assess the efficacy and safety of TAF. Most patients in both trials experienced viral suppression below the threshold limit by week 144. Less than one-third of the patients experienced AEs, with not more than 10 SAEs in each trial, and none were considered to be related to study treatment.

Appendix 7: Summary of Natural History, Diagnosis, Management, and Prognosis of HBV

Natural History

Hepatitis B virus (HBV) belongs to the Hepadnaviridae family of small, enveloped, primarily hepatotropic DNA viruses. HBV DNA is known to have 10 genotypes, A to J, owing to the lack of proofreading mechanisms in the viral genome during replication. Some genotypes are known to have a significant geographic preponderance. Genotype A is seen mainly in northwest Europe, North America, India, and Africa; genotypes B and C in Asia; genotype D in southern Europe, the Middle East, and India; genotype E in West and South Africa; genotype F in Central and South America; genotype G in the US and Europe; and genotype H in Central America.[31,32]

HBV transmission in high-endemic regions (Asia, Africa) primarily results from perinatal or horizontal infection early in childhood. In low-endemic regions (Western countries), transmission through high-risk sexual behaviour and injection drug use are the most common reasons for HBV infection, and the infection is found predominantly in adolescents and adults as a result.[32]

HBV infection is a dynamic process characterized by alternative cycles of replicative and nonreplicative phases. All patients therefore have some form of the virus in the active or inactive phase, depending primarily on host immune response to viral antigens. HBV infection can be broadly categorized as acute (primary) and chronic (persistent) infection, which may be asymptomatic or mild (without significant liver injury) to severe or fulminant. Acute infections in adults, whether symptomatic or otherwise, usually are self-limited, characterized by viral clearance from the blood and liver and lasting immunity to reinfection. A small percentage (3% to 5%) of the HBV primary infection cases in adults and up to 95% of children do not resolve and progress into persistent infection, characterized by continual viral replication in the liver and varying degrees of viremia. Like primary infection, persistent HBV infection can also be symptomatic or asymptomatic. Asymptomatic CHB carriers have subclinical infection and normal or nearly normal liver function and histology. Symptomatic CHB patients, on the other hand, have abnormal liver function and histologic features. Progression of liver fibrosis leads to cirrhosis, the end-stage in liver failure. in addition to liver injury. Approximately one-third of all cases of liver cirrhosis and half of all cases of hepatocellular carcinoma are attributable to CHB.[3,8,9,33]

The phase of CHB is commonly determined by measuring antigens produced by the virus and antibodies (Ab) produced by the body in response to an infection. The three proteins encoded by HBV that are an integral part of the viral structure include HBeAg (HBV envelope antigen, secreted dimeric protein), HBcAg (HBV core antigen, viral capsid protein), and PreS1/PreS2/HBsAg (large, medium, and small surface envelope glycoproteins). These viral proteins, as well as HBV DNA and alanine aminotransferase (ALT) levels, are used to classify CHB into four phases. The high replicative and low inflammatory immune-tolerant phase (phase 1), found more frequently in patients infected perinatally and in young adults, is characterized by the presence of serum HBeAg, HBsAg, and antibodies against HBc (anti-HBc), very high levels of HBV DNA (10^9 to 10^{10} IU/mL), normal ALT levels (ULN approximately 40 IU/L), and minimal or no liver necroinflammation or fibrosis. During this phase, the rate of spontaneous HBeAg loss is very low, and the individuals are highly contagious due to the high levels of HBV DNA. This phase typically lasts for two to four weeks but may last for years among those infected perinatally. HBeAg-

positive immune-active phase (phase 2), seen more commonly among individuals infected during adulthood, is characterized by the presence of serum HBeAg, high levels of HBV DNA, elevated ALT, and moderate or severe liver necroinflammation and accelerated progression of fibrosis. Most patients (67% to 80%) transition from the immune-active to an inactive phase characterized by spontaneous HBeAg seroconversion to antibodies against HBeAg (anti-HBe) and HBV viral suppression. This phase lasts for months to years. Patients who are unable to achieve viral suppression progress to the HBeAg-negative CHB phase (phase 3, previously known as inactive-carrier phase), lasting for many years or even a lifetime. During this phase, anti-HBe is present, HBV DNA level is low or undetectable (< 2,000 IU/mL), and ALT level is normal. Minimal liver necroinflammation and varying degrees of fibrosis are found, resulting from previous liver injury during the immune-active phase. Approximately 1% to 3% patients per year undergo spontaneous HBsAg loss and/or seroconversion, and the HBsAg level in these patients are typically low (< 10,000 IU/mL). Some inactive-carriers (approximately 4% to 20%) can experience reversions back to an HBeAg-positive state. A more advanced HBeAg-negative CHB phase (phase 4) is seen among some patients who seroconvert from HBeAg to anti-HBe. This phase is characterized by the absence of serum HBeAg, accompanied by detectable anti-HBe and fluctuating moderate to high levels of serum HBV DNA (lower than in HBeAg-positive patients) in 10% to 30% of seroconverted patients. In addition, fluctuating or persistently elevated ALT level, liver necroinflammation, and fibrosis are seen in 10% to 20% of these patients. The rate of spontaneous disease remission is low in this phase. Resolved CHB infection (categorized as phase 5 by the European Association for the Study of the Liver [EASL]) is characterized by the lack of HBsAg with detectable anti-HBs and anti-HBc in the serum. Also known as occult HBV infection, patients in this phase have normal ALT values and usually undetectable serum HBV DNA.

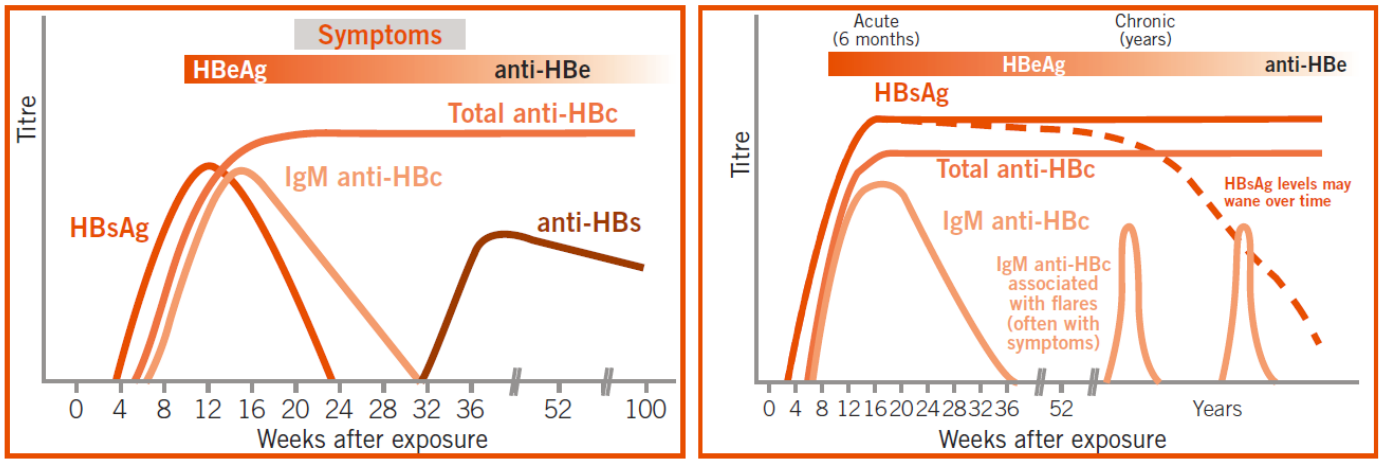
Hepatocellular carcinoma (HCC) occurs more commonly in chronically infected patients than in noncarriers, and the risk is particularly higher in the HBeAg-positive carriers. If HBsAg loss occurs before the onset of cirrhosis, then the risk of progression to cirrhosis, decompensation, HCC, and survival is low. However, if cirrhosis develops before HBsAg loss, the risk of HCC persists. Approximately 0.5% of patients with inactive CHB yearly achieve seroclearance, with the concomitant gain in anti-HBs. [8,9,33]

Diagnosis

The evaluation of CHB includes a complete history, physical examination, assessment of liver disease, and markers of HBV infection. A range of HBV markers are used as a testing profile to diagnose HBV infection, differentiate acute from chronic infection, determine disease stage and treatment strategy, and monitor disease progression and response to treatment. Patterns of HBV markers seen during acute and chronic HBV infection are shown in Figure 2. The presence of HBsAg in the blood is the first sign of viral infection, followed by a surge in anti-HBc within the first two weeks of the appearance of HBsAg, waning by six months. When detectable levels of HBsAg and HBeAg are both present, this indicates high levels of viral replication. HBeAg is associated with viremia and progressive liver disease. In acute HBV infection, viremia is spontaneously resolved by the host's immune response, and manifested as seroconversion to anti-HBe and lack of HBsAg and HBeAg. In the case of CHB, seroconversion of HBeAg to anti-HBe may be delayed for many years, and absence of HBeAg is usually accompanied with the presence of HBsAg. CHB is characterized by the presence of HBsAg for more than six months. Previously resolved HBV infection is defined by the presence of both anti-HBs and anti-HBc, whereas the presence of anti-HBs alone indicates immunity to HBV infection following vaccination.

HBV DNA level is used as a more direct and accurate measure of viral replication. It is correlated with disease progression, as advanced stage and viral resistance are associated with high viral load. Finally, the severity of liver disease is assessed by a battery of biochemical parameters and physical examination. The biochemical parameters include aspartate aminotransferase and ALT, gamma glutamyl transferase (GGT), alkaline phosphatase (ALP), bilirubin, serum albumin and gamma globulins, full blood count, and prothrombin time. Physical examination is done using noninvasive methods, such as ultrasonography, transient elastography, and testing for serum biomarkers of liver fibrosis, or using invasive biopsy.[8,33-35]

Figure 2: Patterns of HBV Markers in Acute and Chronic Infection



Anti HBc = antibodies against HBc; anti-HBe = antibodies against HBe; anti-HBs = antibodies against HBs; HBeAg = HBV envelope antigen; HBsAg = HBV surface antigen; IgM = immunoglobulin M.

Source: WHO guidelines on hepatitis B and C testing. Geneva: WHO; 2017. Licence: CC BY-NC-SA 3.0 IGO. (Fig. 4.2 and Fig. 4.3)[33]

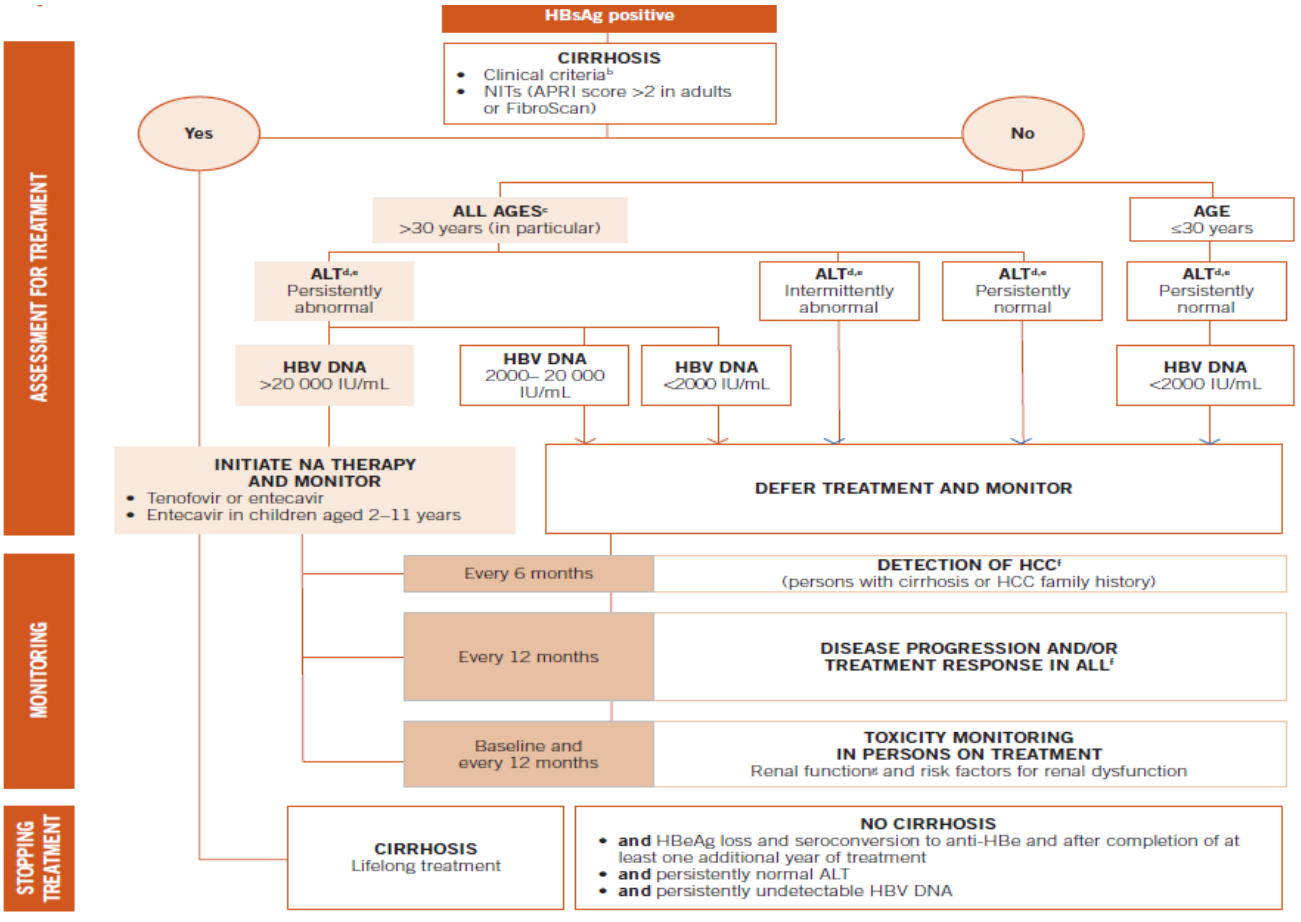
Serological assays are primarily used to screen for viral hepatitis by detecting viral antigens (HBsAg, HBeAg) or antibodies to viral antigens (anti-HBs, anti-HBc, anti-HBe). The presence of viral DNA is detected using nucleic acid testing (NAT). In addition, NAT is used to determine active infection, treatment eligibility, efficacy, and nonresponse or resistance. A number of assay technologies are available, and the method of choice depends on assay performance characteristics (sensitivity, specificity, and accuracy), cost, ease of use, and resources available. An abdominal ultrasound is routinely performed in most patients. In the case of inconclusive results from biochemical and HBV markers, noninvasive tests or liver biopsy are performed. Of the noninvasive methods, liver stiffness measurement by transient elastography and serum biomarkers of liver fibrosis are most common because of their relatively high diagnostic accuracy. However, these noninvasive tests perform better in excluding advanced fibrosis or cirrhosis, rather than confirming these and can be confounded by biochemical parameters. Therefore, they are often used in combination with different methods to assess liver damage.[8,33]

Management

A complete cure for CHB is yet to be discovered; therefore, current treatment is targeted primarily to improve survival and quality of life by preventing viral replication and disease

progression and consequently HCC. Further therapeutic goals are to prevent disease transmission to offspring, HBV reactivation, HBV-associated extrahepatic manifestations, and to achieve regression of fibrosis and cirrhosis. The decision whether to treat the disease or continue monitoring is based on patient's age and a number of HBV markers, including HBV DNA, serology, ALT levels, and the stage of liver disease. The treatment strategies are generally the same in CHB patients regardless of their HBeAg status. These markers should be monitored at least annually, and more frequently for patients receiving antiviral treatment, following such treatment, and not yet meeting the criteria for such treatment. While definite virologic, serological, and biochemical responses to treatment are established, acceptable histological response varies according to the methods used. The World Health Organization (WHO) guidelines has provided recommendations on assessment of patients for initiating or stopping treatment or for continued monitoring without treatment, based on an algorithm shown in Figure 3. The EASL and American Association for the Study of the Liver Disease guidelines largely corroborated these recommendations.[8,9,33]

Figure 3: Algorithm of WHO Recommendations on the Management of CHB



ALT = alanine aminotransferase; APRI = AST to platelet ratio index; HBeAg = HBV envelope antigen; HBsAg = HBV surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; NA = nucleoside analogue; NITs = noninvasive tests.

Source: WHO guidelines on hepatitis B and C testing. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO (p.70)[33]

According to the WHO HBV guidelines, treatment is recommended for all adults, adolescents, and children with CHB (i.e., persistence of HBsAg for more than six months) and clinical features of compensated or decompensated cirrhosis (i.e., ascites, variceal hemorrhage, hepatic encephalopathy, and jaundice), regardless of HBV DNA levels, ALT levels, and HBeAg status. Treatment is also recommended for adults with CHB without cirrhosis, aged 30 years or older, who have persistently high ALT levels (3 × upper limit of normal [ULN]) and a HBV DNA level of more than 20,000 IU/mL, regardless of HBeAg status. On the other hand, antiviral treatment is not recommended for people without clinical symptoms of cirrhosis, persistently normal ALT levels (< 30 U/L for men and < 19 U/L for women), and low levels of HBV replication (HBV DNA < 2,000 IU/mL), regardless of HBeAg status or age. For these individuals, as well as patients with CHB and the following characteristics, treatment is not recommended and continual monitoring (three or six to 12 months) is recommended instead: (1) people without cirrhosis, aged 30 years or younger, with HBV DNA greater than 20,000 IU/mL but persistently normal ALT; (2) HBeAg-negative people without cirrhosis, aged 30 years or younger, fluctuating HBV DNA between 2,000 and 20,000 IU/mL, but intermittently abnormal ALT levels.[8,33]

The level of HBV DNA used to measure viral replication is the strongest single predictive biomarker of disease progression. Therefore, antiviral therapies achieving viral suppression and subsequently inhibiting replication are considered the main end points of interest for CHB-induced fibrosis and cirrhosis.[33] Although a minimal HBV DNA level to indicate remission has not been established, the lower limit of detection (LOD) of modern assays, including the COBAS-AmpliPrep/COBAS Taqman 48 test, is sensitive enough to capture very low levels of viral DNA. The EASL guideline defines virologic response for nucleoside analogues (NA) as undetectable HBV DNA in the serum by a polymerase chain reaction–based assay with an LOD of 10 IU/mL. In patients who discontinue NA therapy, a serum HBV DNA level of < 2,000 IU/mL for at least 12 months following treatment discontinuation is considered sustained off-therapy virologic response. Partial virologic response is defined as a decrease of more than 1 $\log_{10}$ IU/mL, but a detectable level of HBV DNA for at least 12 months. Primary non-responsiveness is defined by a decrease of more than 1 $\log_{10}$ IU/mL in HBV DNA following three months of therapy. Of note, an increase in HBV DNA level of more than 1 $\log_{10}$ IU/mL compared with the on-treatment nadir level is considered virologic breakthrough.[8,9,33]

Normalization of ALT levels at approximately 40 IU/L is an established biomarker of liver damage and activity. Suppression of viral DNA to an undetectable level is typically associated with ALT normalization. However, there is a small chance of fibrosis regression in patients with persistently elevated levels of ALT with complete suppression of viral replication. In these patients, concomitant liver injury is commonly found, resulting from alcoholic or nonalcoholic fatty liver disease. It should be noted that ALT levels often fluctuate over time; therefore, a minimum of one- to two-year follow-up post-treatment at three-month intervals is recommended. Transient ALT flares in CHB patients indicate a good prognosis due to immune reconstitution.[8,9,33]

The loss of HBeAg and seroconversion to anti-HBe characterizes a low replicative (inactive) phase of CHB, which demonstrates partial immune control. However, HBeAg seroconversion can also be present during the HBeAg-negative immune reactivation phase of CHB. Thus, this end point is less reliable to detect disease progression, since the durability of the response can only be confirmed after treatment cessation. Hence, continuing antiviral therapies, regardless of HBeAg level, until HBsAg loss is an alternative treatment-stopping strategy. The loss of HBsAg is considered the optimal treatment end

point, also termed “functional cure,” since this indicates a suppression of viral replication and liver damage without complete eradication of HBV DNA. Therefore, HBsAg loss is a safe treatment discontinuation strategy; however, current treatments rarely achieve this end point. A small percentage of CHB patients may still develop HCC despite spontaneous HBsAg loss (annual rate approximately 0.55%). However, as described previously, the risk is lower if HBsAg loss is achieved at a younger age without significant fibrosis. A minimum level of HBsAg and HBeAg loss and development of anti-HBs and anti-HBe is not known however, the EASL guideline indicates that, for NAs, the effect on HBeAg loss is low in the first year, which increases to moderate with long-term treatment. The effect on HBsAg loss is also low, which slowly increases with treatment time in HBeAg-positive patients but stays very low in HBeAg-negative patients.[8,33]

Prognosis

According to the EASL guideline, the five-year cumulative incidence of cirrhosis ranges from 8% to 20% in untreated CHB patients. Among those with cirrhosis, the five-year cumulative risk of hepatic decompensation is 20%, and the annual risk of HCC ranges from 2% to 5%.[8] The factors affecting the rate of HBV disease progression can be broadly categorized as host-related, viral-related, and external.

Host factors associated with progression of CHB to cirrhosis and its complications include older age, male sex, and disease expression. Studies in Asian and Western populations indicate higher risk of cirrhosis and HCC in patients aged 40 years or older than in younger individuals. It is thought that the aging immune system may not adequately control the disease process, and increasing age is a proxy for a longer duration of HBV infection and liver disease. The risk of fibrosis is higher in male CHB carriers than in women. Although the mechanism for this sex-dependent pattern is unknown, estrogen has been proposed to have an antifibrogenic effect, thereby exerting a protective effect in females. The biochemical and histological expression of fibrosis at diagnosis correlates with the risk of cirrhosis; thus, the risk is higher for stage F3 compared with stage F1 or F2. The risk of progression of cirrhosis to decompensation and HCC is also higher among those with persistently elevated or repeated acute exacerbations of ALT or HBV DNA levels without normalization or viral suppression. Genetic susceptibility is thought to play a role in disease progression, as the risk of HCC is higher in individuals with a family history of HCC.[36,37]

Viral-related factors that affect disease prognosis include viral load, HBV genotypes and mutations, and concurrent infections. High levels of HBV DNA and viral replication accelerate the progression of CHB to cirrhosis, HCC, decompensation, and liver-related mortality. Delayed HBeAg and HBsAg seroclearance, and HBeAg seroreversion following spontaneous seroconversion, also indicate viral replication and fibrosis, and are therefore associated with an increased risk in cirrhosis. There is some evidence that genetic variants modulate the risk of progression of liver fibrosis, as a reduced risk of cirrhosis has been associated with polymorphisms in angiotensin and transforming growth factor beta genes. HBV genotypes have a unique geographic distribution, as discussed previously. Increasing evidence of the role of HBV genotypes in disease prognosis is emerging, particularly for genotypes A, B, C, and D. Studies show that patients with genotype C are more susceptible to cirrhosis and HCC than those with genotype B. However, the opposite finding has been reported in children and young adults. Positive associations have also been found between genotypes A, D, and F and liver cirrhosis and HCC; however, the findings are not consistent across studies. Effects of mutations in HBV DNA on disease prognosis have been documented, mainly in two naturally occurring mutations: pre-core G1896A and dual basal

core promoter (BCP) A1762T/G1764A. The BCP T1762/A1764 mutation increases the risk of liver damage and is found more commonly in genotype C, possibly explaining the poorer prognosis found with this genotype. Coinfection of HBV, HCV, and HDV have been shown to aggravate the severity and progression of liver disease to cirrhosis and ultimately to HCC. Coinfection of HBV and HIV is also known to increase the risk of cirrhosis.[36,37]

Environmental factors that have been shown to increase the risk of progression of liver damage to cirrhosis and HCC include chronic alcoholism, smoking, and dietary carcinogens such as aflatoxins. Prognosis of CHB patients with metabolic diseases, such as steatosis and nonalcoholic fatty liver disease, has been studied. However, the relationship between hepatic steatosis and the severity of fibrosis is inconclusive, and fibrosis is thought to result from metabolic syndrome (obesity, dyslipidemia, hypertension, and insulin resistance) instead. Similarly, data on the impact of diabetes and obesity on progression of liver disease are scarce and inconclusive.[36,37]

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