Efficacy and Safety of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide as Maintenance Treatment in HIV/HBV-Coinfected Patients

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Background: The efficacy and safety of switching from tenofovir disoproxil fumarate-based antiretroviral therapy to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide (E/C/F/TAF) has not been widely investigated in HIV/hepatitis B virus (HBV)-coinfected Asian population.

Methods: Between February and October 2018, HIV/HBV-coinfected patients who had achieved HIV viral suppression with tenofovir disoproxil fumarate-containing regimens were switched to E/C/F/TAF. Assessments of plasma HBV and HIV viral load, HBV serology, renal function, lipid profiles, and bone mineral density (BMD) were performed at weeks 24 and 48 after switch.

Results: A total of 274 HIV/HBV-coinfected participants were enrolled, with 12.8% testing HBeAg-positive and 94.2% having plasma HBV DNA <20 IU/mL at baseline. At weeks 24 and 48, 92.7% and 89.8% achieved plasma HBV DNA <20 IU/mL; 4.7% and 5.1% had HBV DNA ≥20 IU/mL; and 2.6% and 5.1% had no data, respectively. At weeks 24 and 48, 95.6% and 94.2% of participants maintained HIV RNA <50 copies/mL, respectively. Compared with baseline, the median urine β2-microglobulin-to-creatinine ratio at week 48 decreased significantly from 165 to 90 μg/g ($P < 0.001$). The mean BMD of the spine and hip improved at week 48 (+1.77% and +1.33%, respectively). Significantly higher lipid profiles were observed after switch to E/C/F/TAF. Thirteen (4.7%) patients withdrew from the study before week 48, with 7 (2.6%) patients because of adverse effects.

Conclusions: Switch to E/C/F/TAF maintained HBV and HIV viral suppression and resulted in the improvement of proteinuria and BMD of the spine and hip but increased lipid levels in HIV/HBV-coinfected patients at week 48.

Key Words: hepatitis B, antiretroviral therapy, proteinuria, bone mineral density

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INTRODUCTION

In Asia, approximately 15%–25% of the HIV-infected patients have concurrent chronic hepatitis B virus (HBV) infection.[1,2] HIV/HBV-coinfected patients are at a higher risk for acute hepatitis, chronic hepatic complications, and liver-related mortality than those with HBV monoinfection.[3,4] Therefore, sustained maintenance of HBV viral suppression is

important for HIV/HBV-coinfected patients to prevent HBV-related liver damage.[5]

Tenofovir disoproxil fumarate (TDF), an antiretroviral agent used to treat HIV and HBV, has demonstrated long-term HBV suppression and a high genetic barrier to emergence of HBV resistance.[6,7] For patients coinfected with HIV and HBV, combination antiretroviral therapy (ART) containing TDF plus lamivudine (3TC) or emtricitabine (FTC) in addition to a third agent is the recommended first-line regimen.[8] However, long-term exposure to TDF may lead to nephrotoxicity and a greater loss in bone mineral density (BMD),[9,10] particularly among individuals who are aging and have small body habitus and multiple comorbidities.[11,12]

Tenofovir alafenamide (TAF) is a newer prodrug of tenofovir that achieves high active metabolite concentrations in peripheral blood mononuclear cells and lower plasma tenofovir levels.[13] In HIV-monoinfected patients, switching from TDF-containing to TAF-containing ART maintains HIV suppression and shows improvement in glomerular function, overall and tubular proteinuria, and BMD.[14,15] Clinical data also support the use of TAF-containing regimens in HIV-infected patients with mild-to-moderate renal impairment and those on hemodialysis.[16] For patients with chronic HBV monoinfection, 2 large studies reported similar rates of HBV viral suppression between TAF-treated and TDF-treated patients.[17–19] Although TAF is effective for HIV and HBV therapy, data on the efficacy of TAF in maintaining HBV viral suppression remain limited among HIV/HBV-coinfected patients. In a multinational study in which 72 HIV/HBV-coinfected patients were switched to coformulated elvitegravir, cobicistat, emtricitabine, and TAF (E/C/F/TAF),[20] 91.7% of the participants achieved virologic suppression for both HIV and HBV at 48 weeks. Improvements in creatinine clearance and proteinuria and declines in markers of bone turnover were observed; however, BMD was not assessed, and only 7 participants were Asians.[20] Current data from Asian populations living in areas of high HBV endemicity are scarce.

To further the understanding of the efficacy and safety of TAF-containing ART among HIV/HBV-coinfected patients, we conducted this multicenter observational study in Taiwan, where 15%–20% of HIV-infected patients born before the implementation of universal neonatal HBV vaccination have chronic HBV infection.[21]

METHODS

Study Design and Participants

This prospective, observational cohort study was conducted at 13 hospitals designated for HIV care around Taiwan. From February to October 2018, HIV/HBV-coinfected adults (aged ≥20 years) who were switched from TDF/FTC or TDF plus 3TC-based regimens to coformulated E/C/F/TAF as maintenance treatment were enrolled. The inclusion criteria included the use of TDF/FTC or TDF plus 3TC as backbone plus a third agent for 6 months or longer; plasma HIV RNA <50 copies/mL twice over the past 12 months; no known resistance mutations to integrase strand transfer inhibitors (InSTIs); no previous history of HIV treatment failure while receiving InSTI-containing ART; no known resistance mutations to TDF, FTC, or 3TC; no previous history of HIV treatment failure while receiving TDF, FTC, or 3TC-containing ART; estimated glomerular filtration rate (eGFR) ≥30 min/mL (calculated by the CKD-EPI equation); and aspartate aminotransferase and alanine aminotransferase (ALT) lower than 2-fold the upper limit of normal. The patients were excluded if they had the following conditions: active opportunistic illness, on treatment of tuberculosis, pregnancy or lactation, hepatic decompensation (Child-Pugh class C), allergy to TDF, TAF, FTC, 3TC, or InSTIs, intolerance of InSTIs, HCV coinfection with treatment with direct-acting antiviral agents or interferon/ribavirin planned within 48 weeks, and concurrent use of medications that were contraindicated with E/C/F/TAF. All included patients were followed for 48 weeks.

Our primary end points were the proportions of participants who failed to achieve undetectable plasma HBV DNA (<20 IU/mL) and plasma HIV RNA (<50 copies/mL) at week 48 after switching to E/C/F/TAF. The secondary end points included the proportions of undetectable plasma HBV DNA (<20 IU/mL) and plasma HIV RNA (<50 copies/mL), the serologic response of HBV to E/C/F/TAF, and the interval changes of eGFR, proteinuria, and BMD.

Ethics Statement

The study was approved by the research ethics committee or institutional review boards of the 13 participating hospitals (registration number: 201710056RINB, 107025-F, TYGH107001, 18MMHIS012e, CMUH107-REC2-081, 107-005-E, CS18052, CF18037B, 171203, 10701-008, 201701662A3, KMUHIRB-SV(II)-20170065, and VGHKS18-CT1-18). All participants gave written informed consent before enrollment. The study was registered with ClinicalTrials.gov (NCT03425994).

Data Collection and Definitions

A standardized case record form was used to collect the information on the demographics, sexual preference, weight at enrollment, comorbidity, concomitant medications, treatment history of HIV and HBV, and the results of laboratory investigations. Tests for plasma HIV RNA, CD4 lymphocyte count, rapid plasma reagin titer, serum creatinine, liver function, lipid profile, and fasting blood glucose or glycated hemoglobin (HbA1C) were performed every 3–6 months by following the national HIV treatment guidelines in Taiwan. For HBV coinfection, plasma HBV DNA, HBsAg, anti-HBs, HBeAg, anti-HBe, and anti-HDV IgG were tested at a central laboratory at baseline and every 24 weeks after switching to E/C/F/TAF. For patients with a positive anti-HDV IgG, HDV RNA was determined. Abdominal sonography and assessments of eGFR, urine sediment, urine protein–creatinine ratio, urine albumin–creatinine ratio (UACR), and urine β2-microglobulin–creatinine ratio were performed at baseline and weeks 24 and 48. BMDs were measured at baseline and 24 and 48 weeks after switching to E/C/F/TAF.

Chronic HBV infection was defined as the persistence of HBsAg for >6 months.[22] HIV treatment failure was defined as a plasma HIV RNA >400 copies/mL.[23]

Undetectable plasma HBV and HIV were defined as <20 IU/mL and <50 copies/mL, respectively. The upper limit of normal for the serum ALT level was 40 IU/mL.

Laboratory Investigations

Plasma HBV DNA was quantified using the COBAS AmpliPrep/COBAS TaqMan HBV test (version 2.0, Roche Molecular Systems, Inc., Pleasanton, CA). The HBV serological markers (HBsAg, anti-HBs antibody, HBeAg, and anti-HBe antibody) were determined using the chemiluminescent microparticle immunoassay (Abbott Laboratories, Abbott Park, IL). HDV RNA was quantified using the previously described method,[24] and anti-HDV IgG was determined by competitive enzyme immunoassay according to the manufacturer's instructions (Dia.Pro Diagnostic BioProbes Srl, Milan, Italy). The urine protein, urine albumin, and urine β2-microglobulin were also quantified (Angene Biotechnology Co., Ltd., Taiwan).

BMD Measurement

BMD assessment was performed in 181 participants enrolled at 4 participating hospitals. BMD of the lumbar spine (L1-L4) and total hip were assessed using dual energy x-ray absorptiometry (Lunar Prodigy; GE Healthcare, Machelen, Belgium). According to the WHO criteria, osteopenia is defined as a BMD T-score between −1.0 and −2.5, and osteoporosis is defined as a BMD T-score less than or equal to −2.5.[25] WHO recommends using Z-scores in reporting BMD for premenopausal women or men younger than 50 years, and a Z-score of −2.0 or lower is defined as low BMD for chronological age.[26]

Statistical Analysis

The distributions of participants' demographics and baseline characteristics were presented with descriptive statistics. Categorical variables were compared using the χ^2 test or Fisher exact test, and continuous variables using the Mann–Whitney *U* test. For paired data, categorical variables were compared using the McNemar test, and continuous variables using the Wilcoxon signed-rank test. Measurements of plasma HBV DNA at each time point were analyzed using generalized estimating equations for repeated measurements in the longitudinal follow-up. A linear regression model was applied to test the association between changes in weight and lipids. All *P* values were 2 sided, and a *P* value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS software version 25.0 (SPSS Inc., Chicago, IL).

RESULTS

Participant Characteristics

During the study period, 274 HIV/HBV-coinfected participants who met the inclusion criteria were enrolled. Among them, 268 and 261 completed the 24 and 48 weeks of follow-up, and 13 (4.7%) withdrew from the study before week 48, with 7 (2.6%) withdrew because of adverse effects (Fig. 1). The adverse events leading to discontinuations of E/C/F/TAF were gastrointestinal discomfort in 3 participants, insomnia in 2, depression in one, and headache in one.

The baseline characteristics of the participants are shown in Table 1. Most were middle-aged men who have sex with men. Before switching to E/C/F/TAF, the median duration of exposure to TDF was 4.0 years (range, 2.4–6.0). Overall, 12.8% of the participants tested HBeAg-positive, and 94.2% had a plasma HBV DNA <20 IU/mL. For participants with detectable HBV DNA (≥20 IU/mL) before E/C/F/TAF, the median HBV DNA was 47 IU/mL (range, 29–108).

Virologic Efficacy

The virologic responses of HBV and HIV to E/C/F/TAF at weeks 24 and 48 are shown in Figure 2, in which 92.7% and 89.8% of the participants achieved plasma HBV DNA <20 IU/mL and 4.7% and 5.1% of participants had HBV DNA ≥20 IU/mL at weeks 24 and 48, respectively (Fig. 2A). The median HBV DNA of 14 participants with a detectable HBV DNA at week 48 was 31 IU/mL (range, 28–38). During the follow-up period, 5 participants had >1 $\log_{10}$ increase in plasma HBV DNA from having achieved <20 IU/mL and 2 had persistent detectable HBV DNA, and the highest HBV DNA level detected was 1000 IU/mL. All 7 participants had undetectable HIV RNA at the end of the study. After adjusting for age, baseline CD4 count, duration of TDF exposure, baseline HBsAg level, HBV DNA level, and HBeAg positivity, a detectable

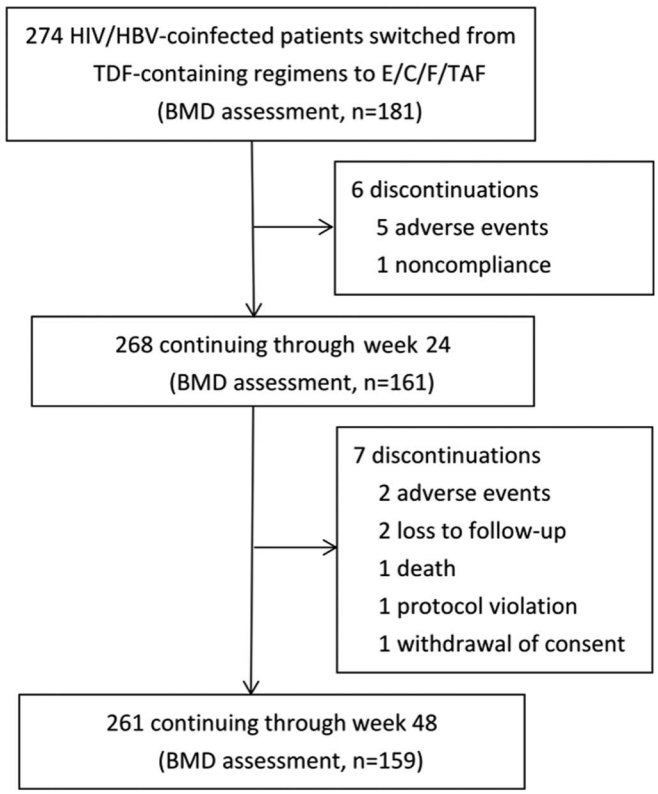

FIGURE 1. Flow diagram of the study. E/C/F/TAF, coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide.

TABLE 1. Demographic and Clinical Characteristics of the Participants at Baseline and Week 48

	Baseline (n = 274)	Week 48 (n = 261)	Baseline vs Week 48, *P*
Age, median (IQR), yr	41 (36–47)	—	
Male sex, n (%)	269 (98.2)	—	
Men who have sex with men, n (%)	238 (86.9)	—	
Injection drug users, n (%)	20 (7.3)	—	
Years since HIV diagnosis, median (IQR)	7.3 (4.0–10.8)	—	
Duration of TDF use, median (IQR), yr	4.0 (2.4–6.0)	—	
Weight,* median (IQR), kg	69 (60–77)	72 (64–79)	<0.001
Anti-HCV positivity, n (%)	36/266 (13.5)	27/170 (15.9)	0.453
Anti-HDV positivity, n (%)	40 (14.6)	37/260 (14.2)	0.999
Positive RPR titer, n (%)	119/271 (43.9)	112/251 (44.6)	0.999
Plasma HIV RNA <50 copies/mL, n (%)	274 (100)	258/260 (99.2)	0.500
CD4 count, median (IQR), cells/μL	570 (433–721)	588 (439–742)	0.028
ALT, median (IQR), IU/mL	26 (20–37)	24 (17–33)	0.001
AST, median (IQR), IU/mL	25 (21–31)	22 (19–29)	<0.001
Cirrhosis of the liver, n (%)	4/250 (1.6)	4/170 (2.4)	0.999
Serum creatinine, median (IQR), mg/dL	0.94 (0.84–1.08)	1.00 (0.90–1.10)	<0.001
eGFR, median (IQR), mL/min/1.73m^2	98.8 (85.6–109.2)	94.9 (82.4–105.5)	<0.001
HBV DNA and serological markers			
Plasma HBV DNA <20 IU/mL, n (%)	258 (94.2)	246/260 (94.6)	0.839
HBeAg positivity, n (%)	35 (12.8)	33/260 (12.7)	0.625
Anti-HBe positivity, n (%)	206 (75.2)	192/260 (73.8)	0.508
HBsAg positivity, n (%)	274 (100)	257/260 (98.4)	0.250
HBsAg level, median (IQR), IU/mL	678 (90–1703)	656 (95–1590)	0.011
HBsAg level, median (IQR), Log_{10} IU/mL	2.8 (2.0–3.2)	2.8 (2.0–3.2)	0.142
Positive or equivocal anti-HBs Ab, n (%)	5 (1.8)	6/260 (2.3)	0.999
Third agent of ART at inclusion, n (%)			
NNRTI	198 (72.3)	—	
Efavirenz	119 (43.4)	—	
Nevirapine	16 (5.8)	—	
Rilpivirine	63 (23.0)	—	
Protease inhibitor	54 (19.7)	—	
Integrase inhibitor	22 (8.0)	—	
Diabetes mellitus, n (%)	9 (3.4)	—	
Hypertension, n (%)	18 (6.6)	—	

*Only 89 patients had body weight data at both baseline and week 48.

AST, aspartate transaminase; HBeAg, hepatitis B virus envelope antigen; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HDV, hepatitis D virus; IQR, interquartile range; NNRTI, non-nucleoside reverse transcriptase inhibitor; RPR, rapid plasma reagin.

HBV DNA (≥20 IU/mL) was significantly correlated with baseline HBeAg positivity (adjusted odds ratio 3.652, 95% confidence interval 1.248 to 10.690, $P = 0.018$) and duration of previous TDF therapy (per 1-year increase, adjusted odds ratio 0.812, 95% CI: 0.677 to 0.975, $P = 0.026$) by a generalized estimating equation analysis (see Table 1, Supplemental Digital Content 1, http://links.lww.com/QAI/B580). The proportion of participants who maintained HIV suppression at weeks 24 and 48 was 95.6% and 94.2%, respectively (Fig. 2B).

Serologic Response of HBV and Liver Function

At week 48 of E/C/F/TAF, 3 (8.6%) of 35 HBeAg-positive participants had a loss of HBeAg and 2 (5.7%) had HBeAg seroconversion. One HBeAg-negative participant had HBeAg seroreversion at week 48. The median HBsAg level decreased significantly in HBeAg-positive participants from 3.3 log_{10} IU/mL to 3.2 log_{10} IU/mL ($P < 0.001$) but not in HBeAg-negative participants (see Fig. 1, Supplemental Digital Content 1, http://links.lww.com/QAI/B580). The loss of HBsAg occurred in 3 (1.1%) participants, and one of them had an equivocal anti-HBs titer at week 48. The median ALT and aspartate aminotransferase levels of the participants decreased significantly, and 26 (53.1%) of 49 participants who had ALT ≥40 IU/mL at baseline achieved ALT normalization.

Evolution of Renal Function and Lipid Profile

The median serum creatinine increased from 0.94 mg/dL to 1.00 mg/dL, and the median eGFR decreased from 98.8 mL/min/1.73m^2 to 94.9 mL/min/1.73m^2 through 48 weeks (both $P < 0.001$). The participants experienced significant decreases in urine protein–creatinine ratio, UACR, and urine β2-microglobulin–creatinine ratio (Fig. 3A). All fasting lipid levels increased from baseline to week 48, including total cholesterol (TC) to high-density lipoprotein (HDL)-cholesterol (TC/HDL-cholesterol) ratio (Fig. 3B). The mean percentage increase from

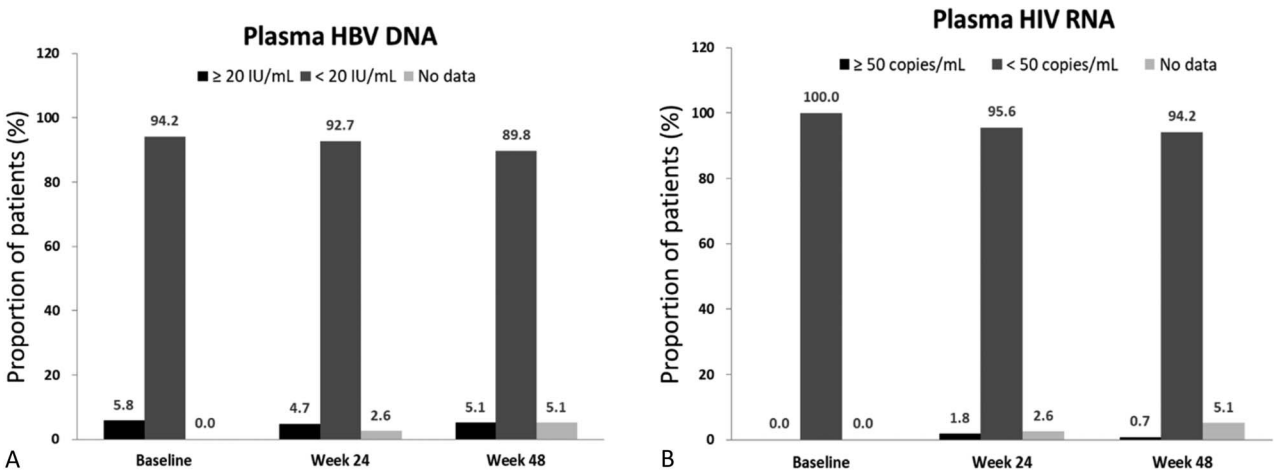

FIGURE 2. Virologic responses of (A) HBV (HBV DNA <20 IU/mL) and (B) HIV (HIV RNA <50 copies/mL) to E/C/F/TAF at weeks 24 and 48.

baselines in triglycerides, total cholesterol, LDL-cholesterol, and HDL-cholesterol was 38%, 17%, 22%, and 12%, respectively, at week 48. A modest weight gain was noted among 89 patients with follow-up measurements, with a median weight increase from 69 kg at baseline to 72 kg at week 48 ($P < 0.001$). No correlation was found between the increases in lipids and weight gain with linear regression. There were no statistically significant changes in fasting blood glucose and HbA1C from baseline to week 48 (see Table 2, Supplemental Digital Content 1, http://links.lww.com/QAI/B580).

Evolution of Bone Mineral Density

Of the 181 (66.1%) participants who underwent BMD assessment, the mean BMD of the spine and hip increased significantly at week 48 (+1.77% and +1.33%, respectively) (Fig. 4A). The comparisons between the participants who underwent the BMD assessment and those who did not are shown in Supplemental Digital Content 1 (see Table 3, http://links.lww.com/QAI/B580). The prevalence of osteopenia at the spine and hip decreased from 20.6% and 27.6% to 18.4% and 24.5%, respectively, through week 48. The prevalence of osteoporosis at the spine and hip also decreased from 1.7% and 3.3% at baseline to 0.6% and 1.3%, respectively, at week 48 (Fig. 4B). The changes in BMD, T-score, and Z-score are shown in Supplemental Digital Content 1 (see Table 2, http://links.lww.com/QAI/B580).

HDV Coinfection

The seroprevalance of anti-HDV IgG remained stable from baseline (14.6%) to week 48 (13.5%) (see Fig. 2A, Supplemental Digital Content 1, http://links.lww.com/QAI/B580). Three participants (1.1%) had anti-HDV seroconversion during the follow-up. Among participants with positive anti-HDV IgG, 25% (10/40) and 18.9% (7/37) had detectable

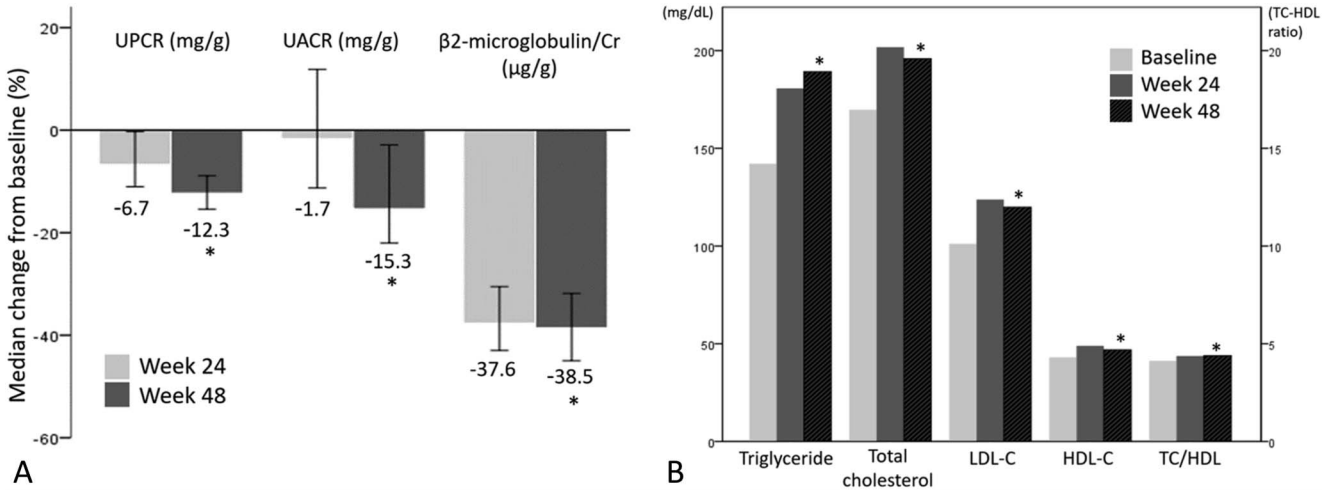

FIGURE 3. Changes in (A) quantitative proteinuria [median (95% confidence interval)] and (B) lipid profile through week 48. The asterisk (*) indicates that the median level at week 48 is significantly different from baseline ($P < 0.05$). UPCR, urine protein-to-creatinine ratio; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

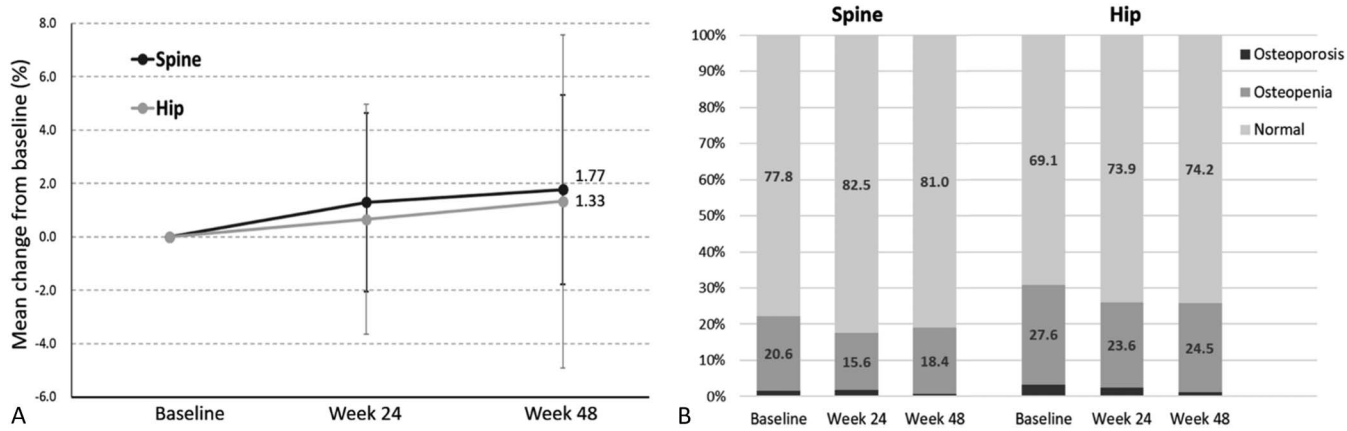

FIGURE 4. Changes in (A) BMD of the spine and hip and (B) the proportion of participants with osteopenia and osteoporosis through week 48.

plasma HDV RNA (≥100 copies/mL) at baseline and week 48, respectively. Five participants (1.8%) had persistent HDV viremia during the study period. The median HDV RNA among participants with detectable HDV RNA was 4.7 $\log_{10}$ copies/mL and 4.1 $\log_{10}$ copies/mL at baseline and week 48, respectively (see Fig. 2B, Supplemental Digital Content 1, http://links.lww.com/QAI/B580). Seven (41%) of the 17 participants with detectable HDV RNA experienced ALT elevation for greater than 2-fold of the upper limits of normal during the 48 weeks of follow-up.

DISCUSSION

In this cohort of HIV/HBV-coinfected Asians who were switched from TDF-based regimens to E/C/F/TAF, 89.8% and 94.2% of participants maintained HBV and HIV suppression at week 48, respectively. Seroconversion occurred in 5.7% of HBeAg-positive participants, and 1.1% of all participants lost HBsAg. After switch to E/C/F/TAF, the participants had improved proteinuria and BMD. All components of the fasting lipid profile increased, including HDL-cholesterol. E/C/F/TAF was well tolerated, with only 2.6% of the participants discontinuing the treatment because of drug-related adverse events.

Our results confirm the efficacy of TAF in maintaining HBV viral suppression in HIV/HBV-coinfected patients. In the study of Gallant et al,[20] 91.7% of 72 patients had HBV DNA <29 IU/mL at 48 weeks after switch from TDF-containing ART to E/C/F/TAF. Using the same cutoff value (<29 IU/mL), up to 91.2% (250/274) of our participants achieved HBV suppression at week 48. Another study of HBV-monoinfected patients with suppressed HBV DNA (<20 IU/mL) found that 96.3% (234/243) of patients switching from TDF to TAF maintained HBV DNA <20 IU/mL at 48 weeks,[27] and the study concluded that TAF can be a substitute for TDF in HBV-infected patients. In contrast to the report of Gallant et al,[20] in which no individual with baseline undetectable HBV DNA became detectable at week 48, 17 (6.6%) of 258 participants with baseline undetectable HBV DNA in our cohort had HBV DNA ≥20 IU/mL at weeks 24 or 48. All of these 17 participants had HIV RNA <50 copies/mL (data not shown), and 5 participants had a 2-fold or greater elevation of ALT (1 had HDV superinfection; 2 due to concurrent use of health supplement or herbal medicine that might have affected the bioavailability of E/C/F/TAF; 1 acute HCV infection; and 1 with no specific causes identified). A detectable HBV DNA during TDF-based therapy is not unusual.[28] Of patients reporting good ART adherence, suboptimal HBV suppression might be due to the genetic variability of HBV or a stricter adherence requirement for HBV than HIV suppression.[29] Transient HBV viral blips might also represent random assay variability.[30] In our study, patients who did not achieve primary end points had low-level HBV viremia. Previous clinical studies showed that the percentage of patients with HBV viremia declined over long-term TDF treatment,[31] and the emergence of HBV resistance to TDF or TAF was rare.[19,30] Although more studies are warranted to investigate the long-term outcomes of HIV/HBV-coinfected patients who had HBV viremia on TAF treatment, currently available data suggest that low-level HBV viremia at 48 weeks of TAF-containing therapy does not indicate an increased risk of virologic failure or development of TAF resistance, and TAF treatment could be continued.[19,30,31] In our study, 14 of the 17 participants whose HBV DNA became detectable continued E/C/F/TAF and all had HBV DNA <20 IU/mL at week 96. No liver-related morbidity or mortality occurred up to week 96 (data not shown).

Seropositivity for HBeAg was recognized as a surrogate marker of active HBV replication.[32] In our study, HBeAg-positive patients had a higher rate of detectable HBV DNA at week 48 than HBeAg-negative patients (96.0% vs 85.7%, $P = 0.027$). HBeAg positivity has also been associated with failure to achieve HBV suppression in patients who received TDF therapy.[31,33] The loss of HBeAg and HBeAg seroconversion occurred infrequently in our cohort (8.6% and 5.7%), which is similar to the low rates observed in HBV-monoinfected patients (8% and 3%).[27]

Switch from TDF-containing to TAF-containing regimens lead to favorable changes in proteinuria and

BMD in HIV/HBV-coinfected patients. These findings are consistent with those of the studies on HIV-monoinfected or HBV-monoinfected populations.[14,27,34,35] In a pooled analysis including only 6% of Asians, virologically suppressed HIV-infected patients taking a TAF-containing regimen had a decrease in the median UACR and urine β2-microglobulin-to-creatinine ratio by 5.4% and 25.8%, respectively, at week 96.[34] In this study consisting of participants of ethnic Chinese, we showed a greater improvement of proteinuria (15.3% and 38.5% at week 48), which could be attributed to the fact that Asians are characterized by a smaller body weight relative to people in North America and Western Europe and low body weight has been shown to be associated with higher plasma tenofovir trough concentrations and an increased risk of TDF-related renal dysfunction.[11,12,36–38] A subanalysis of trials evaluating E/C/F/TAF in Asian participants showed no renal adverse events leading to E/C/F/TAF discontinuations in ART-naive and experienced Asians, whereas discontinuations due to renal adverse events occurred in non-Asians.[39]

For bone safety, we observed an increase in the mean BMD of the spine by 1.77% at week 48 of switch to E/C/F/TAF, which is comparable with 1.56% and 1.74% increase in BMD of the spine among HIV-monoinfected and HBV-monoinfected patients, respectively.[14,27] In our study, the median serum creatinine increased significantly from 0.94 to 1.00 mg/dL at week 48. This could be attributed to the high proportion (65%, including 43.4% and 5.8% received efavirenz-based and nevirapine-based regimens, respectively) of our participants who switched from an ART regimen without a creatinine transport inhibitor, such as rilpivirine, dolutegravir, bictegravir, cobicistat, or ritonavir, to a regimen containing cobicistat.[40,41] In subgroup analysis, the median serum creatinine increased significantly in patients taking ART regimens not containing creatinine transport inhibitors (baseline vs week 48, 0.94 mg/dL vs 1.00 mg/dL, $P < 0.001$) but not in patients taking creatinine transport inhibitor-containing ART at baseline (baseline vs week 48, 1.00 mg/dL vs 0.96 mg/dL, $P = 0.170$) (data not shown).

Published data have shown that TAF-containing regimens had a less favorable effect on lipids than TDF-containing regimens,[19,35,42] and the increases in lipids when switching from TAF-containing to TDF-containing regimens could be reversible if switch back.[43] Although most studies reported a stable TC/HDL-cholesterol ratio,[14,27,35] we found a small but significant increase in TC/HDL-cholesterol ratio among our participants. The clinical significance of this alteration in lipid parameters remains uncertain, however. In a 96-week study, lipid changes with TAF did not affect cardiovascular disease risk profiles in comparison with TDF.[44]

InSTIs have recently been shown to be associated with more weight gain than protease inhibitors or non-nucleoside reverse transcriptase inhibitors[42,45]; moreover, weight gain on InSTIs could be accompanied by worsening of lipid and glucose profiles.[42,46] In our study, we observed a significant but modest weight gain (3 kg) in 89 patients with follow-up measurements, yet no correlation between the changes in weight and lipids was found over the 48-week follow-up. In patients with chronic HBV infection, metabolic syndrome may increase the risk of liver fibrosis progression.[47,48] Therefore, the metabolic derangements among HBV/HIV-coinfected patients taking TAF-containing or InSTI-containing regimens warrant more attention and should be actively managed to prevent potential liver and cardiovascular adverse effects.

In this study, 14% of participants had HDV seropositivity, and HDV viremia was detected in 20%–25% of anti–HDV-positive participants. Studies in Taiwan had shown a higher prevalence of HDV infection in HIV/HBV-coinfected patients than HBV-monoinfected patients,[49] with an increasing trend of recent HDV infection.[24] Infection with HDV often presents as hepatitis flares and may accelerate liver fibrosis.[50] For HIV/HBV-coinfected patients, it is necessary to consider the anti-HDV antibody and HDV RNA testing when clinical hepatitis is evident. It is also important to maintain long-term HBV suppression because a decrease in the HBsAg level has been shown to be associated with decreases of HDV RNA.[51,52]

The strength of the study is the relatively large number of HIV/HBV-coinfected individuals in whom the efficacy of E/C/F/TAF on HBV suppression is prospectively evaluated in a country that is hyperendemic for HBV infection. There are several limitations to our study, however. First, this was a single-arm study without a comparator group. Second, our study excluded HIV/HBV-coinfected patients who had an eGFR less than 30 mL/min/1.73m^2 or decompensated cirrhosis; therefore, the results cannot be generalized to patients with severe renal or hepatic impairment. Third, only 89 participants had serial weight measurements, and the weight change observed in this study might not be representative. However, a moderate amount of weight gain (+1.75 kg) was also reported by Kuo et al[42] in a study including 693 HIV-infected Taiwanese who were switched to E/C/F/TAF from TDF-containing regimens. Fourth, the duration of this study (48 weeks) is short. The long-term impact of switch to E/C/F/TAF on renal function, BMD, and lipids warrants attention. Finally, we only measured HDV RNA in participants who tested positive for anti-HDV IgG. Therefore, the prevalence of HDV viremia might have been underestimated.

In conclusion, in HIV/HBV-coinfected patients, switch to E/C/F/TAF is well tolerated and can maintain HBV and HIV suppression and lead to improvements in proteinuria and BMD. Long-term investigations are needed to determine the clinical relevance of changes in lipids and weight after switch to E/C/F/TAF.

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