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Treatment and Renal Outcomes Up to 96 Weeks After Tenofovir Alafenamide Switch From Tenofovir Disoproxil Fumarate in Routine Practice

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BACKGROUND AND AIMS: Real-world data for treatment effectiveness and renal outcomes in chronic hepatitis B (CHB) patients who were switched to the new and safer prodrug tenofovir alafenamide (TAF) from tenofovir disoproxil fumarate (TDF) are limited. Therefore, we aimed to evaluate treatment and renal outcomes of this population.

APPROACH AND RESULTS: We analyzed 834 patients with CHB previously treated with TDF for ≥12 months who were switched to TAF in routine practice at 13 US and Asian centers for changes in viral (HBV DNA < 20 IU/mL), biochemical (alanine aminotransferase [ALT] < 35/25 U/L for male/female), and complete (viral+biochemical) responses, as well as estimated glomerular filtration rate (eGFR; milliliters per minute per 1.73 square meters) up to 96 weeks after switch. Viral suppression (P < 0.001) and ALT normalization (P = 0.003) rates increased significantly after switch, with a trend for increasing complete response (P_{trend} = 0.004), while the eGFR trend (P_{trend} > 0.44) or mean eGFR (P > 0.83, adjusted for age, sex, baseline eGFR, and diabetes, hypertension, or cirrhosis by generalized linear modeling) remained stable. However, among those with baseline eGFR < 90 (chronic kidney disease [CKD] stage ≥2), mean eGFR decreased significantly while on TDF (P = 0.029) but not after TAF switch (P = 0.90). By week 96, 21% (55/267) of patients with CKD stage 2 at switch improved to stage 1 and 35% (30/85) of CKD stage 3-5 patients improved to stage 2 and 1.2% (1/85) to stage 1.

CONCLUSIONS: Overall, we observed continued improvement in virologic response, ALT normalization, and no significant changes in eGFR following switch to TAF from TDF. (Hepatology 2021;0:1-11).

HBV continues to be pervasive throughout the world despite the ongoing global initiative to eliminate viral hepatitis by the year 2030.[1-4] Currently, there are no curative treatments for HBV, but there are medications that can suppress the virus

Abbreviations: ALT, alanine aminotransferase; CHB, chronic hepatitis B; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ETV, entecavir; GEE, generalized estimating equation; GLM, generalized linear modeling; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

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and help to slow the progression of chronic hepatitis B (CHB).[5] As such, suppression of HBV remains one of the pillars of CHB management.[6] Tenofovir disoproxil fumarate (TDF) and entecavir (ETV) have been the mainstays of therapy over the past decade; however, each is associated with side effects including renal impairment and bone loss[7,8] with TDF and potential viral resistance with ETV, especially in those with a history of resistance to the older nucleoside analogue lamivudine.[9] More recently, an HBV viral suppression drug was approved, tenofovir alafenamide (TAF).

TAF is a prodrug of tenofovir (TFV), which has shown potent inhibition of HBV replication at a low dose, with high intracellular concentration and >90% lower systemic TFV concentration than TDF.[10,11] In two randomized, double-blind, multinational, phase 3, noninferiority trials for HBeAg-positive and HBeAg-negative patients, TAF 25 mg orally once-daily was associated with a significantly higher alanine aminotransferase (ALT) normalization rate (male, ALT ≤ 30 U/L; female, ALT ≤ 19 U/L) than was seen with TDF at 48 weeks without incurring adverse renal and bone events at a longer follow-up period of 96 weeks.[10,12-14] Regarding outcomes of patients switched to TAF from TDF, one small, prospective, single-arm, open-label clinical trial of 75 patients with CHB previously treated with TDF and with HBV DNA < 21 IU/mL who were switched to TAF found improved bone and renal tubular markers by end of study follow-up at 24 weeks.[13] Since then, a randomized, double-blind, phase 3, multicenter, noninferiority trial comparing virologically suppressed patients with CHB who were switched from TDF to TAF (n = 243) or continued on TDF (n = 245) also found improved bone and renal markers at week 48 without a loss in efficacy.[15] However, real-world data and longer follow-up are necessary to determine the clinical relevance of the differences in response to TAF in comparison with TDF for patients being managed in routine clinical practice, but these data are limited. To the best of our knowledge, there has been only one published real-world study, which included 36 patients switched to TAF from TDF in routine practice who were followed for only 24 weeks after switch to TAF.[16] Therefore, we aimed to examine the effectiveness and renal outcomes of sequential therapy with TAF in a large cohort of patients with CHB from routine practice who had received TDF for at least 12 months at 13 clinical centers in the United States and Asia. Specifically, we determined the viral, biochemical, and complete response rates as well as the changes in estimated glomerular filtration rate (eGFR) and chronic kidney disease (CKD) stages up to 96 weeks after switching to TAF.

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Patients and Methods

STUDY DESIGN AND STUDY POPULATION

We performed a retrospective cohort study of patients with CHB who were switched to TAF (for any reason and without interruption) after at least 12 months of TDF monotherapy, then monitored every 3-6 months in routine practice at 13 centers in the United States, Korea, Japan, Singapore, and Taiwan. We excluded patients with viral coinfection or immunosuppression.

OUTCOMES AND DEFINITIONS

The primary outcomes were complete response, defined as viral suppression with an HBV DNA level <20 IU/mL, as well as ALT normalization, with an ALT level of <35 (IU/mL) for men and <25 (IU/mL) for women (biochemical response), up to 96 weeks postswitch.[9]

The renal outcomes were defined as changes in mean eGFR after switch and as a clinically significant change in renal function, i.e., the number of patients who changed renal disease categories as defined below. To determine these changes, we calculated eGFR using the Chronic Kidney Disease Epidemiology Collaboration formula as $141 \times \min\{\text{creatinine/k}, 1\}^{\alpha} \times \max\{\text{creatinine/k}, 1\}^{-1.209} \times 0.993^{\text{age [years]}} \times 1.018$ [if female], where k is 0.7 for females and 0.9 for males and α is −0.329 for females and −0.411 for males.[17] We defined "moderate" renal impairment as eGFR < 60 mL/min/1.73 m^2 (CKD stage 3-5) and "mild" renal impairment as 60 ≤ eGFR < 90 mL/min/1.73 m^2 (CKD stage 2), per the Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Chronic Kidney Disease.[18]

Cirrhosis was determined by histology, elastography, and clinical, radiologic, endoscopic, and laboratory evidence of cirrhosis and/or portal hypertension. Steatosis was confirmed by ultrasound. The presence of hypertension and or diabetes mellitus was confirmed through medical chart review.

The study protocol was performed in accordance with the Declaration of Helsinki and approved by the institutional review board of Stanford University (Stanford, CA) and each participating study center.

STATISTICAL ANALYSIS

Chi-squared tests were used to compare rates of virologic, biochemical, and complete responses between switch and different time points over the course of TDF and TAF. The Cochran-Armitage test was used to calculate P_{trend} for changes in treatment response rates over the 96 weeks following TAF switch. We also used the Cochran-Armitage test to calculate P_{trend} for changes in CKD stages over the 96 weeks following TAF switch. Additionally, we used the multivariable generalized estimating equation (GEE) model to assess for factors associated with changes in eGFR with adjustment for age, sex, hypertension or diabetes mellitus or cirrhosis, and baseline eGFR. Furthermore, we performed generalized linear modeling (GLM) to generate adjusted mean eGFRs after adjusting for similar relevant clinical markers. Because treatment with other nucleos(t)ide analogues prior to TDF can influence treatment outcome on subsequent therapy with TAF, we performed sensitivity analyses on the subgroup of patients who were treatment-naive prior to TDF therapy. We also performed sensitivity analysis for the subgroup of patients with hepatic steatosis because the presence of steatosis may affect changes in ALT levels. Lastly, because eGFR can also be assessed by the Cockcroft-Gault (CG)[19] and Modification of Diet in Renal Disease (MDRD) Study[20] equations, we performed renal outcome analyses using these equations as a sensitivity analysis.

For all analyses, statistical significance was defined as a two-sided P value of <0.05. All statistical analyses were performed by Stata 15.1 (StataCorp, College Station, TX).

Results

STUDY POPULATION

Our study included 834 patients who switched to TAF after receiving TDF for at least 12 months, of whom 415 had no treatment prior to TDF (Supporting Fig. S1). At baseline (defined as the time when patients were switched to TAF), the cohort was 54.64 ± 14.11 years in mean age, 23.29 ± 3.64 kg/m^2 in mean body mass index, 57% male, 89% Asian, 23%

hypertensive, 9.5% diabetic, 28.9% with steatosis, and 12.5% with cirrhosis. At time of switch, mean ALT level was 29.29 ± 28.56 U/L, 11.8% of patients had detectable HBV DNA (>20 IU/mL), 30.4% had elevated ALT, and 12.5% had cirrhosis. The average eGFR was 89.97 ± 20.79 mL/min/1.73 m^2, with about 32% of the cohort having mild renal impairment and 10.43% having moderate to severe renal impairment (eGFR 60-89 and <60 mL/min/1.73 m^2, respectively). The average time on TDF treatment was 4.42 ± 2.63 years (Table 1). Of the 28 patients with an eGFR < 50, 7 had their TDF dosage reduced to every other day, 2 to every 72 hours, and 3 to once a week with hemodialysis. The characteristics of the TDF treatment-naive patients were similar to those of the overall cohort. These patients were 52.44 ± 14.03 years old on average, 53% male, 86.5% Asian, 7.8% diabetic, 21.1% hypertensive, and 10.4% with cirrhosis, with 11.7% with detectable HBV DNA and 29.5% having elevated ALT, an average ALT level of 28.38 ± 18.71, and an average eGFR of 90.94 ± 20.26 at TAF switch time. They were also on TDF for an average of 4.47 ± 2.43 years before switching to TAF (Table 1). The treatment-experienced subcohort was 56.81 ± 13.85 years old on average, 61.6% male, 91.4% Asian, 11.5% diabetic, 25% hypertensive, and 13.8% with cirrhosis, with 11.9% having detectable HBV DNA, 31.2% having elevated ALT, and an average eGFR of 88.81 ± 21.27 at TAF switch time. Prior treatment exposure among these patients included lamivudine (14.4%), adefovir-based (33.2%), ETV (45.4%), or other antiviral therapy (7%) (Table 1).

CHANGES IN VIROLOGIC, BIOCHEMICAL, AND COMPLETE RESPONSES

The percent of patients who achieved HBV DNA suppression increased significantly from 88.19% (717/813) at the time of switch to 91.64% (581/634, $P = 0.032$) at 48 weeks postswitch and to 94.89% (390/411, $P < 0.001$) at 96 weeks postswitch (Table 2). There was also an increase in ALT normalization rates at each follow-up time point compared to that at the TAF switch time. At the point of switch, 69.63% (571/820) had achieved ALT normalization, but by week 48, 76.85% (508/661, $P = 0.001$) had achieved ALT normalization, which further increased to 77.78% (322/414, $P < 0.003$) by week 96. However, there was no statistically significant differences in the ALT normalization rates in any time points between 96 weeks while on TDF prior to switch to TAF ($P = 0.20$-0.74). We also observed an increase in ALT normalization rates in our subgroup analysis of patients with virologic suppression at switch and found that the ALT normalization rate at switch for this subgroup was 71.91% (507/705) and 78.71% (281/357) 96 weeks after ($P = 0.02$) (Supporting Table S1). Similarly, the percent of patients with complete response increased significantly from the switch time (63.22%, 507/802) to each postswitch follow-up time point to 74.69% (301/403, $P < 0.001$) at 96 weeks postswitch follow-up, while there were no statistically significant differences between the 48-week (60.20%, $P = 0.25$) and 24-week (61.61%, $P = 0.54$) time points while on TDF therapy compared to those at TAF switch (Table 2). Trend analysis also revealed a significant increase in the percent of patients with virologic ($P < 0.001$), biochemical ($P = 0.002$), and complete ($P < 0.001$) responses over the entire follow-up to 96 weeks post–TAF switch. Sensitivity analysis of the TDF treatment-naive cohort found similar results, with a significantly higher percentage of patients with complete response between switch time and 96 weeks after TAF (63.66%-73.03%, $P = 0.027$), which remained significant upon trend analysis over the 96-week follow-up post–TAF switch ($P = 0.004$). Among patients with hepatitis steatosis (Supporting Table S2), there were also significant increases in biochemical and complete response rates from the switch time (62.55% and 58.97%, respectively) to 96 weeks postswitch follow-up (75.79% and 71.2%, $P = 0.01$ and $P = 0.02$, respectively) but not consistently at earlier time points, though there were much fewer patients in this subcohort (n = 241).

RENAL OUTCOMES

Changes in Mean eGFR Over Time

Using a GLM model adjusted for age, sex, diabetes mellitus, hypertension, and cirrhosis, we reported mean eGFR before switch and up to 96 weeks after switching to TAF for the subgroup of patients with normal renal function (CKD stage 1, eGFR ≥ 90 mL/min/1.73 m^2) (Supporting Fig. S2) and for the subgroup of patients with renal impairment (CKD

TABLE 1. Baseline (at Switch) Characteristics of Patients Who Switched From TDF to TAF

Characteristics	Total Cohort (N = 834)	Treatment-Naive Subcohort (n = 415)	Treatment-Experienced Subcohort (n = 419)
Age (years)	54.64 ± 14.11	52.44 ± 14.03	56.81 ± 13.85
Male	478 (57.31)	220 (53.01)	258 (61.58)
Body mass index (kg/m^2) (N = 799, n = 401, n = 398)	23.29 ± 3.64	23.34 ± 3.85	23.25 ± 3.43
Race/ethnicity			
Asian	742 (88.97)	359 (86.51)	383 (91.41)
Non-Asian	92 (11.03)	56 (13.49)	36 (8.59)
ACE inhibitors and/or diuretics (N = 607, n = 318, n = 289)	55 (9.06)	31 (9.75)	24 (8.30)
Diabetes mellitus (N = 828, n = 412, n = 416)	80 (9.50)	32 (7.77)	48 (11.54)
Hypertension (N = 829, n = 413, n = 416)	191 (23.04)	87 (21.07)	104 (25.00)
Hepatic steatosis	241 (28.90)	110 (26.51)	131 (31.26)
Cirrhosis (N = 831, n = 412, n = 419)	101 (12.51)	43 (10.44)	58 (13.84)
Model for End-Stage Liver Disease (N = 43, n = 17, n = 26)			
<15	42 (97.67)	16 (94.12)	26 (100)
≥15	1 (2.33)	1 (5.88)	0 (0)
HCC (N = 825, n = 412, n = 413)	33 (4.00)	12 (2.91)	21 (5.08)
HBeAg+ (N = 662, n = 314, n = 348)	204 (30.82)	84 (26.75)	120 (34.48)
qHBsAg (IU/mL) (N = 163, n = 48, n = 115)	861.93 (178.32-3,794.52)	1173.70 (447.50-4,894.49)	718.46 (165.21-3,379.04)
% Detectable HBV DNA (N = 813, n = 403, n = 410)	96 (11.81)	47 (11.66)	49 (11.95)
HBV DNA of incomplete responders	43 (40-135.5)	46 (40-140)	40 (40-86)
% Elevated ALT (N = 820, n = 410, n = 410)	249 (30.37)	121 (29.51)	128 (31.22)
ALT (U/L) (N = 820, n = 410, n = 410)	29.29 ± 28.56	28.38 ± 18.71	30.20 ± 35.80
Aspartate aminotransferase (U/L) (N = 818, n = 408, n = 410)	27.22 ± 17.50	26.70 ± 12.27	27.72 ± 21.49
Creatinine (mg/dL) (N = 815, n = 405, n = 410)	0.90 ± 0.44	0.87 ± 0.24	0.92 ± 0.57
eGFR (N = 815, n = 405, n = 410)	89.87 ± 20.79	90.94 ± 20.26	88.81 ± 21.27
eGFR group (N = 815, n = 405, n = 410)			
≥90	463 (56.81)	238 (58.77)	225 (54.88)
60-89	267 (32.76)	126 (31.11)	141 (34.39)
<60	85 (10.43)	41 (10.12)	44 (10.73)
Treatment prior to TDF (N = 416)			
Lamivudine	60 (14.42)	NA	60 (14.42)
Adefovir-based therapy	138 (33.17)	NA	138 (33.17)
Entecavir	189 (45.43)	NA	189 (45.43)
Other	29 (6.97)	NA	29 (6.97)
Reason for switching		NA	NA
Partial/no response	15 (1.8%)		
Dose adjustment issue with renal sufficiency	131 (15.7%)		
For other/unspecified physician/patient preference	688 (82.5%)		
Renal replacement therapy (N = 815, n = 405, n = 410)	3 (0.36)	0 (0)	3 (0.36)
Duration on TDF (years)	4.42 ± 2.63	4.47 ± 2.43	4.37 ± 2.81

Values expressed as mean ± standard deviation, median (interquartile range), or number (%). eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration formula.
Abbreviations: ACE, angiotensin-converting enzyme; NA, not available; qHBsAg, quantitative HBsAg.

stage ≥ 2, eGFR < 90 mL/min/1.73 m^2) (Fig. 1). Among patients with normal renal function, there was no statistically significant difference in the adjusted mean eGFR while the patients were on TDF before switch (102.2 vs. 102.2 mL/min/1.73 m^2, P = 0.94) or between switch and 96-week postswitch follow-up (104.2 to 102.2 mL/min/1.73 m^2, P = 0.49). We also found no significant changes in mean eGFR in GLM

TABLE 2. Changes in Virologic, Biochemical, and Complete Responses

Drug	n (%)	Time (Weeks)	*P**
Virologic response (% HBV DNA ≤ 20)			
TDF	323/402 (80.35)	–96	<0.001
TDF	349/411 (84.91)	–72	0.11
TDF	498/594 (83.84)	–48	<0.001
TDF	494/566 (87.28)	–24	0.61
Switch	717/813 (88.19)	0	NA
TAF	619/688 (89.97)	24	0.27
TAF	581/634 (91.64)	48	0.032
TAF	496/534 (92.88)	72	0.005
TAF	390/411 (94.89)	96	<0.001
Biochemical response (% ALT < 35 [men] or ALT < 25 [women])			
TDF	284/427 (66.51)	–96	0.26
TDF	295/446 (66.14)	–72	0.20
TDF	422/616 (68.51)	–48	0.65
TDF	408/593 (68.80)	–24	0.74
Switch	571/820 (69.63)	0	NA
TAF	543/714 (76.05)	24	0.005
TAF	508/661 (76.85)	48	0.001
TAF	428/547 (78.24)	72	<0.001
TAF	322/414 (77.78)	96	0.003
Complete response (% HBV DNA ≤ 20 and ALT < 35 [men] or ALT < 25 [women])			
TDF	228/407 (56.02)	–96	0.015
TDF	241/421 (57.24)	–72	0.042
TDF	357/593 (60.20)	–48	0.25
TDF	353/573 (61.61)	–24	0.54
Switch	507/802 (63.22)	0	NA
TAF	473/685 (69.05)	24	0.018
TAF	446/628 (71.02)	48	0.002
TAF	381/527 (72.30)	72	<0.001
TAF	301/403 (74.69)	96	<0.001

**P*-value is in reference to time 0 (switch) and data also presented in Graphical Summary.
Abbreviaton: NA, not available.

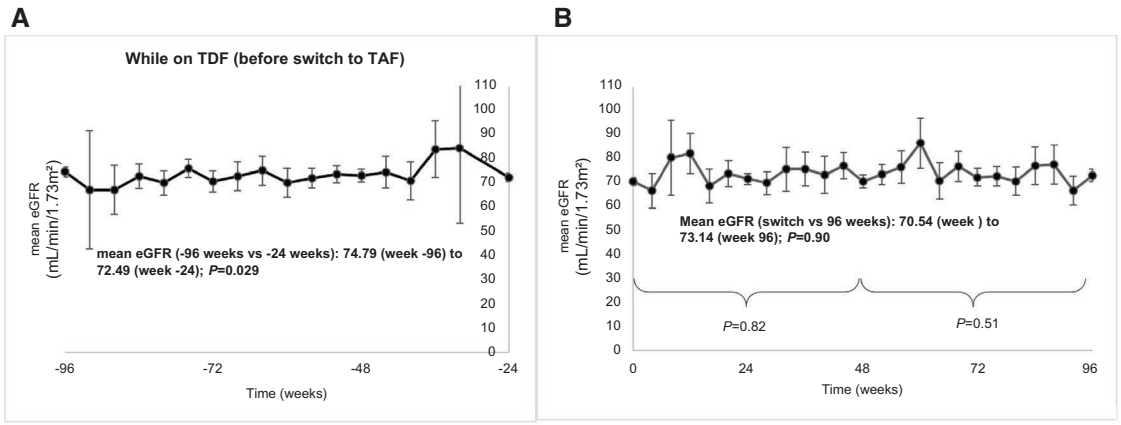
analysis for up to 48 weeks postswitch (P = 0.16) and between 48 and 96 weeks postswitch (P = 0.18) (Supporting Fig. S2). However, among those with renal impairment (Fig. 1), while the adjusted mean eGFR decreased significantly during TDF treatment (74.79 vs. 72.49 mL/min/1.73 m^2, P = 0.029), the adjusted mean eGFR did not change significantly after switch to TAF (P = 0.90). Similar results were observed up to 48 weeks postswitch (P = 0.82) and between 48 and 96 weeks postswitch (P = 0.51). In our sensitivity analysis of the treatment-naive group, we found similar results of stable adjusted mean eGFR between switch time and 96 weeks after switch to TAF (overall, 90.45 vs. 91.72 mL/min/1.73 m^2, P = 0.77; normal renal function cohort, 104.9 vs. 102.3 mL/min/1.73 m^2, P = 0.41; and impaired renal function cohort, 71.20 vs. 75.63 mL/min/1.73 m^2, P = 0.95).

In GLM models for adjusted mean eGFR trends with the CG in patients with eGFR < 90 mL/min/1.73 m^2, we found no significant changes in adjusted mean eGFR while on TDF before switch (P = 0.42) as well as after switching to TAF (P = 0.33) (Supporting Fig. S3). Similar analysis with the MDRD equation yielded a statistically significant but minimal increase in adjusted mean eGFR (74.02 vs. 74.17 mL/min/1.73 m^2, P = 0.01) during TDF treatment but no changes after switching to TAF (P = 0.63) (Supporting Fig. S4).

We also further stratified renally impaired patients into those with eGFR < 60 and 60-89.9 mL/min/1.73 m^2 and similarly found no significant changes in adjusted mean eGFR while on TDF (P = 0.22) or after switching to TAF (P = 0.57) for the eGFR < 60 mL/min/1.73 m^2 group (Supporting Fig. S5). Similar results were seen in patients with eGFR between 60 and 90 mL/min/1.73 m^2 (P > 0.05) (Supporting Fig. S6).

Changes in CKD Stages over Time

When we inspected the cohort by CKD stages at the switch point and their evolution over the 96-week follow-up (Fig. 2), we found that 55 of 267 (20.6%) CKD stage 2 (mild renal impairment, eGFR < 90 but ≥60 mL/min/1.73 m^2) patients at switch regressed to CKD stage 1, signifying return to normal renal function and that 30 of 85 (35.3%) CKD stage 3-5 (eGFR < 60 mL/min/1.73 m^2) patients regressed to CKD stage 2 and 1 (1.2%) to normal renal function. At the same time, among those with stage 1 (normal renal function, eGFR ≥ 90 mL/min/1.73 m^2) disease at the switch (n = 463), 52 (11.2%) progressed to CKD stage 2 and 2 (0.4%) progressed to CKD stage 3-5. Patients who improved at least one CKD stage were younger (59.1 ± 12.4 vs. 63.2 ± 12.6 years, P = 0.008). When assessing CKD stage migration at the end of 48 weeks of follow-up, we found similar



Follow-up (weeks)	-96	-72	-48	-24	Follow-up (weeks)	0	24	48	72	96
TDF-TAF switch (N)	304	297	275	245	TDF-TAF switch (N)	352	331	303	232	140

FIG. 1. GLM analysis for mean eGFR over time in baseline eGFR < 90 subgroup (A) while on TDF before switching to TAF and (B) after switching to TAF. All eGFR values adjusted for age, sex, diabetes mellitus or hypertension, and cirrhosis by GLM. eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration formula.

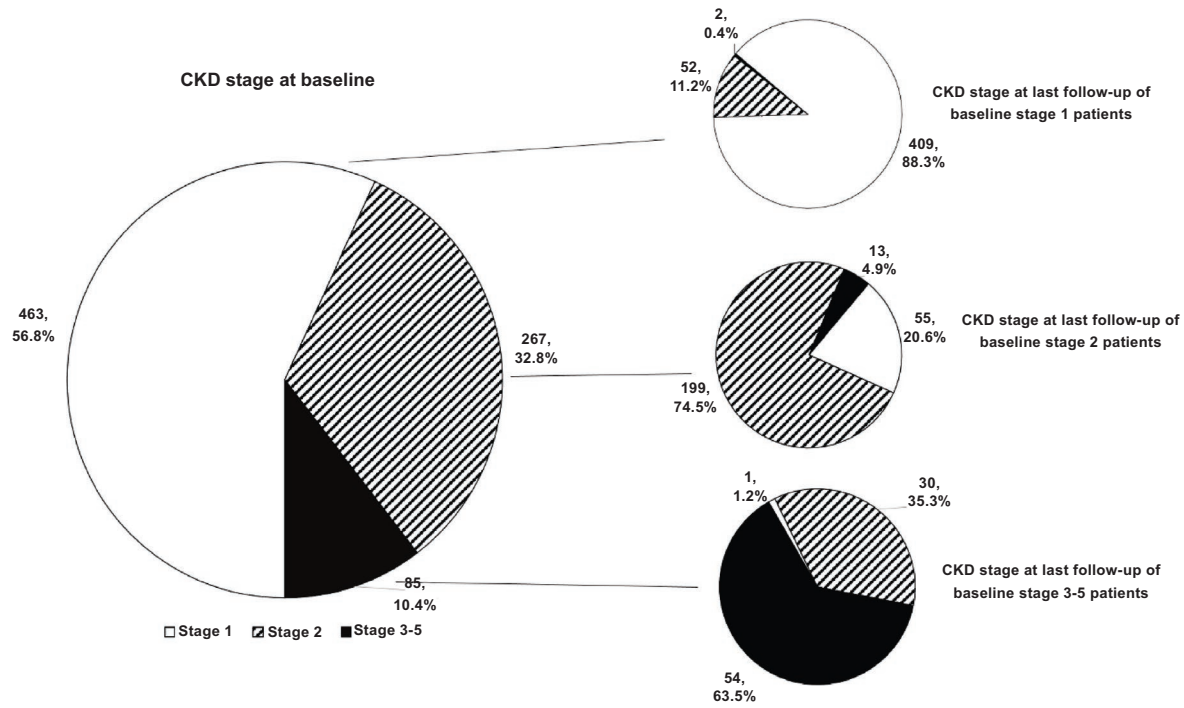


FIG. 2. CKD stage migration after switching to TAF. CKD based on eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration formula.

patterns: 51 of 267 (19.1%) CKD stage 2 patients at switch regressed to stage 1, and 26 of 85 CKD stage 3-5 patients at switch regressed to stage 2 (Supporting Fig. S7A).

We also determined the proportion of patients with <20% change and ≥20% change in eGFR over the study observation up to 96 weeks after switch to TAF in the total cohort (Fig. 3). The largest changes were

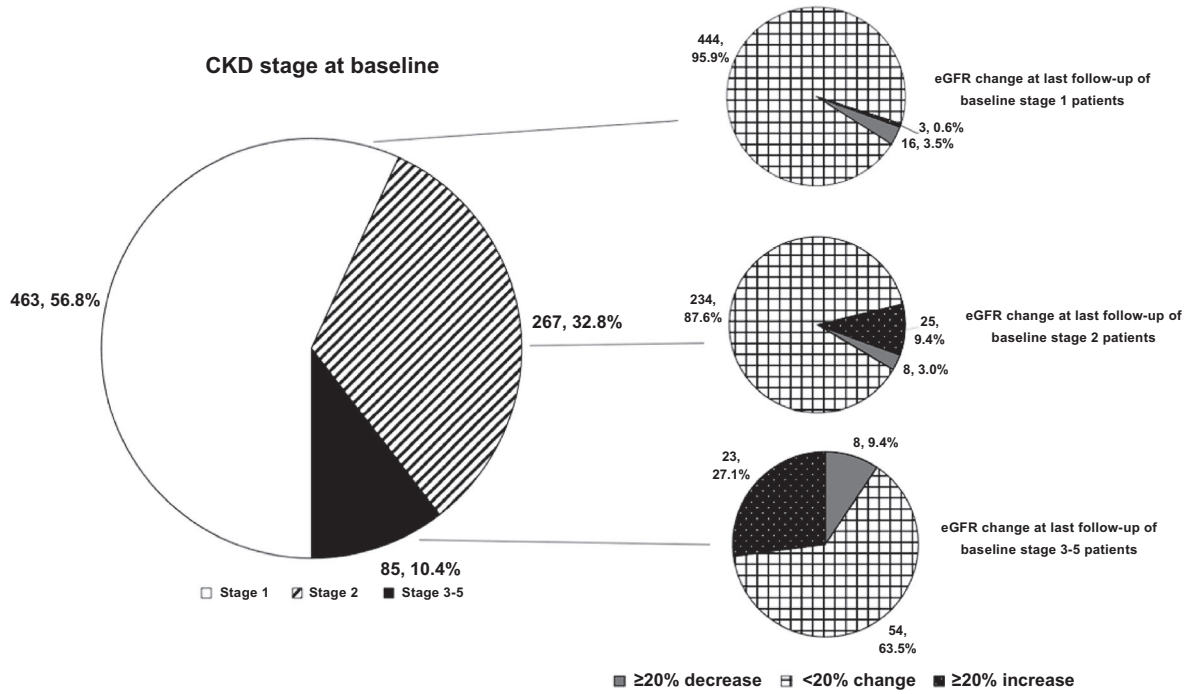


FIG. 3. Proportions of patients with 20% change in eGFR and with <20% change after switching to TAF in the total cohort. CKD and eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration formula.

observed in patients with CKD stage 3-5 at switch, 27.1% (23/85) of whom experienced ≥20% increase in eGFR, while 9.4% (8/85) experienced ≥20% decrease in eGFR.

In the sensitivity analysis of the TDF treatment-naive cohort, over the 96 weeks following TAF switch, we also found that 23% (29/126) of CKD stage 2 patients at switch point regressed to CKD stage 1 (5.6% [7/126] to stage 3-5), 41.5% (17/41) CKD stage 3-5 patients regressed to CKD stage 2, and 1 (2.4%) CKD stage 3-5 patients to stage 1, while among those with CKD stage 1 disease at the switch (n = 238), 27 (11.3%) progressed to stage 2 but none to stages 3-5 (Supporting Fig. S8). At the end of follow-up at 48 weeks, 22.2% (28/126) stage 2 patients at switch regressed to stage 1, and 41.5% (17/41) stage 3-5 patients regressed to stage 2. (Supporting Fig. S7B).

Factors Associated with Changes in eGFR

Using GEE analysis adjusting for age, ethnicity (Asian vs. non-Asian), sex, hypertension or diabetes mellitus or cirrhosis, and baseline eGFR (Table 3), we found that older age (coefficient, −0.43; 95% CI, −0.48 to −0.37; $P < 0.001$), being male (coefficient, −3.00; 95% CI, −4.32 to −1.67; $P < 0.001$), having a baseline eGFR of 60-89 (coefficient, −17.88; 95% CI, −19.48 to −16.29; $P < 0.001$), or a baseline eGFR < 60 (coefficient, −39.30; 95% CI, −41.83 to −36.76; $P < 0.001$) were associated with decreasing eGFR levels after switching to TAF over the 96 weeks of follow-up after switch (Table 3A) but not ethnicity (coefficient, −1.001; 95% CI, −3.10 to 1.10; $P = 0.35$), which was also not significant on univariable analysis (Asian vs. non-Asian, coefficient, −0.58; 95% CI, −4.97 to 3.82; $P = 0.80$). Analysis with the same model up to 48 weeks of follow-up postswitch (Table 3B) and between 48 weeks and 96 weeks postswitch (Table 3C) showed similar results.

These findings were similar for the treatment-naive group as being older (coefficient, −0.44; 95% CI, −0.52 to −0.36; $P < 0.001$), male (coefficient, −3.30; 95% CI, −5.11 to −1.49; $P < 0.001$), having a baseline eGFR of 60-89 (coefficient, −18.06; 95% CI, −20.25 to −15.86; $P < 0.001$), and having a baseline eGFR < 60 (coefficient, −39.75; 95% CI, −39.75 to −32.76; $P < 0.001$) were all associated with decreasing eGFR.

TABLE 3. GEE Analysis for Estimated Predictors of Changes in eGFR (per milliliter per minute per 1.73 square meters) (A) up to 96 Weeks, (B) up to 48 Weeks, and (C) for 48-96 Weeks of Follow-Up

Characteristics	Coefficient* (95% CI)	*P*
(A) eGFR		
Age	−0.43 (−0.48 to −0.37)	<0.001
Ethnicity		
Non-Asian	Referent	—
Asian	−1.001 (−3.10 to 1.10)	0.35
Sex		
Female	Referent	—
Male	−3.00 (−4.32 to −1.67)	<0.001
Hypertension or diabetes mellitus or cirrhosis	−1.47 (−2.99 to 0.048)	0.058
Baseline eGFR		
≥90	Referent	—
60-89	−17.88 (−19.48 to −16.29)	<0.001
<60	−39.30 (−41.83 to −36.76)	<0.001
(B) eGFR		
Age	−0.42 (−0.48 to −0.36)	<0.001
Ethnicity		
Non-Asian	Referent	—
Asian	−1.13 (−3.22 to 0.95)	0.29
Sex		
Female	Referent	—
Male	−2.83 (−4.15 to −1.52)	<0.001
Hypertension or diabetes mellitus or cirrhosis	−1.63 (−3.14 to −0.11)	0.036
Baseline eGFR		
≥90	Referent	—
60-89	−18.33 (−19.92 to −16.74)	<0.001
<60	−40.29 (−42.81 to −37.76)	<0.001
(C) eGFR		
Age	−0.45 (−0.52 to −0.38)	<0.001
Ethnicity		
Non-Asian	Referent	—
Asian	−1.35 (−4.00 to 1.29)	0.32
Sex		
Female	Referent	—
Male	−3.33 (−4.88 to −1.77)	<0.001
Hypertension or diabetes mellitus or cirrhosis	−1.44 (−3.21 to 0.32)	0.11
Baseline eGFR		
≥90	Referent	—
60-89	−16.00 (−17.87 to −14.12)	<0.001
<60	−37.25 (−40.25 to −34.25)	<0.001

*Adjusted for age, sex, hypertension or diabetes mellitus or cirrhosis, and baseline eGFR. eGFR, calculated using the Chronic Kidney Disease Epidemiology Collaboration formula.

Discussion

In this large, multicenter, real-world study of patients with CHB on TAF sequential therapy after receiving TDF for close to 5 years, we found continued increase in viral, biochemical, and complete response rates up to 96 weeks after switching from TDF to TAF as well as stable levels of mean eGFR following adjustment for age, sex, baseline eGFR, and diabetes, hypertension, or cirrhosis. These findings of continued improvement in viral suppression and complete response obtained with TAF treatment are in line with other reports, adding strength to the evidence that TAF also provides excellent therapeutic results in routine clinical practice.[10-16]

With regard to renal function, we found that the adjusted mean eGFR remained stable while on TDF and after the switch to TAF for patients with normal renal function. However, we noted that among those with eGFR < 90, while the adjusted mean was stable after switch to TAF, it had decreased significantly while on TDF prior to switch. These findings suggest that there may be a renal advantage with TAF compared to TDF; however, further research is needed to validate this point.

On the other hand, overall, we did not find a significant increase in the mean eGFR after the switch as reported in the noninferiority randomized controlled trial by Lampertico et al.[15] We hypothesize that the differences in our results may be due to a variety of reasons. One, the randomized controlled trial study, in its TDF comparison arm, compared the eGFR between the two groups, with one having an increased eGFR and the other one having a decreased eGFR. However, the increase in median eGFR in the TAF group was only by 0.94 mL/min, and the mean eGFR in this study was not adjusted for factors that can affect renal function decline over time such as age, baseline GFR, diabetes mellitus, and hypertension.[21] Our GLM analysis took into account these confounding factors, which may provide a more accurate assessment of the evolution of renal function over time. In addition, as mentioned, although there were no statistically significant changes in renal function on TAF including those with impaired renal function at switch, we did find a statistically significant decrease in the adjusted mean

eGFR of patients with impaired renal function during TDF treatment, suggesting a more favorable renal outcome with TAF. Furthermore, slow decline in renal function is expected to occur after the fourth decade of life even in those without kidney disease by about 8 mL/min/1.73 m^2 per decade,[21] suggesting that a lack of significant decline in eGFR over the 2 years on TAF may, in fact, suggest some recovery of renal function after exposure to TDF was discontinued.

In analysis by CKD stage, we found patients migrating by CKD stages in both directions, with a small percent (11.7%) of those with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2) at switch progressing to mildly impaired renal function (eGFR < 90 but ≥60 mL/min/1.73 m^2) by 96 weeks after switch, while at the same time about 20% of those with mild renal impairment at switch returned to normal renal function, and a few (3.4%) progressed to a higher stage. Among those with moderate to severe (eGFR < 60 mL/min/1.73 m^2) renal function at switch, 35% regressed to only mild renal impairment, and 1% returned to normal renal function.

A strength of our study is the large number of real-world patients from multiple clinical centers from both Asia and the United States who underwent the switch from TDF to TAF and were followed for up to 96 weeks. Our findings help to confirm results from clinical trials in that TAF allows for continued increase in not only viral suppression but also ALT normalization, which can reduce the risk for development of cirrhosis and HCC.[22] Another strength was that we examined changes in renal function using GLM modeling to adjust for effects of age, cirrhosis, diabetes mellitus, hypertension, and baseline eGFR on renal outcomes to help discern the effects of TAF from other known influencers of renal function.

However, our study is not without its limitations, which include not having serum and urinary tubular markers, bone biomarkers, serum phosphorus level, as well as other markers such as bone density and serial serum lipids, as they are generally not recommended by current CHB practice guidelines and thus not routinely performed in clinical practice.[9] Access to some of these data may provide better insight into the positive effects of TAF, especially among those who were considered to have mild renal impairment rather than using the more global indicator of renal function, eGFR, to better determine who would benefit the most from switching from TDF to TAF.[23] Additionally, we did not include data on the effects of TAF on special populations such as pregnant women and transplanted or immunosuppressed patients, so further studies regarding these populations are needed. We also recognize that we did not have a control arm for those who stayed on TDF; therefore, increasing rates of treatment response after switch to TAF does not necessarily mean that TAF is a superior therapy. However, we assessed changes of various markers prior to TAF and, for example, showed that while there were no changes in renal function after TAF, there was a decline in renal function during TDF administration prior to TAF. We also did not have precise information on the reason for the switch, and hence the switch might be done by providers and/or patients who perceived the patients to be at high risk (e.g., patients with diabetes and hypertension, preexisting renal impairment). However, our renal outcome analysis was adjusted by several factors that can affect these outcomes. Additional studies with longer follow-up are also needed because a significant proportion of our study cohort did not reach the 96-week postswitch follow-up, given that TAF is a relatively new drug with associated insurance/reimbursement restriction, especially in the first few years post–drug approval. Finally, although our data were geographically diverse, from the United States and Asia, the vast majority of our patients were Asian. Nevertheless, because the majority of HBV infections in the United States are imported with the largest group being immigrants from Asia, our patient population is probably representative of the majority of HBV cases in the United States; and there was no significant difference in regard to eGFR changes in Asian compared to non-Asian patients in our GEE analysis. In addition, prior US data have shown no significant difference in kidney function decline in people of Asian origin and whites.[24]

In our cohort of patients with CHB and sequential TDF-to-TAF therapy, we observed continued improvement in virologic response, ALT normalization, and no significant changes in eGFR following switch to TAF from TDF. In addition, renal function was not adversely affected by the switch even among those with renal impairment prior to the switch.

Author Contributions: M.H.N. was the guarantor of the article and was responsible for study concept, design, and supervision. M.H.N. and H.D. were responsible

for data analysis. M.H.N., H.T., L.H., and H.D. were responsible for drafting the article. All authors were responsible for data collection, data interpretation, and review and/or revision of the manuscript.

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