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ORIGINAL ARTICLE

First-line therapies for hepatitis B in the United States: A 3-year prospective and multicenter real-world study after approval of tenofovir alefenamide

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Abstract

Real-world data are limited on tenofovir alafenamide (TAF). We aimed to study TAF real-world outcomes with other first-line regimens for chronic hepatitis B (CHB). We enrolled patients with CHB from 10 centers retrospectively and followed them for 36 months prospectively. We analyzed switching patterns of antiviral therapy and treatment outcomes of TAF, tenofovir disoproxil fumarate (TDF), and entecavir therapy. For efficacy and safety, we analyzed a subset of patients with complete data at 24 months after switching to TAF or remaining on TDF or entecavir. Among 1037 enrollees, 889 patients were analyzed. The mean age was 52%, and 72% were hepatitis B e antigen–negative. After enrollment, shifts in therapies were mostly in reduced use of TDF from 63% to 30% due to switching to TAF. Clinical parameters were compared at enrollment or initiation to measures at 24 months for patients remaining on TAF (187), TDF (229), or entecavir (181). At 24 months, a significantly higher portion of patients on TAF achieved hepatitis B virus (HBV) DNA ≤20 IU/ml (93% vs. 86%; $p = 0.012$) and normalized alanine aminotransferase (ALT) (66% vs. 56%; $p = 0.031$) with stable estimated glomerular filtration rates (eGFRs). However, a higher percentage of the patient with eGFR <60 ml/mi/1.7 m^2 was observed in the TDF-treated group (9% vs. 4%; $p = 0.010$). In patients who remained on entecavir or TDF for 24 months, ALT and HBV-DNA results did not differ significantly from baseline. Treatment of CHB in the United States has significantly shifted from TDF to TAF. Our data suggest that switching from TDF or entecavir to TAF may result in increased frequency of ALT normalization and potential clearance of viremia at the 24-month time point.

INTRODUCTION

It is estimated that 1.4 to 3 million people in the United States live with chronic hepatitis B (CHB),[1] which is associated with a higher risk of progressing to liver cirrhosis and developing hepatocellular carcinoma (HCC).[2] The goal of treatment for CHB is to improve survival by preventing disease progression to cirrhosis, liver failure, and HCC.[3,4] On treatment, virological suppression has been associated with histological improvement and regression of cirrhosis, as well as reduced risk of hepatic decompensation and HCC and can be achieved by long-term treatment with antiviral agents.[3,4] Current international guidelines recommend entecavir (ETV), tenofovir alafenamide (TAF), and tenofovir disoproxil fumarate (TDF) as the first-line oral antiviral for CHB.[3,4] Although randomized controlled trials (RCTs) have reported the aforementioned antivirals' efficacy and safety profiles,[5–9] real-world data are very important in terms of providing a more complete picture of clinical outcomes in highly diverse patients encountered in routine practice and capturing uncommon adverse events underreported by RCTs.[10,11]

Several, but not all, real-world studies on TDF and ETV reported results in line with these clinical trials. In a study in Turkey on 355 treatment-naïve patients with CHB, Idilman et al. observed that ETV and TDF had similar efficacy and comparable safety profiles during a 4-year treatment.[12] Subsequently, larger studies in France and Germany showed that the outcomes of TDF in the real-world setting were consistent with results from pivotal trials.[13,14] In addition, several real-world studies in Asia reported similar outcomes of ETV or TDF therapy in Asian patients when compared with those in pivotal trials.[15–19] Another real-world study by Wong et al. in the United States suggested that the treatment outcomes of ETV and TDF were also comparable with those in pivotal trials.[20] However, in a recent report on 658 patients treated with ETV in the United States for a median duration of 4 years, Ahn et al. found that the alanine aminotransferase (ALT) normalization and hepatitis B virus (HBV) DNA suppression rates were lower than previously reported in pivotal trials.[21]

While many real-world studies have examined the efficacy and safety of ETV versus TDF, few have assessed the actual treatment patterns of the regimen used in the United States, especially since the availability of TAF, which was approved by the Food and Drug Administration in November 2016. Awareness of actual treatment patterns in the United States is particularly important for improving the quality of care for these patients because a recent study showed the inconsistency of practice patterns leading to different outcomes in the United States.[22] Furthermore, given the shorter time frame of TAF availability relative to other HBV therapies, data are limited on the real-world outcomes of TAF and the alternative options. With that in mind, we established the TRIO HBV registry and conducted a retrospective and prospective national cohort study in the United States between November 2016 and January 2020. We aimed to describe the antiviral treatment landscapes for CHB in the United States. In addition, the treatment outcomes on the first-line antiviral therapies were also compared. As the U.S. Department of Health and Human Services is developing the next National Strategic Plan: A Roadmap to Elimination for the United States, 2021–2025,[23] we believe that our study could provide evidence to potentially address the gap in the care for patients with CHB and important data of antiviral outcomes in the real-world setting, which are critical steps to reduce hepatitis B burdens in the United States.

METHODS

Study patient selections and data collection

This is a multicenter, observational, retrospective, and prospective study in the United States that enrolled 1037 adult patients with CHB (age above 18 years old) from November 2016, the approval date of TAF, to January 2017 with the intent of capturing clinical and treatment data at each office visit for 3 years after enrollment up to January 2020 (Figure S1). An additional 5 months following the observation period, through June 2020, was allowed for data entry by the provider. Patients with CHB on oral antiviral agents (including those patients who were treatment-naïve and initiating therapy) were eligible to be enrolled at the index visit. The exclusion criteria were as follows: patients with documented radiological or histological HCC, serum AFP > 500 ng/ml at enrollment, unlikely to survive at least 2 years, inability to participate in the follow-up for at least 2 years, or co-infected with human immunodeficiency virus. Patients were also excluded from the current study if they had undergone solid organ transplantation, received chemotherapy, were treated with other immunosuppressive therapy, or were enrolled in other clinical trials. For the qualification of being included in the final analysis data set, patients were required to have HBV virological testing at the baseline and completed a minimum follow-up of 24 months following enrollment. For the safety and efficacy data, the subset of patients who had complete virological data at baseline and month 24 were included. The data reported here were limited to 889 patients with known hepatitis B e antigen (HBeAg) status at enrollment and completed at least 2 years of follow-up (max and mean follow-up durations were 39 and 35 months, respectively).

Data were obtained from six academic and four community-based centers across the nation, serving 17 U.S. states. As visit times varied among practices,

patient assessments after the enrollment were assigned a nominal visit month every 6 ± 1 month (e.g., 6 months, 12 months) from the enrollment. Treatment details and laboratory measures were collected retrospectively at enrollment and limited to data no more than 180 days before enrollment. Prospective data were collected from the enrollment to the last visit within the observation period. Patient data were captured using an electronic case report form. Prompted data fields included patient demographics, CHB treatment at enrollment, treatment during the observation period, the reason for therapy change, adherence to therapy, and comorbidities such as anxiety, depression, hyperlipidemia, hypertension, diabetes mellitus, osteopenia, osteoporosis, hemodialysis, and chronic kidney disease. Outcome data including liver transplant or development of HCC were also recorded. Laboratory data and other test results were collected, which included the complete blood count, aspartate aminotransferase (AST), ALT, alkaline phosphatase, bilirubin, albumin, total protein, serum creatinine, alpha-fetoprotein (AFP), bone density T-scores, and HBV virological test results. The study was approved by the Western Institutional Review Board (IRB) and the IRB at each participating study site. The aforementioned central IRB was used for centers or private practices that did not have their own institutional IRB. All patients provided consent before entering the study.

Assessments and endpoints

Our primary objective was to evaluate the practice patterns in terms of therapy selection and switching therapy during the study period. To assess the frequency of treatment change, the study population was distributed by the number of different regimens received during the entire observation period. To visualize the shifts in treatment preferences over time, the study population was classified by the treatment received at enrollment and entry into each subsequent 6-month period. To assess changes in laboratory measures or HBeAg status over time, assessments were conducted using either an index date of enrollment or an index date of the treatment start date, depending on the analysis. Index dates were compared with the first values observed in month 24 or after.

The secondary assessments were efficacy and safety of the first-line antiviral therapies on study patients. Patients were stratified into three subgroups who received ETV, TDF, or TAF for further comparison. The efficacy assessments included the percentage of patients who had HBV DNA ≤ 20 IU/ml and normalization of ALT during the 24-month prospective follow-up period, respectively. All data evaluated were at the 24 ± 1-month time point, which was determined as the study endpoint for efficacy and safety. The safety analyses included several important parameters for disease progression and laboratory adverse events such as albumin < 3.4 g/dl, platelet count < 150 × 9log10/L, and the estimated glomerular filtration rates (eGFR) < 60 ml/min/1.73 m^2. We also assessed the percentage of patients who had Fibrosis-4 index (FIB-4) > 3.25, HBeAg positivity, or Reach-B ≥ 10 at the end of the study as the exploratory endpoints in the three groups.

Standard of care and laboratory testing

All study sites prospectively assessed patients' clinical progress every 3 to 6 months (window ± 1 month) as per local standard of care. All laboratory testing was performed at the respective local laboratories for each center. For HBV-DNA detection, the lower limit of quantitation was 20 IU/ml. For measures, FIB-4 scores were calculated per Sterling et al.[24] The eGFR was calculated using the CKD-EPI Creatinine Equation.[25] The risk of HCC was estimated by REACH-B scores per Yang et al.[26] In the current study, completed viral suppression was considered when the local laboratories reported the serum HBV DNA ≤ 20 IU/ml. The normalization of ALT was defined for males as ≤ 31 IU/L and females ≤ 19 IU/L, and impaired renal status was considered as eGFR < 60 ml/min/1.73 m^2. An independent data monitor from Trio Health performed the data quality control by reviewing the submitted electronic case report forms for data completeness and accuracy.

Statistical analyses

Statistical analyses were conducted using the statistical software package of IBM SPSS Statistics 24 (IBM SPSS, New York, NY, USA) or R-3.6.2 software (The R Foundation, Wien, Austria). Categorical variable comparisons were via chi-square analysis with subsequent *z*-tests of column proportions or by the McNemar test. Bonferroni correction was applied for repeated measures. For continuous variables, comparisons between groups were made using the Mann-Whitney U test for independent samples. The treatment pattern analyses were performed for the entire cohort and also separately for the subgroup of patients recruited at community-based centers and those recruited at university-based centers. In addition, a subgroup analysis of treatment patterns was evaluated based on the HBeAg status. For the efficacy and safety of each antiviral treatment, analyses were performed on patients with test results available at specific time intervals from each treatment group, and variables at baseline were compared among the three groups. Statistical significance was set at the 0.05 level.

RESULTS

Study population characteristics at enrollment

The current study analyzed 889 of 1037 patients who had completed data, whereas 14% (148 of 1037) of enrollees who missed follow-ups or lacked data during the study were not included. The patient enrollment and treatment status during the study is presented in Figure 1. The characteristics of study patients and subgroups at enrollment are given in Table 1. Most of the patients (87%) were Asian, 6% African or African-American, 5% White, and 2% were of other races or unknown. The mean (SD) age was 52 (±13) years with 43% <50 years old. At enrollment, 28% (250 of 889) were HBeAg-positive and 72% (639 of 889) were HBeAg-negative. The most common comorbidities included hypertension (23%), hyperlipidemia (13%), and diabetes mellitus (10%). Almost all patients (98%) were on treatment at baseline: 63% (561 of 889) TDF, 25% (223 of 889) ETV, 4% (32 of 889) TDF plus emtricitabine, 3% (28 of 889) lamivudine, 1% (12 of 889) initiated TAF, and 1% (9 of 889) adefovir dipivoxil. Baseline mean (SD) ALT was 31 (±36) U/L and 17% (148 of 889) of patients had detectable levels of serum HBV DNA. Impaired renal function (measured by eGFR <60 ml/min/1.73 m^2) was recorded for 7% (58 of 886). Bone density scans were only available for 3% (26 of 889) of the study population precluding further analysis. Disease stages were assessed at baseline in 825 of 889 patients with FIB-4 scores, which showed 30% (247 of 825) with evidence of FIB-4 scores between 1.45 and 3.25, and 5% (42 of 825) with cirrhosis (FIB-4 scores >3.25). The mean (SD) REACH-B score was 6.6 (±2.5).

When patients were stratified by HBeAg status for the comparison of baseline variables, the HBeAg positive group was younger (mean of 48 years vs. 53 years, $p<0.001$), had a lower mean FIB-4 score (1.2 vs. 1.7, $p<0.001$), a higher proportion of patients with detectable HBV DNA (31% vs. 11%, $p<0.001$), elevated ALT (51% vs. 42%, $p = 0.013$), and higher REACH-B (7.8 vs. 6.1, $p<0.001$). In addition, treatment regimens at enrollment were significantly different between the two groups, most notably for a significantly higher percentage of HBeAg-positive patients on TDF (69% vs. 61%; $p<0.001$), whereas ETV was selected frequently in HBeAg-negative patients when compared to those with HBeAg-positive (28% vs. 18%; $p<0.001$). However, HBeAg groups were not significantly different for gender, body mass index (BMI), race, region of origin, payer type, or site of care (academic vs. community).

Most patients received care in sites classified as academic (62%, $n = 550$ of 889). Populations by site type differed in race, the region of origin, and primary payer type but not by gender, age, BMI, or proportions with detectable levels of serum HBV DNA or elevated ALT (Table 1). When compared with community sites, the academic practices had a lower fraction of patients with platelets $<150\times10^9$/L (20% [67 of 335] vs. 13% [69 of 546]; $p = 0.005$), higher prevalence of anxiety (1% vs. 4%; $p = 0.014$), and higher frequency of depression (1% vs. 5%; $p = 0.013$). In academic practices at enrollment, a significantly higher percentage of patients received ETV (28% vs. 20%; $p<0.001$), and a significantly lower

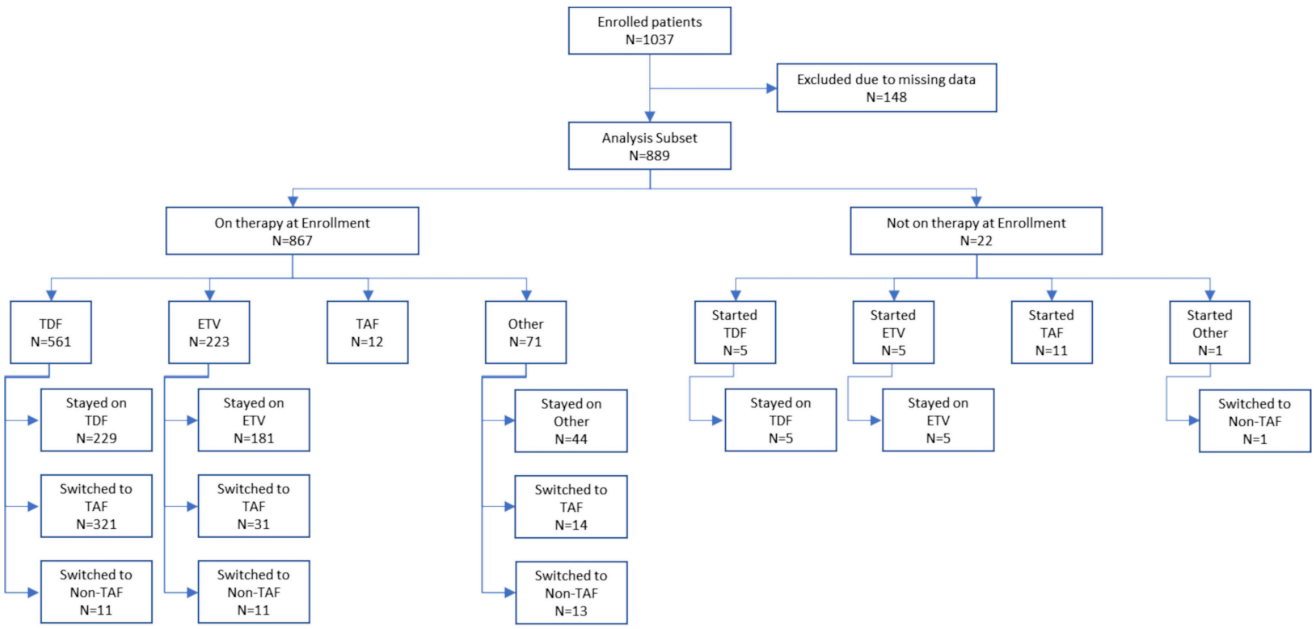

FIGURE 1 Enrollment and treatment status of the study patients. ETV, entecavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate

percentage of patients were treated with TDF (58% vs. 72%; $p < 0.001$) compared with community practices.

Antiviral treatment patterns after TAF approval

Of 889 patients, 867 (98%) were on therapy at enrollment, and the remaining 22 (2%) initiated treatment during the observation period (Figure 1). The proportion of patients remaining on their enrollment treatment throughout the observation window was 52% (463) and was not significantly different ($p = 0.58$) between HBeAg-negative (51%, 328 of 639) and HBeAg-positive (54%, 135 of 250) (Table S1). However, the proportion of patients on the same therapy throughout the study in academic sites significantly differed from that in the community practices (63% [349 of 550] vs. 34% [114 of 339]; $p < 0.001$). After enrollment shifts in treatments were mostly in reduced use of TDF from 63% to 30% and increased use of TAF from 2% to 38% in 24 months. The use of entecavir decreased from 25% to 22% (Figure 2A) during the same period. When the subgroup analyses were performed for TAF use at the 24-month time point, we found that the use of TAF was similar (Figure 2B,C) between the HBeAg-positive and HBeAg-negative subgroups (36% [91 of 250] versus 39% [251 of 639]; $p = 0.473$). However, there was a significantly higher proportion of patients treated with TAF in the community practices (Figure 2D,E) compared with academic settings (62% [209 of 339] vs. 25% [139 of 550]; $p < 0.001$).

Patients switched to TAF versus those remaining on TDF or ETV

Among 389 patients who initiated TAF during the study period, 6% (23 of 389) initiated TAF at enrollment, 4% (14 of 389) switched from second-line therapies, 83% (321 of 389) switched from TDF, and 8% (31 of 389) switched from ETV. The reason for the switch to TAF was assessed by the principal investigators at the time of switch and is given in Table S1. Most of the switches to TAF were listed for either safety (TDF, 63%; ETV, 77%) or physician preference. To better understand the clinical profile of patients who switched to TAF from TDF or ETV compared with those who remained on these enrollment therapies during the study period, we examined the characteristics at enrollment for four subgroups (Table 2): (A) switched to TAF from TDF ($n = 321$), (B) remaining on TDF ($n = 229$), (C) switched to TAF from ETV ($n = 31$), and (D) remaining on ETV ($n = 181$). In the subgroup assessment, among patients who switched to TAF therapy (group A, $n = 321$) from TDF, 58% (186/321) of them were from community practices. In contrast, 76% (175 of 229) of patients remaining on TDF were in care at academic sites (group B). Similarly, for patients switching to TAF from ETV (group C, $n = 31$), 55% (17 of 31) of patients who switched to TAF came from community sites, whereas 73% (133 of 181) of patients remaining on ETV (group D) were from academic sites. In the academic sites, the number of patients who remained on TDF or ETV was significantly higher than that to be treated with TAF ($p < 0.001$ TDF and $p = 0.003$ ETV).

At enrollment, a significantly lower portion of patients in group A (TDF–TAF) was HBeAg-positive (25% vs. 37%, $p = 0.005$) and receiving care in the academic practices (42% vs. 76%, $p < 0.001$) compared with group B (remaining on TDF), whereas in the comparison between group C (from ETV to TAF) and group D (remaining on ETV), a significantly lower percentage of patients in group C were treated at academic sites (45% vs. 73%, $p = 0.003$). To assess the independence of association with switching treatment from TDF or ETV to TAF, we examined demographic, payer, and clinical data at enrollment. Using logistic regression with backward selection (Table S1), the following variables at enrollment were independent predictors for switching therapy from TDF to TAF: being HBeAg-positive (OR: 0.60 [95% CI: 0.39–0.93], $p = 0.023$) or receiving care in community practices (OR: 5.24 [95% CI: 3.53–7.90], $p < 0.001$). The independent predictors for increased likelihood of switching from ETV to TAF were being treated in community practices (OR: 6.57 [95% CI: 2.47–19.12], $p < 0.001$), BMI (OR: 0.86 [95% CI: 0.75–0.98], $p = 0.030$), and hyperlipidemia (OR: 0.23 [95% CI 0.04, 0.83], $p = 0.043$). Among 229 patients who remained on TDF therapy through 24 months of study, we identified 67 of 229 (29%) patients who had met the criteria to be switched to TAF or ETV based on the recommendation from European Association for the Study of the Liver guidelines in 2017.[27] These patients had at least one of the following indications: age over 60 years ($n = 63$), eGFR < 60 ml/min/1.73 m^2 ($n = 10$), or osteoporosis ($n = 6$). The percentage of patients who continued on TDF with risk factors was similar between academic and community sites (30% [52 of 175] vs. 28% [15 of 54]; $p = 0.870$).

Real-world experience with TAF and other first-line regimens

Of the patients initiating TAF at enrollment or during the observation period ($n = 389$), 91% (355 of 389) were on TAF at the date of censure, and 9% (34 of 389) had discontinued. Among patients on TAF, 48% (187 of 389) received therapy for ≥ 24 months. These patients ($n = 187$) were included in the efficacy and safety analyses and were compared with patients who remained on TDF ($n = 229$) or ETV ($n = 181$) during the study period of 24 months (Table S1). In patients with TAF

TABLE 1 Patient characteristics overall and by subgroups at enrollment

No. (%) unless noted	Total (*n* = 889)	(A) HBeAg− (*n* = 639)	(B) HBeAg+ (*n* = 250)	*p* (A) vs. (B)	(C) Academic (*n* = 550)	(D) Community (*n* = 339)	*p* (C) vs. (D)
Months of follow-up, mean (SD)	35.1 (2.7)	35.2 (2.6)	35.1 (2.9)	0.651	35.4 (2.5)	34.7 (3.0)	<0.001*
Male	518 (58%)	376 (59%)	142 (57%)	0.579	324 (59%)	194 (57%)	0.625
Age, mean (SD)	52 (13)	53 (13)	48 (13)	<0.001*	51 (13)	52 (12)	0.485
Age group, years				<0.001*			0.511
18–34	90 (10%)	47 (7%)	43 (17%)	z	59 (11%)	31 (9%)	
35–49	293 (33%)	204 (32%)	89 (36%)		185 (34%)	108 (32%)	
50–64	361 (41%)	265 (41%)	96 (38%)		214 (39%)	147 (43%)	
65+	145 (16%)	123 (19%)	22 (9%)	z	92 (17%)	53 (16%)	
BMI, mean (SD)	25 (4)	25 (4)	25 (4)	0.470	25 (4)	25 (4)	0.303
BMI group				0.801			0.505
<18.5	36 (4%)	24 (4%)	12 (5%)		25 (5%)	11 (3%)	
18.5–24.9	458 (52%)	327 (51%)	131 (52%)		277 (50%)	181 (53%)	
25.0–29.9	306 (34%)	225 (35%)	81 (32%)		188 (34%)	118 (35%)	
30+	89 (10%)	63 (10%)	26 (10%)		60 (11%)	29 (9%)	
Race				0.848			<0.001*
Asian	768 (87%)	548 (87%)	220 (89%)		457 (83%)	311 (92%)	z
Black	51 (6%)	39 (6%)	12 (5%)		36 (7%)	15 (4%)	
White	46 (5%)	34 (5%)	12 (5%)		38 (7%)	8 (2%)	z
Other or unknown	16 (2%)	12 (2%)	4 (2%)		19 (4%)	5 (2%)	
Region of origin				0.434			<0.001*
Africa	27 of 873 (3%)	23 of 627 (4%)	4 of 246 (2%)		20 of 534 (4%)	7 (2%)	
Asia	735 of 873 (84%)	524 of 627 (84%)	211 of 246 (86%)		433 of 534 (81%)	304 (90%)	z
Europe	15 of 873 (2%)	10 of 627 (2%)	5 of 246 (2%)		13 of 534 (2%)	0 (0%)	z
Americas	96 of 873 (11%)	70 of 627 (11%)	26 of 246 (11%)		68 of 534 (13%)	28 (8%)	z
Academic site of care	550 (62%)	392 (61%)	158 (63%)	0.609			
Primary payer				0.105			<0.001*
Commercial	555 (62%)	394 (62%)	161 (64%)		361 (66%)	194 (57%)	z
Medicaid	117 (13%)	83 (13%)	34 (14%)		49 (9%)	68 (20%)	z
Medicare	135 (15%)	108 (17%)	27 (11%)		92 (17%)	43 (13%)	
Other or unknown	82 (9%)	54 (8%)	28 (11%)		48 (9%)	34 (10%)	
Laboratory							
HBV DNA >20 IU/ml	148 (17%)	71 (11%)	77 (31%)	<0.001*	100 (18%)	48 (14%)	0.138

No. (%) unless noted	Total (*n* = 889)	(A) HBeAg− (*n* = 639)	(B) HBeAg+ (*n* = 250)	*p* (A) vs. (B)	(C) Academic (*n* = 550)	(D) Community (*n* = 339)	*p* (C) vs. (D)
Elevated ALT	396 (45%)	268 (42%)	128 (51%)	0.013*	241 (44%)	155 (46%)	0.579
AST > ALT	397 (45%)	307 (48%)	90 (36%)	0.001*	247 (45%)	150 (44%)	0.890
FIB-4				<0.001*			0.150
<1.45	536 of 825 (65%)	352 of 590 (60%)	184 of 235 (78%)	*z*	331 of 494 (67%)	205 of 331 (62%)	
1.45–3.25	247 of 825 (30%)	202 of 590 (34%)	45/235 (19%)	*z*	143 of 494 (29%)	104 of 331 (31%)	
>3.25	42/825 (5%)	36 of 590 (6%)	6/235 (3%)	*z*	20 of 494 (4%)	22 of 331 (7%)	
eGFR < 60 ml/min/1.73 m^2	58 of 886 (7%)	45 of 636 (7%)	13/250 (5%)	0.310	38 of 547 (7%)	20 of 339 (6%)	0.579
Platelets < 150 × 10^9/L	136 (15%)	114 (17.8)	22 (8.8)	<0.001*	69 of 546 (13%)	67 of 339 (20%)	0.005*
ALT, mean (SD)	31.2 (35.8)	29 (26.5)	36.9 (52.3)	0.024*	31 (29)	31 (45)	0.887
AST, mean (SD)	26.7 (17.1)	26.3 (14.5)	27.9 (22.3)	0.288	27 (13)	27 (22)	0.792
FIB-4, mean (SD)	1.5 (1.5) *n* = 825	1.7 (1.6) *n* = 590	1.2 (1) *n* = 235	<0.001*	1.4 (1.3) *n* = 494	1.7 (1.7) *n* = 331	0.046
eGFR, mean (SD)	91.6 (19.4) *n* = 886	90.8 (19.4) *n* = 636	93.8 (19.4) *n* = 250	0.035*	92.0 (20.4) *n* = 547	91.0 (17.9) *n* = 339	0.450
REACH-B, mean (SD)	6.6 (2.5) *n* = 822	6.1 (2.3) *n* = 539	7.8 (2.4) *n* = 229	<0.001*	6.6 (2.6) *n* = 495	6.6 (2.3) *n* = 327	0.934
Comorbidities							
Anxiety	26 (3%)	17 (3%)	9 (4%)	0.455	22 (4%)	4 (1%)	0.014*
Depression	31 (3%)	17 (3%)	14 (6%)	0.032*	26 (5%)	5 (1%)	0.013*
Diabetes	92 (10%)	74 (12%)	18 (7%)	0.054	49 (9%)	43 (13%)	0.089
Hyperlipidemia	115 (13%)	76 (12%)	39 (16%)	0.139	65 (12%)	50 (15%)	0.218
Hypertension	204 (23%)	165 (26%)	39 (16%)	0.001*	118 (22%)	86 (25%)	0.189
Treatment				<0.001*			<0.001*
Not on treatment	22 (2%)	17 (3%)	5 (2%)		15 (3%)	7 (2%)	
3TC	28 (3%)	26 (4%)	2 (1%)	*z*	28 (5%)	0 (0%)	*z*
ADV	9 (1%)	8 (1%)	1 (0%)		7 (1%)	2 (1%)	
ETV	223 (25%)	177 (28%)	46 (18%)	*z*	154 (28%)	69 (20%)	*z*
TDF/FTC	32 (4%)	11 (2%)	21 (8%)	*z*	21 (4%)	11 (3%)	
IFN	1 (0%)	1 (0%)	0 (0%)		1 (0%)	0 (0%)	
TBV	1 (0%)	1 (0%)	0 (0%)		1 (0%)	0 (0%)	
TAF	12 (1%)	9 (1%)	3 (1%)		5 (1%)	7 (2%)	
TDF	561 (63%)	389 (61%)	172 (69%)	*z*	318 (58%)	243 (72%)	*z*

Abbreviations: 3TC, lamivudine; ADV, adefovir; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; FIB-4, Fibrosis-4 index; HBV, hepatitis B virus; TBV telbivudine.

*Indicates significant difference at $p = 0.05$ or less; *z* indicates column proportions that are significantly different by *z*-test for variables with more than two levels.

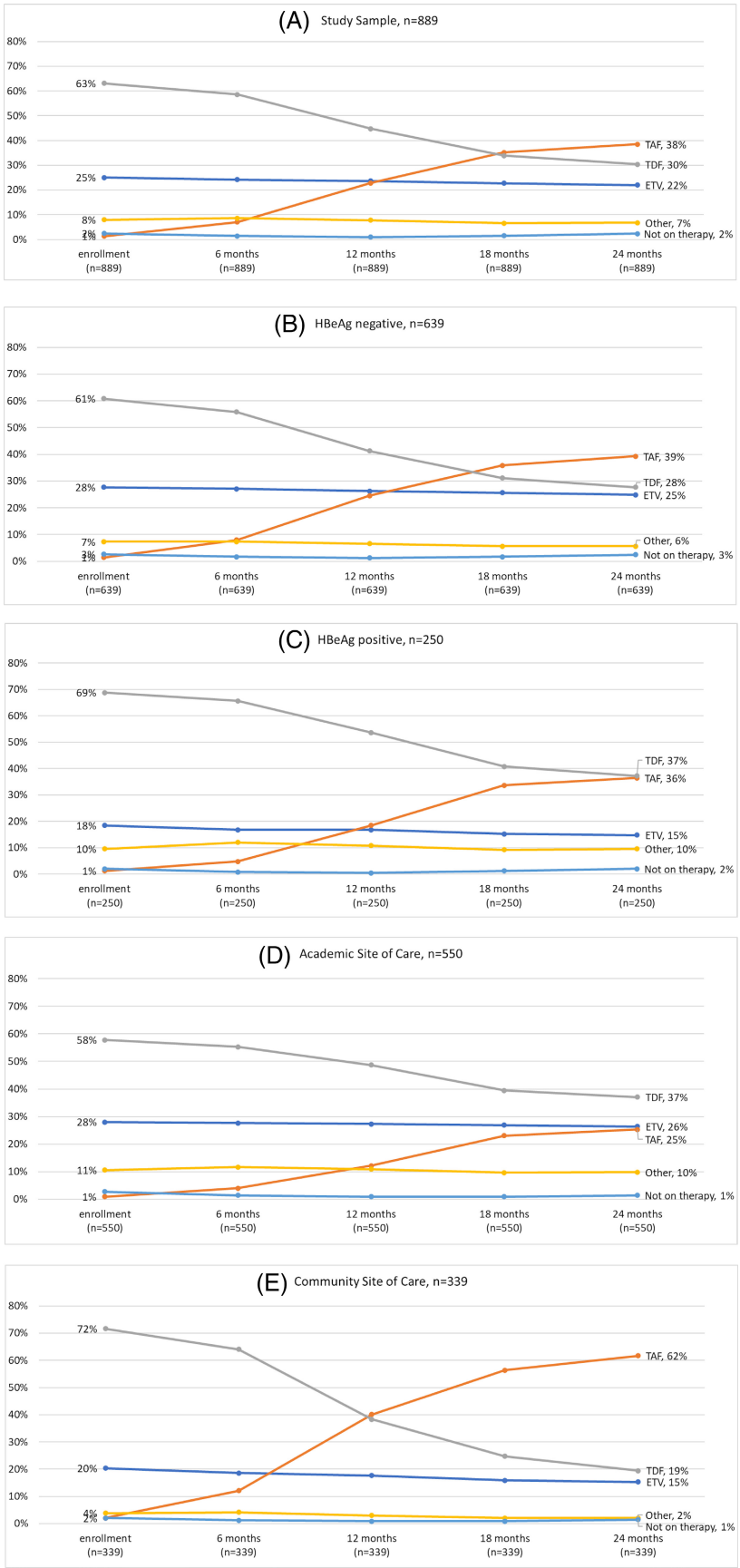

FIGURE 2 Treatment patterns and landscape in the United States following TAF availability: overall (A), hepatitis B e antigen (HBeAg)–negative patients (B), HBeAg-positive patients (C), patients at academic sites (D), and patients at community sites (E)

TABLE 2 Characteristics at enrollment of patients switched to TAF compared with those remaining on TDF or ETV

No. (%) unless noted	(A) Patients switching to TAF from TDF (*n* = 321)	(B) Patients maintaining TDF (*n* = 229)	(C) Patients switching to TAF from ETV (*n* = 31)	(D) Patients maintaining ETV (*n* = 181)	*p* (A) vs. (B)	*p* (C) vs. (D)
Months of follow-up, mean (SD)	35.0 (2.7)	35.2 (2.8)	34.7 (3.0)	35.7 (2.4)	0.446	0.111
Male	180 (56%)	121 (53%)	18 (58%)	112 (62%)	0.487	0.694
Age, mean (SD)	51 (13)	49 (14)	54 (14)	55 (11)	0.158	0.647
Age group, years					0.427	0.639
18–34	35 (11%)	32 (14%)	3 (10%)	6 (3%)		
35–49	110 (34%)	83 (36%)	6 (19%)	49 (27%)		
50–64	128 (40%)	84 (37%)	13 (42%)	86 (48%)		
65+	48 (15%)	30 (13%)	9 (29%)	40 (22%)		
BMI, mean (SD)	25 (4)	25 (4)	24 (3)	26 (4)	0.663	0.008
BMI group					0.965	0.087
<18.5	15 (5%)	10 (4%)		5 (3%)		
18.5–24.9	171 (53%)	127 (55%)	21 (68%)	79 (44%)		
25.0–29.9	104 (32%)	70 (31%)	9 (29%)	72 (40%)		
30+	31 (10%)	22 (10%)	1 (3%)	25 (14%)		
Race						
Asian	290 (90%)	199 (87%)	27 (87%)	149 (82%)	0.523	0.303
Black	14 (4%)	16 (7%)	NA	15 (8%)		
White	12 (4%)	9 (4%)	3 (10%)	13 (7%)		
Other or unknown	5 (2%)	5 (2%)	1 (3%)	4 (2%)		
Region of origin					0.238	0.751
Africa	8 of 318 (3%)	8 of 226 (4%)		8 of 174 (5%)		
Asia	280 of 318 (88%)	187 of 226 (83%)	27 of 30 (90%)	139 of 174 (80%)		
Europe	1 of 318 (0%)	3 of 226 (1%)	1 of 30 (3%)	7 of 174 (4%)		
Americas	29 of 318 (9%)	28 of 226 (12%)	2 of 30 (7%)	20 of 174 (11%)		
Academic site of care	135 (42%)	175 (76%)	14 (45%)	133 (73%)	<0.001	0.003
Primary payer					0.789	0.166
Commercial	198 (62%)	142 (62%)	15 (48%)	106 (59%)		
Medicaid	44 (14%)	28 (12%)	9 (29%)	25 (14%)		
Medicare	45 (14%)	38 (17%)	6 (19%)	33 (18%)		
Other or unknown	34 (11%)	21 (9%)	1 (3%)	17 (9%)		
Laboratory values						

(Continues)

TABLE 2 (Continued)

No. (%) unless noted	(A) Patients switching to TAF from TDF (*n* = 321)	(B) Patients maintaining TDF (*n* = 229)	(C) Patients switching to TAF from ETV (*n* = 31)	(D) Patients maintaining ETV (*n* = 181)	*p* (A) vs. (B)	*p* (C) vs. (D)
HBeAg-positive	81 (25%)	84 (37%)	9 (29%)	32 (18%)	0.005	0.145
HBV DNA >20 IU/ml	38 (12%)	42 (18%)	6 (19%)	20 (11%)	0.037	0.232
Elevated ALT	156 (49%)	106 (46%)	12 (39%)	64 (35%)	0.604	0.840
AST > ALT	143 (45%)	103 (45%)	14 (45%)	86 (48%)	0.931	0.848
FIB-4					0.23	0.537
<1.45	202 of 303 (67%)	145 of 211 (69%)	18 of 29 (62%)	96 of 170 (56%)		
1.45–3.25	88 of 303 (29%)	51 of 211 (24%)	9 of 29 (31%)	67 of 170 (39%)		
>3.25	13 of 303 (4%)	15 of 211 (7%)	2 of 29 (7%)	7 of 170 (4%)		
eGFR < 60 ml/min/1.73 m^2	20 of 319 (6%)	10 (4%)	5 (16%)	17 of 180 (9%)	0.447	0.334
Platelets < 150 × 10^9/L	44 of 320 (14%)	37 of 228 (16%)	6 (19%)	29 of 180 (16%)	0.464	0.609
ALT, mean (SD)	29 (20)	33 (49)	25 (14)	30 (33)	0.241	0.230
AST, mean (SD)	26 (10)	28 (21)	23 (7)	25 (15)	0.185	0.135
FIB-4, mean (SD)	1.5 (1.4)	1.6 (1.8)	1.7 (1.7)	1.6 (1.2)	0.524	0.773
eGFR, mean (SD)	91.7 (19.1)	93.1 (18.3)	83.5 (22.7)	89.6 (20.6)	0.398	0.17
REACH-B, mean (SD)	6.4 (2.5)	6.3 (2.4)	6.8 (2.4)	6.9 (2.3)	0.792	0.898
Comorbidities						
Anxiety	5 (2%)	8 (3%)	1 (3%)	8 (4%)	0.162	>0.99
Depression	10 (3%)	10 (4%)	1 (3%)	6 (3%)	0.492	>0.99
Diabetes	33 (10%)	18 (8%)	4 (13%)	27 (15%)	0.373	>0.99
Hyperlipidemia	29 (9%)	31 (14%)	3 (10%)	40 (22%)	0.098	0.148
Hypertension	67 (21%)	50 (22%)	8 (26%)	53 (29%)	0.833	0.831

treatment for 2 years or longer, the comparison of key measurements at 24 months (Table 3) to those at the time of TAF initiation (limited to patients with measures at both time points) revealed a significant decrease in the number of patients with elevated ALT (44% [79 of 181] vs. 34% [62 of 181]; p = 0.031) and a significant increase in HBV-DNA suppression (86% [155 of 180] vs. 93% [168 of 180]; p = 0.012). The proportions of patients with eGFR <60 ml/min/1.73 m^2, FIB-4 > 3.25, platelets < 150 × 9log10/L, or REACH-B ≥ 10 were not significantly different between the time points of initiating TAF and at 24 months.

Of the 561 patients on TDF at enrollment, 41% (229/561) did not switch therapy and completed the 24-month follow-up. Comparisons of variables for efficacy and safety were made between the data obtained at enrollment and at/after 24 months (limited to patients with measures at both time points), which showed that HBV-DNA suppression to the levels of ≤20 IU/ml was achieved in a significantly higher percentage of patients at the end of 24 months (80% [173 of 215] vs. 87% [187 of 215]; p = 0.014). In addition, the percentage of patients with eGFR <60 ml/min/1.73 m^2 increased significantly at/after 24 months (4% [8 of 196] vs. 9% [18 of 196]; p = 0.010). However, the percentages of patients who had albumin <3.4 g/dl, elevated ALT levels, AST > 33 U/L, FIB-4 > 3.25, HBeAg positivity, platelets < 150 × 9log10/L, or Reach-B ≥ 10 were not significantly different between the two time points (Table 3).

Among 223 patients on ETV at enrollment, 81% (181 of 223) did not switch therapy and completed the 24-month follow-up. When compared with the baseline efficacy and safety parameters at enrollment (limited to patients with measures at both time points), we

TABLE 3 Changes in laboratory variables from treatment initiation (TAF) or enrollment (TDF, ETV) to month 24 of therapy

			Treatment initiation/ enrollment		Variables assessment at month 24		
Laboratory variables	**Treatment**	***n*[a]**	**%**	**95% CI**	**%**	**95% CI**	***p***
Albumin <3.4 g/dl	ETV	154	4%	(1.4–8.3)	2%	(0.4–5.6)	0.371
	TAF	155	1%	(0.2–4.6)	2%	(0.4–5.6)	>0.99
	TDF	193	4%	(1.8–8.0)	4%	(1.8–8.0)	>0.99
Elevated ALT	ETV	177	38%	(30.7–45.4)	36%	(28.6–43.1)	0.635
	TAF	181	44%	(36.3–51.2)	34%	(27.4–41.7)	0.031
	TDF	216	47%	(40.0–53.6)	43%	(36.4–49.9)	0.302
AST > 33 U/L	ETV	177	11%	(7.0–16.9)	11%	(7.0–16.9)	>0.99
	TAF	181	11%	(6.9–16.5)	7%	(3.9–12.0)	0.169
	TDF	215	14%	(10.0–19.8)	13%	(8.8–18.3)	0.677
eGFR <60 ml/min/1.73 m^2	ETV	161	8%	(4.4–13.4)	9%	(5.3–14.9)	0.683
	TAF	178	6%	(3.1–10.8)	7%	(3.9–12.2)	0.683
	TDF	196	4%	(1.4–7.2)	9%	(5.5–14.1)	0.010
FIB-4 > 3.25	ETV	153	5%	(1.9–9.2)	8%	(4.6–14.1)	0.041
	TAF	166	5%	(2.1–9.3)	4%	(1.3–7.7)	0.617
	TDF	193	8%	(4.8–13.1)	10%	(6.0–14.9)	0.248
HBeAg+	ETV	64	28%	(17.6–40.8)	22%	(12.5–34.0)	0.289
	TAF	116	29%	(21.2–38.5)	25%	(17.4–33.9)	0.182
	TDF	104	51%	(41.0–60.9)	48%	(38.2–58.1)	0.579
HBV DNA ≤20 IU/ml	ETV	173	86%	(80.1–90.9)	91%	(85.4–94.6)	0.099
	TAF	180	86%	(80.2–90.8)	93%	(88.6–96.5)	0.012
	TDF	215	80%	(74.5–85.5)	87%	(81.7–91.2)	0.014
Platelets < 150 × 10^9/L	ETV	165	17%	(11.6–23.6)	16%	(11.1–22.9)	>0.99
	TAF	173	16%	(11.0–22.5)	18%	(12.5–24.5)	0.546
	TDF	215	16%	(11.6–21.9)	14%	(10.0–19.8)	0.221
Reach-B ≥ 10	ETV	157	8%	(4.5–13.7)	5%	(2.2–9.8)	0.131
	TAF	172	6%	(2.8–10.4)	3%	(1.3–7.4)	0.134
	TDF	194	8%	(4.4–12.4)	7%	(4.0–11.8)	>0.99

[a]The number of patients who completed 24 months of follow-up in TAF, TDF, and ETV were 187, 229 and 181, respectively. The number of patients who had data captured for each variable with both time points is presented in this column. p-values were generated using the McNemar test.

observed a significant high portion of patients with FIB-4 > 3.25 at/after 24 months of ETV therapy (5% [7 of 153] vs. 8% [13 of 153]; $p = 0.041$). However, other outcome parameters did not significantly differ between the two time points, which included the percentages of patients who had albumin < 3.4 g/dl, normalized ALT levels, HBV DNA below the levels of detection, AST > 33 U/L, eGFR < 60 ml/min/1.73 m^2, HBeAg positivity, platelets < 150 × 9log10/L, or Reach-B ≥ 10 (Table 3).

DISCUSSION

In this U.S. patient registry of predominantly Asian, over-50-year-old patients with HBeAg-negative CHB, we observed treatment shifting significantly from TDF as a dominant regimen (63% of all therapies) in 2017 to TAF (38%) at the start of 2020. Adoption of TAF was similar between HBeAg-positive and HBeAg-negative subgroups, although considerably greater in populations treated in the community (62% of patients at 24 months) compared with academic (25% of patients at 24 months) practices. TAF adoption for treatment of HBeAg-negative disease was anticipated, given the renal safety profile of TAF and long-term therapy required to achieve a functional cure in this population.[3,4,28] The rapid uptakes of TAF observed in HBeAg-positive patients and community settings were expected, because HBeAg-positive cases had a higher frequency of viremia and elevation of ALT on other regimens, and patients in the community often had comorbidity and compensated disease (TAF was off-label for decompensated disease during the study period).[7,8,29,30] The most common reason given for switching to TAF was patient safety, but interestingly, a significant number of patients ($n = 63$) who met the criteria for a switch with renal disease, older age, or diabetes were not switched over the study duration.

Although a few real-world studies on TAF (primarily in Asia) have been published, data are limited to the TAF effects on ETV-treated patients with a relatively small sample size (ranging from 100–300 patients).[30–33] To our knowledge, the current study is by far the largest one to assess real-world outcomes of all first-line regimens. We found that patients who switched from TDF or ETV to TAF had a significantly higher frequency of clearing their viremia and/or normalizing ALT at 24 months, whereas patients who continued ETV did not achieve those outcomes, and patients who continued on TDF only improved viremia but not the frequency of ALT normalization at 24 months. In the initial registration studies comparing TAF to TDF, a higher frequency of ALT normalization was also seen on TAF.[7,8] Many studies have shown that low-level viremia or persistent abnormal ALT while on antivirals increases the risk of disease progression and HCC.[34–37] Our data suggested that switching ETV or TDF therapy to TAF may be a more favorable option for patients with persistent viremia and/or abnormal ALT, which further enhances our understanding of the efficacy of TAF treatment (pivotal RCTs only showed that TAF was superior to TDF on ALT normalization).[7,8,29] In terms of safety, significantly more patients on TDF therapy had worsening eGFR from baseline after 24 months of therapy. In contrast, there were no safety concerns for patients with TAF or ETV. These outcomes were consistent with the findings in pivotal trials.[6–8,29] The reasons for more patients with FIB-4 > 3.25 at/after 24 months of ETV therapy compared with baseline were not fully understood, due to the limitation of the study design and the small number of patients. We believe that failure to achieve outcomes on both viremic control and ALT normalization may contribute to the worsening of FIB-4 scores in this group.[34]

There are several study limitations primarily associated with the non-randomized design and loss to follow-up, although this is a small proportion of patients in a real-world setting. The efficacy data are interesting but should be interpreted with the caveats that they do not represent the entire patient population, even though the subset analyzed was well matched at baseline. When comparing baseline profiles between the TAF and ETV groups, the TAF group had a significantly higher portion of patients with elevation of ALT, which could potentially underestimate the TAF effects on ALT. In addition, patients treated with ETV were older and often associated with HBeAg negativity, high BMI, or hyperlipidemia. These factors, including metabolic syndrome, may reduce the generality of these findings, particularly on ALT normalization. Finally, our findings may not be fully applicable to the non-Asian populations, as they are underrepresented in our study.

In conclusion, we found a significant shift in the treatment paradigm from TDF to TAF in this U.S. registry cohort and identified gaps in managing patients with CHB, including deviations from the standard of care. In comparison, of the first-line antiviral therapies, our data suggest that TAF is a good first option for patients with CHB in the United States, and within the limitations of this real-world study may also be considered for populations with abnormal ALT or viremia on other therapies.

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CONFLICT OF INTEREST

Dr. Pan is a speaker for Gilead, AbbVie, and Intercept. His institution has received research support from Gilead, Assembly Bio, and Trio Health. Dr. Afdhal is a paid consultant/advisory board member for Gilead,

Echosens, Ligand, Shionogi and Trio Health, owns stock in SpringBank and Allurion and has stock options in SpringBank, receives royalty income from UpToDate, and is on the board of directors for the nonprofit Liver Institute for Education and Research. Dr. Ankoma-Sey is a speaker for Gilead and Bristol Meyers Squibb. Dr. Bae is a speaker for Gilead and has received research grants from Gilead. Dr. Curry consults for Trio Health Analytics and Gilead. Dr. Dieterich consults and is a speaker for Gilead, and does research for Enanta and Assembly. L. Frazier is a speaker for Gilead and is on an advisory board for Gilead. Andrew Frick and Dr. Milligan are employed by Trio Health Analytics and have received research support from Gilead, Merck, AbbVie, ViiV, Janssen, Takeda, and UCB. Dr. Hann is an advisor for Gilead and has received research support from Gilead, Assembly Bio, and Trio Health. Dr. Kwo has received grant support from Gilead, BMS, and Assembly and is on advisory boards for Gilead and Aligos. Dr. Tong is on an advisory board and consults for Gilead. Dr. Reddy is on an advisory board for Mallinckrodt and has received research support from Mallinckrodt, Gilead, Merck, BMS, Intercept, Sequana, Grifols, Exact Sciences, HCC-TARGET, NASH-TARGET, and DSMB-Novartis.

AUTHOR CONTRIBUTIONS

Guarantor of the article: Calvin Q. Pan. *Study design*: Nezam H. Afdhal. *Analysis*: Andrew Frick and Scott Milligan. *Data acquisition*: Calvin Q. Pan, Nezam H. Afdhal, Victor Ankoma-Sey, Ho Bae, Michael P. Curry, Douglas Dieterich, Lynn Frazier, Hie-Won Hann, W. Ray Kim, Paul Kwo, Myron Tong, and K. Rajender Reddy. *Manuscript draft*: Calvin Q. Pan, Nezam H. Afdhal, Michael P. Curry, Andrew Frick, W. Ray Kim, Paul Kwo, Scott Milligan, and K. Rajender Reddy. *Critical revisions (interpretation of data)*: Calvin Q. Pan, Nezam H. Afdhal, Michael P. Curry, Andrew Frick, W. Ray Kim, Paul Kwo, Scott Milligan, and K. Rajender Reddy. *Communication with the journal and reviewers' comments*: Calvin Q. Pan and Nezam H. Afdhal with statistical support from Scott Milligan and Andrew Frick. All the authors vouch for the veracity and completeness of the data and analyses presented. The final version of the manuscript has been reviewed and approved by the authors. Although Gilead Sciences provided research funding support, it had no part in the design or performance of the trial, in the data analysis, in the writing or editing of the manuscript, nor in the decision to submit the manuscript for publication.

INTERIM DATA PRESENTATIONS

Interim data from this registry were presented at the European Association for the Study of the Liver International Liver Congress (August 27–29, 2020; April 10–14, 2019); the International Society for Pharmacoeconomics and Outcomes Research Annual Meeting (May 18–20, 2020; May 18–22, 2019); the American Association for the Study of Liver Disease Annual Meeting (November 8–12, 2019; November 9–13, 2018); and the Asian Pacific Association for the Study of the Liver Meeting (February 20–24, 2019).

TRIAL REGISTRATION STATUS

This study was not registered with any public registration site.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Trio Health on reasonable request. Participant data without names and identifiers may be shared with other researchers after approval from the research committee of Trio Health and the institutional IRB of the investigational sites. A proposal with a detailed description of study objectives and a statistical analysis plan will be needed for evaluation of the reasonability to request for our data. The committee will make a decision based on these materials.

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SUPPORTING INFORMATION

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