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RESEARCH ARTICLE

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Metabolic effects and cardiovascular disease risks of antiviral treatments in patients with chronic hepatitis B

Hyunjae Shin[1,2] | Gyung Sun Lim[1] | Jae Woong Yoon[1] | Yunmi Ko[1] | Youngsu Park[1] | Jeayeon Park[1] | Moon Haeng Hur[1] | Min Kyung Park[1] | Yuri Cho[2] | Yun Bin Lee[1] | Eun Ju Cho[1] | Bo Hyun Kim[2] | Jeong-Hoon Lee[1] | Su Jong Yu[1] | Jung-Hwan Yoon[1] | Yoon Jun Kim[1]

[1]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, South Korea

[2]Center for Liver and Pancreatobiliary Cancer, National Cancer Center, Goyang, South Korea

Correspondence

Yoon Jun Kim, Department of Internal Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, South Korea.
Email: yoonjun@snu.ac.kr

Abstract

Different antiviral treatments for chronic hepatitis B (CHB) have been known to have different metabolic effects. This study aimed to reveal whether tenofovir alafenamide (TAF)-induced dyslipidemia and its associated outcomes are significant. This study utilized 15-year historical cohort including patients with CHB in Korea and consisted of two parts: the single-antiviral and switch-antiviral cohorts. In the single-antiviral cohort, patients were divided into four groups (entecavir [ETV]-only, tenofovir disoproxil fumarate [TDF]-only, TAF-only, and non-antiviral). Propensity score matching (PSM) and linear regression model were sequentially applied to compare metabolic profiles and estimated atherosclerotic cardiovascular disease (ASCVD) risks longitudinally. In the switch-antiviral cohort, pairwise analyses were conducted in patients who switched NAs to TAF or from TAF. In the single-antiviral cohort, body weight and statin use showed significant differences between groups before PSM, but well-balanced after PSM. Changes in total cholesterol were significantly different between groups (−2.57 mg/dL/year in the TDF-only group and +2.88 mg/dL/year in the TAF-only group; $p = 0.002$ and $p = 0.02$, respectively). In the TDF-only group, HDL cholesterol decreased as well (−0.55 mg/dL/year; $p < 0.001$). The TAF-only group had the greatest increase in ASCVD risk, followed by the TDF-only group and the non-antiviral group. In the switch-antiviral cohort, patients who switched from TDF to TAF had a higher total cholesterol after switching (+9.4 mg/dL/year) than before switching (−1.0 mg/dL/year; $p = 0.047$). Sensitivity analysis on data with an observation period set to a maximum of 3 years for NA treatment showed consistent results on total cholesterol (−2.96 mg/dL/year in the TDF-only group and +3.09 mg/dL/year in the TAF-only group; $p = 0.001$ and $p = 0.005$, respectively).

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CHB, chronic hepatitis B; ETV, entecavir; FRS, framingham risk score; HBeAg, hepatitis B virus envelope antigen; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDL cholesterol, high density lipoprotein cholesterol; HIV, human immunodeficiency virus; IQR, interquartile range; LDL cholesterol, low density lipoprotein cholesterol; NA, nucleos(t)ide analogue; PCE, pooled cohort equation; PS, propensity score; PSM, propensity score matching; PWH, people with HIV; SMD, standardized mean difference; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Another sensitivity analysis conducted on statin-treated patients revealed no significant change in cholesterol and ASCVD risk. TAF was associated with increased total cholesterol, whereas TDF was associated with decreased total and HDL cholesterol. Both TAF and TDF were associated with increased ASCVD risks, and statin use might mitigate these risks.

KEYWORDS
azotemia, dyslipidemia, LDL cholesterol, metabolic profile, tenofovir alafenamide

1 | INTRODUCTION

Patients with chronic hepatitis B (CHB) benefit from antiviral treatment in preventing liver cirrhosis and hepatocellular carcinoma (HCC).[1,2] Tenofovir alafenamide (TAF) has recently emerged as an important nucleos(t)ide analogue (NA) treatment.[3,4] TAF, initially used to treat human immunodeficiency virus (HIV) infection, has been widely administered to patients with CHB after its efficacy became widely known.[5] TAF has gradually replaced tenofovir disoproxil fumarate (TDF) globally because of its well-established efficacy in inhibiting hepatitis B virus (HBV) suppression.[3,6]

Several adverse effects of NA treatment in patients with CHB have been identified.[6–8] Long-term TDF use had also been associated with azotemia, Fanconi syndrome, hypophosphatemia, and bone mineral density loss.[9,10] Similarly, in people living with HIV (PWH), several adverse effects of NAs have been reported. TAF is suspected to have potentially harmful metabolic effects, such as an increase in serum total cholesterol, resulting in an increase in the estimated risk of atherosclerotic cardiovascular disease (ASCVD).[11–13] Similarly, TAF is strongly suspected to cause hyperlipidemia in patients with CHB, whereas TDF reduces serum total cholesterol.[14–18] However, in previous studies, various confounding variables affecting metabolic profiles were not accounted for.[19]

In recent years, as the average age of CHB patients has increased, the prevalence of comorbidities such as hypertension, dyslipidemia, and chronic kidney disease has increased among CHB patients. In addition, liver-related mortality is decreasing and survival is increasing due to antiviral treatment with high efficacy, therefore, it may be required to control comorbidities precisely. Given that metabolic diseases such as diabetes mellitus and dyslipidemia, may influence the development of liver cirrhosis or HCC in patients with chronic liver disease, identifying the distinct metabolic effects of TAF relative to other NAs may be an important research topic.[20]

To determine the effects of long-term treatment with TAF on metabolic profiles, we conducted a comprehensive study at single university-affiliated tertiary center. Based on their baseline characteristics, patients treated with or without NAs were matched using propensity scores and analyzed longitudinally. In addition, patients who switched to NA were compared pairwisely before and after switching.

2 | METHODS

2.1 | Patients

We established a retrospective cohort of all patients diagnosed with CHB between January 2008 and December 2022 (Figure 1). Patients were enrolled at the time of their first visit to the center. Patients were followed until either the date of the last follow-up, death, or the date of switching NAs. Patients who switched from TAF to other NAs or from other NAs to TAF were also included in the study. Patients who met one of the following criteria were excluded: (i) treated with lamivudine, adefovir, or clevudine; (ii) aged less than 20 years; (iii) steroid, oral contraceptive, amiodarone, or thiazolidinedione use; (iv) history of liver transplantation or infection with other hepatotropic viruses; and (v) followed for less than 12 months. Patient demographics and baseline characteristics were gathered through a comprehensive review of medical records and prescription data (Supporting Information: Table 1).

We conducted the study in two cohorts, a single-antiviral cohort and a switch-antiviral cohort. The single-antiviral cohort enrolled patients who were treated with entecavir (ETV, $n = 7591$), TDF ($n = 4105$), or TAF ($n = 670$), as well as a control group of CHB patients who were not treated with NAs ($n = 16\,396$). The switch-antiviral cohort enrolled patients who switched NAs to TAF from TDF ($n = 33$) or ETV ($n = 17$), switched to TDF from TAF ($n = 11$), and were followed up for at least 3 months before and after switching NAs. All patients in the switch-antiviral cohort were observed for at least 3 months on each antiviral treatment.

The Institutional Review Board of Seoul National University approved this study, and because of its retrospective nature, the requirement for informed consent was waived.

2.2 | Outcomes and assessment

In this single-antiviral cohort, the outcomes were defined as changes over time in laboratory variables (serum total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride, fasting glucose, and creatinine levels) and demographic variables (body weight and statin use) associated with metabolic diseases. We calculated the annual changes in laboratory variables as the difference in lipid levels

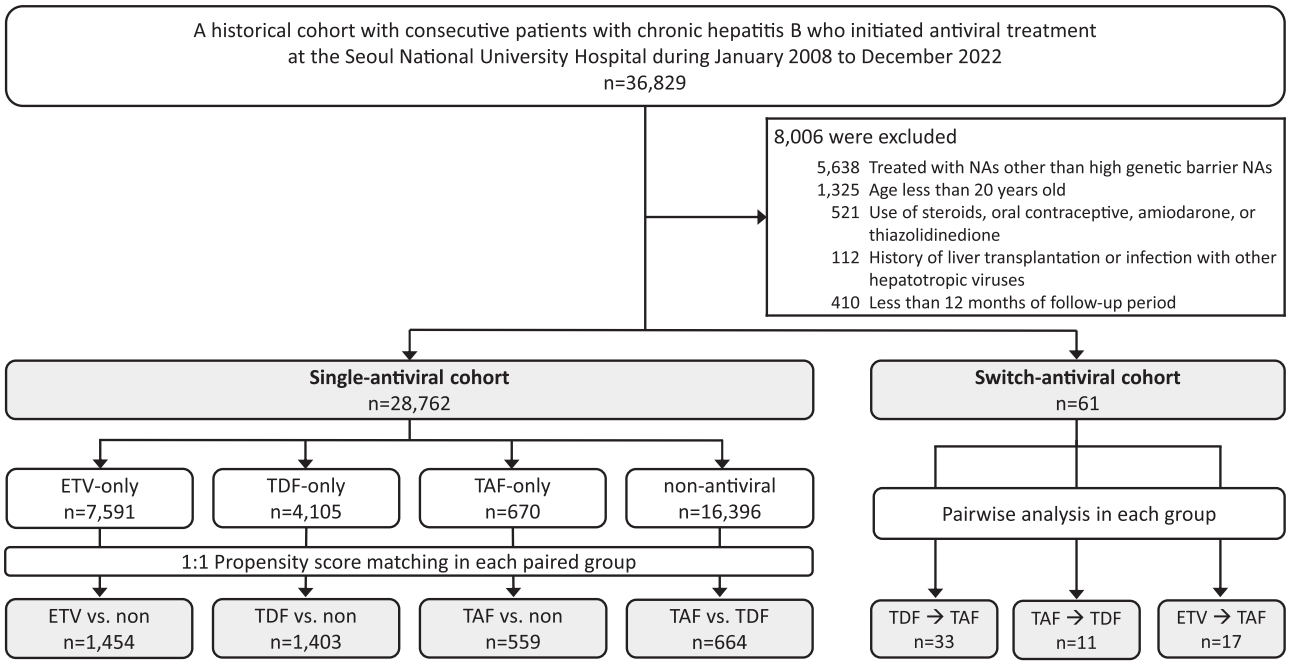

FIGURE 1 Patient flow diagram. ETV, entecavir; NA, nucleos(t)ide analogue; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

between the baseline date and the last follow-up date. In addition, the 10-year estimated ASCVD risks were calculated based on the Pooled Cohort Equations (PCE) from the American College of Cardiology/American Heart Association.[21] Missing data were imputed with values based on local demographics to calculate ASCVD risk using PCE. Additionally, Framingham Risk Score (FRS) was calculated to estimate 10-year ASCVD risk as a sensitivity analysis.[22] The linear regression model was utilized to adjust the impact of the major confounding variables.

In the switched antiviral study, serum total cholesterol and creatinine levels were selected as the primary outcomes and were compared pairwise before and after the antiviral switch. Due to insufficient data and population, cholesterol subsets and ASCVD risks were not evaluated, and patients who switched from TAF to ETV were not included in the study.

2.3 | Statistical analysis

Nonparametric continuous variables are presented as medians with interquartile ranges (IQR) unless otherwise specified. Categorical variables were presented as absolute numbers of cases and/or percentages. χ^2 test and Fisher test were used to compare categorical variables, and Student's *t* test or Wilcoxon signed rank test were used to compare continuous variables based on the results of normality tests. Propensity score matching (PSM) was used to balance the subgroups using the following key baseline variables: age, sex, platelet count, serum total cholesterol, albumin, prothrombin time, body weight, and statin use. Standardized mean differences (SMD) were calculated to evaluate balance quality before and after PSM. After PSM, a linear regression model was applied to adjust for the impact of time-varying variables during the observation period, which included changes in body weight, statin use, and the rates of change in cholesterol, glucose, and creatinine levels. Analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute Inc.) and R 4.2.0 (R Foundation for Statistical Computing). All statistical tests were two-sided, and p values < 0.05 were considered statistically significant.

3 | RESULTS

3.1 | Single-antiviral cohort

The single-antiviral cohort included 28 762 patients with CHB who visited Seoul National University Hospital. Compared with the TAF-only and non-antiviral groups, the TDF-only and ETV-only groups had a higher prevalence of liver cirrhosis and HCC. In contrast, the TAF-only group had lower rates of initial statin use than the ETV-only and TDF-only groups (Table 1). PSM with the 1:1 nearest neighbor method was used in four paired groups: ETV-only versus non-antiviral, TDF-only versus non-antiviral, TAF-only versus non-antiviral, and TAF-only versus TDF-only. After PSM, baseline characteristics of each paired group were well balanced with each SMD ≤ 0.1 (Table 2). Baseline HCC and LC could not be balanced due to different usage criteria for each medication, but they could be well-balanced in the TAF-only versus TDF-only group.

The median follow-up duration for the NA-treated groups ranged from 2.2 to 5.0 years. Before adjusting for key confounders (Table 2), the TAF-only group had a higher serum total cholesterol level [median, 1.08 (IQR, −8.95 to 9.44) mg/dL/year] than the non-antiviral

TABLE 1 Baseline characteristics of the ETV-only, TDF-only, TAF-only, and non-antiviral groups in the single-antiviral cohort.

	Total *N* = 28 762	non-antiviral group *N* = 16 396	ETV-only group *N* = 7591	TDF-only group *N* = 4105	TAF-only group *N* = 670	*p*
Age, years	53 [44 to 61]	52 [41 to 60]	55 [48 to 62]	55 [46 to 61]	51 [43 to 59]	<0.001
Sex, male	17 628 (61.3%)	9362 (57.1%)	5117 (67.4%)	2798 (68.2%)	351 (52.4%)	<0.001
Platelet, 10^3/μL	181 [136 to 221]	184 [165 to 231]	146 [97 to 196]	164 [117 to 213]	186 [145 to 222]	<0.001
Albumin, g/dL	4.2 [3.9 to 4.4]	4.2 [4.0 to 4.5]	4.1 [3.6 to 4.4]	4.2 [3.8 to 4.4]	4.3 [4.0 to 4.5]	<0.001
Prothrombin time, INR	1.04 [1.00 to 1.10]	1.04 [0.99 to 1.06]	1.07 [1.01 to 1.17]	1.05 [1.00 to 1.13]	1.03 [0.98 to 1.08]	<0.001
Total cholesterol, mg/dL	171 [148 to 196]	177 [154 to 200]	163 [139 to 187]	164 [140 to 189]	181 [156 to 206]	<0.001
Body weight, kg	65.0 [57.2 to 73.0]	64.0 [56.0 to 72.0]	65.0 [57.4 to 73.0]	65.5 [58.2 to 73.8]	65.1 [56.8 to 75.1]	<0.001
Liver cirrhosis, (%)	5212 (18.12%)	1845 (11.25%)	2509 (33.05%)	813 (19.81%)	45 (6.72%)	<0.001
Hepatocellular carcinoma, (%)	7872 (27.37%)	1450 (8.84%)	3965 (52.23%)	2253 (54.88%)	204 (30.45%)	<0.001
Diabetes mellitus on OHA, at baseline (%)	2727 (9.48%)	809 (4.93%)	1182 (15.57%)	644 (15.69%)	92 (13.73%)	<0.001
Hypertension, (%)	2096 (7.29%)	1323 (8.07%)	523 (6.89%)	205 (4.99%)	45 (6.72%)	<0.001
HBsAg positivity, (%)	27 268 (94.8%)	15 281 (93.2%)	7295 (96.1%)	4027 (98.1%)	665 (99.3%)	<0.001
HBeAg positivity, (%)	7637 (26.6%)	4115 (25.1%)	2133 (28.1%)	1264 (30.8%)	125 (18.7%)	<0.001
HBV DNA, $\log_{10}$ U/mL	2.4 [0.5 to 6.7]	1.2 [0.0 to 2.7]	2.4 [0.4 to 6.9]	2.2 [0.5 to 6.4]	2.4 [0.0 to 6.0]	<0.001
Statin use, at baseline, (%)	4126 (14.35%)	2162 (13.19%)	1230 (16.20%)	659 (16.05%)	75 (11.19%)	<0.001
Statin use, at last, (%)	5937 (20.64%)	3203 (19.54%)	1756 (23.13%)	835 (20.34%)	143 (21.34%)	<0.001
Observation period, years	5.4 [2.3 to 10.0]	6.1 [3.1 to 11.5]	5.2 [1.6 to 10.7]	4.1 [1.5 to 6.8]	2.2 [1.1 to 3.5]	<0.001
10-year ASCVD risk, at baseline, %						
PCE	5.65 [2.51 to 11.07]	6.15 [2.75 to 12.58]	5.22 [2.34 to 10.15]	6.07 [2.89 to 10.79]	4.00 [1.31 to 7.32]	<0.001
FRS	3.49 [1.26 to 7.67]	3.37 [1.26 to 7.89]	3.51 [1.29 to 7.37]	3.94 [1.35 to 8.11]	2.13 [0.85 to 5.69]	<0.001
Body weight change, kg/year	−0.19 [−1.08 to +0.32]	−0.15 [−0.69 to +0.39]	−0.15 [−0.98 to +0.29]	−0.32 [−1.53 to +0.27]	0.14 [−0.74 to +1.21]	<0.001
Cholesterol change, mg/dL/year	−0.54 [−6.06 to +3.67]	−0.55 [−5.23 to +2.88]	0.39 [−5.88 to +5.04]	−2.10 [−9.31 to +3.40]	0.67 [−9.01 to +9.44]	<0.001
LDL cholesterol change, mg/dL/year	−0.90 [−5.44 to +2.38]	−1.72 [−7.24 to +2.36]	−0.45 [−3.72 to +2.15]	−0.77 [−4.98 to +2.35]	−0.44 [−12.21 to +7.30]	<0.001
HDL cholesterol change, mg/dL/year	−0.22 [−1.62 to +1.04]	−0.19 [−1.51 to +1.04]	−0.13 [−1.29 to +0.98]	−0.48 [−2.33 to +0.96]	−0.90 [−3.77 to +2.01]	<0.001
Triglyceride change, mg/dL/year	−0.52 [−5.28 to +4.18]	−0.68 [−6.01 to +3.83]	−0.45 [−4.42 to +3.69]	−0.51 [−5.10 to +4.50]	1.48 [−9.05 to +11.23]	0.01

TABLE 1 (Continued)

	Total N = 28 762	non-antiviral group N = 16 396	ETV-only group N = 7591	TDF-only group N = 4105	TAF-only group N = 670	p
10-year ASCVD risk change, %/year						
PCE	+0.69 [+0.36 to +1.20]	+0.72 [+0.35 to +1.35]	+0.69 [+0.38 to +1.16]	+0.68 [+0.34 to +1.16]	+0.65 [+0.38 to +1.25]	0.11
FRS	+0.41 [+0.22 to +0.83]	+0.35 [+0.21 to +0.70]	+0.44 [+0.22 to +0.83]	+0.44 [+0.21 to +0.92]	+0.57 [+0.32 to +1.01]	<0.001
Glucose change, mg/dL/year	+0.53 [−1.92 to +2.58]	+0.48 [−1.29 to +2.03]	+0.82 [−2.42 to +3.60]	−0.13 [−4.17 to +2.45]	+0.66 [−3.23 to +3.45]	<0.001
Creatinine change, mg/dL/year	−0.003 [−0.018 to +0.018]	−0.004 [−0.016 to +0.013]	−0.003 [−0.022 to +0.024]	+0.007 [−0.017 to +0.034]	−0.006 [−0.033 to +0.021]	<0.001

Note: Sex, Statin use, liver cirrhosis, hepatocellular carcinoma, diabetes mellitus, hypertension, HBsAg positivity, and HBeAg positivity are represented by the number of patients and percentage, while the other values are represented by their median and IQR.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; ETV, entecavir; FRS, framingham risk score; HBeAg, hepatitis B virus envelope antigen; HBsAg, hepatitis B virus surface antigen; HDL cholesterol, high density lipoprotein cholesterol; LDL cholesterol, low density lipoprotein cholesterol; OHA, oral hypoglycemic agent; PCE, pooled cohort equation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

group [median, −0.60 (IQR, −6.47 to 2.52) mg/dL/year; $p = 0.002$]. In contrast, the TDF-only group had a lower total cholesterol level [median, −2.74 (IQR, −9.53 to 2.43) mg/dL/year] than the non-antiviral group [median, −0.35 (IQR, −4.75 to 2.80) mg/dL/year; $p < 0.001$]. The only noticeable change in the cholesterol subsets was a statistically significant decrease in HDL cholesterol in the TDF-only group versus the non-antiviral group [median, −0.57 (IQR, −2.54 to 0.63) mg/dL/year versus −0.16 (IQR, −1.12 to 0.81) mg/dL/year; $p < 0.001$]. Body weight change was also statistically significant in the TAF-only group compared with the TDF-only group [median, 0.14 (IQR, −0.74 to 1.20) kg/year versus −0.21 (IQR, −1.33 to 0.30) kg/year; $p < 0.001$]. Linear regression model analysis was performed to evaluate the impact of the variables of interest by adjusting for potential confounding variables (Table 3). Changes in body weight ($p < 0.001$) and statin use ($p = 0.001$) had a significant impact on total cholesterol levels in the PS-matched TAF-only and TDF-only groups. Linear regression analysis were then applied for adjusting the impact of these major variables (changes in body weight and statin use). After adjustment, The TAF-only group demonstrated higher total cholesterol levels than the non-antiviral group [median, 2.88 (IQR, 0.52–5.23) mg/dL/year; $p = 0.02$] and TDF-only group [median, 4.80 (IQR, 2.21–7.39) mg/dL/year; $p < 0.001$]. In addition, the TDF-only group showed lower total cholesterol levels [median, −2.57 (IQR, −4.22 to −0.92) mg/dL/year; $p = 0.002$] and HDL cholesterol levels [median, −0.55 (IQR, −0.79 to −0.31) mg/dL/year; $p < 0.001$; Figure 2] than the non-antiviral group. The LDL-cholesterol levels of the TDF-only group and the non-antiviral group did not differ statistically [median, −0.46 (IQR, −1.15 to 0.22) mg/dL/year; $p = 0.18$]. The change in estimated 10-year ASCVD risk by PCE was greater in the TAF-only group than in the TDF-only group [median, 0.59 (IQR, 0.24–0.94) %/year; $p = 0.001$]. Both the TAF-only and TDF-only groups had a greater risk of developing ASCVD than the non-antiviral group.

The differences in serum creatinine changes between the TDF-only and non-antiviral groups were not statistically significant [median, +0.02 (IQR, −0.01 to 0.05) mg/dL/year; $p = 0.24$]. The ETV-only and TAF-only groups did not differ statistically from the non-antiviral group ($p = 0.61$ and $p = 0.44$, respectively).

3.2 | Switch-antiviral cohort

The switch-antiviral cohort enrolled 61 patients who switched from TDF to TAF ($n = 33$), ETV to TAF ($n = 17$), and TAF to TDF ($n = 11$). The baseline characteristics of the study participants are described in Supporting Information: Table 2. Pairwise analysis of serum cholesterol and creatinine levels before and after switching to NAs revealed lipid profile changes with trends comparable with those observed in the single-antiviral cohort. Switching from TDF to TAF was associated with an increase in total cholesterol [median, +9.4 (IQR, +0.0 to 47.4) mg/dL/year] compared with the period before switching [median, −1.0 (IQR, −4.0 to 3.3) mg/dL/year; $p = 0.047$; Figure 3]. However, patients who switched from TAF to TDF did not experience a statistically significant change in total cholesterol after the switch [median, −7.2

TABLE 2 Baseline characteristics of each pair of groups (ETV-only vs. non-antiviral, TDF-only vs. non-antiviral, TAF-only vs. non-antiviral, and TAF-only vs. TDF-only) by propensity score matching in the single-antiviral cohort.

Baseline characteristics	ETV-only *N* = 1454	Non-antiviral *N* = 1454	*p*	SMD	TDF-only *N* = 1403	Non-antiviral *N* = 1403	*p*	SMD	TAF-only *N* = 559	Non-antiviral *N* = 559	*p*	SMD	TAF-only *N* = 664	TDF-only *N* = 664	*p*	SMD
Baseline variables																
Age, years	54 [45 to 61]	53 [44 to 61]	0.49	0.038	52 [43 to 60]	53 [42 to 62]	0.35	0.021	51 [43 to 59]	52 [42 to 60]	0.74	0.009	51 [43 to 59]	52 [43 to 60]	0.60	0.001
Sex, male	871 (59.9%)	869 (59.8%)	0.97	0.003	857 (61.1%)	806 (57.5%)	0.06	0.074	286 (51.2%)	300 (53.7%)	0.44	0.050	349 (52.6%)	370 (55.7%)	0.27	0.063
Platelet, 10^3/μL	181 [142 to 225]	183 [146 to 222]	0.48	0.029	187 [145 to 231]	192 [153 to 232]	0.10	0.004	189 [149 to 224]	189 [151 to 231]	0.66	0.016	186 [145 to 222]	186 [139 to 228]	0.55	0.024
Albumin, g/dL	4.3 [4.0 to 4.5]	4.2 [4.0 to 4.4]	0.13	0.000	4.3 [4.0 to 4.5]	4.2 [4.0 to 4.5]	0.24	0.014	4.3 [4.0 to 4.5]	4.3 [4.0 to 4.5]	0.58	0.065	4.3 [4.0 to 4.5]	4.3 [4.0 to 4.5]	0.66	0.019
Prothrombin time, INR	1.04 [0.99 to 1.10]	1.04 [1.00 to 1.07]	0.17	0.074	1.03 [0.99 to 1.06]	1.04 [0.99 to 1.06]	0.08	0.069	1.03 [0.98 to 1.08]	1.04 [1.00 to 1.06]	0.06	0.117	1.03 [0.98 to 1.08]	1.03 [0.98 to 1.09]	0.84	0.039
Total cholesterol, mg/dL	173 [151 to 198]	172 [151 to 196]	0.45	0.045	173 [151 to 197]	175 [154 to 198]	0.13	0.055	180 [155 to 205]	179 [155 to 205]	0.97	0.017	181 [156 to 205]	179 [156 to 203]	0.55	0.019
Body weight, kg	64.2 [56.0 to 72.5]	64.0 [57.0 to 72.0]	0.69	0.007	63.5 [56.5 to 71.0]	62.0 [55.0 to 73.0]	0.36	0.037	64.1 [55.8 to 73.5]	65.0 [57.0 to 72.0]	0.61	0.003	65.1 [56.8 to 72.5]	65.6 [58.3 to 75.2]	0.17	0.083
Statin use, at baseline, (%)	197 (13.5%)	202 (13.9%)	0.83	0.010	171 (12.2%)	170 (12.1%)	1.00	0.002	59 (10.6%)	73 (13.1%)	0.23	0.078	75 (11.3%)	58 (8.7%)	0.14	0.085
Liver cirrhosis, (%)	351 (24.1%)	186 (12.8%)	<0.001		239 (17.0%)	172 (12.3%)	<0.001		43 (7.7%)	54 (9.7%)	0.29		45 (6.8%)	37 (5.6%)	0.43	
Hepatocellular carcinoma, (%)	596 (40.1%)	146 (10.0%)	<0.001		641 (45.7%)	122 (8.7%)	<0.001		102 (18.2%)	118 (21.1%)	0.26		204 (30.7%)	212 (31.9%)	0.68	
Diabetes mellitus, (%)	208 (14.3%)	75 (5.2%)	<0.001		198 (14.1%)	59 (4.2%)	<0.001		73 (13.1%)	30 (5.4%)	<0.001		92 (13.9%)	76 (11.4%)	0.22	
Hypertension, (%)	102 (7.0%)	117 (8.0%)	0.33		68 (4.8%)	120 (8.6%)	<0.001		41 (7.3%)	46 (8.2%)	0.66		44 (6.6%)	47 (7.1%)	0.83	
10-year ASCVD risk, at baseline, %																
PCE	5.90 [3.16 to 11.29]	8.30 [4.53 to 15.84]	<0.001		5.43 [3.12 to 9.65]	8.54 [4.30 to 14.58]	<0.001		5.47 [2.58 to 8.50]	6.40 [3.25 to 11.68]	0.06		5.52 [2.64 to 8.44]	6.40 [3.59 to 11.57]	0.03	
FRS	4.40 [1.93 to 9.14]	6.39 [2.51 to 11.40]	<0.001		3.67 [1.30 to 8.23]	5.27 [2.18 to 10.82]	<0.001		2.04 [0.78 to 5.46]	2.51 [1.16 to 6.12]	0.02		2.13 [0.85 to 5.71]	2.45 [0.80 to 6.04]	0.38	

TABLE 2 (Continued)

Baseline characteristics	ETV-only *N* = 1454	Non-antiviral *N* = 1454	*p*	SMD	TDF-only *N* = 1403	Non-antiviral *N* = 1403	*p*	SMD	TAF-only *N* = 559	Non-antiviral *N* = 559	*p*	SMD	TAF-only *N* = 664	TDF-only *N* = 664	*p*	SMD
Variables in observation period																
Statin use, at last, (%)	323 (22.2%)	293 (20.2%)	0.19		229 (16.3%)	246 (17.5%)	0.42		121 (21.6%)	103 (18.4%)	0.20		140 (21.1%)	91 (13.7%)	0.001	
Observation period, years	5.0 [1.6 to 10.4]	6.1 [3.3 to 11.5]	<0.001		4.3 [1.5 to 6.8]	6.1 [3.2 to 12.3]	<0.001		2.2 [1.2 to 3.5]	5.7 [3.0 to 10.7]	<0.001		2.2 [1.1 to 3.5]	4.2 [1.6 to 6.9]	<0.001	
Variables of interest																
Body weight change, kg/year	−0.09 [−0.70 to 0.39]	−0.05 [−0.67 to 0.56]	0.41		−0.24 [−1.12 to 0.36]	−0.19 [−0.61 to 0.24]	0.53		0.14 [−0.71 to 1.11]	−0.15 [−0.70 to 0.33]	0.20		0.14 [−0.74 to 1.20][a]	−0.21 [−1.33 to 0.30][a]	<0.001	
Cholesterol change, mg/dL/year	0.33 [−5.92 to 4.43]	−0.82 [−4.80 to 2.46]	0.001		−2.74 [−9.53 to 2.43][a]	−0.35 [−4.75 to 2.80][a]	<0.001		1.08 [−8.95 to 9.44][a]	−0.60 [−6.47 to 2.52][a]	0.002		0.811 [−8.952 to 9.52]	−2.48 [−9.42 to 2.20]	<0.001	
LDL cholesterol change, mg/dL/year	−1.33 [−4.77 to −0.53]	−1.27 [−3.25 to −0.48]	0.25		−1.51 [−5.97 to 2.04]	−0.33 [−5.61 to 3.12]	0.11		0.72 [−11.07 to 7.98]	−1.23 [−6.79 to 2.82]	0.29		0.36 [−12.12 to 7.38]	−0.87 [−6.699 to 1.993]	0.08	
HDL cholesterol change, mg/dL/year	−0.23 [−0.88 to −0.08]	−0.18 [−0.62 to −0.06]	0.01		−0.57 [−2.54 to 0.63][a]	−0.16 [−1.12 to 0.81][a]	<0.001		−0.83 [−3.12 to 2.00]	−0.36 [−1.94 to 0.78]	0.49		−0.83 [−3.54 to 2.14]	−0.76 [−3.23 to 0.49]	0.28	
Triglyceride change, mg/dL/year	−0.72 [−2.80 to −0.24]	−0.54 [−1.99 to −0.17]	0.003		−0.83 [−5.12 to 3.46]	−0.27 [−6.25 to 5.55]	0.52		1.36 [−8.93 to 10.93]	0.41 [−3.54 to 5.37]	0.92		−1.48 [−9.05 to 11.23]	−0.74 [−4.60 to 4.07]	0.30	
10-year ASCVD risk change, %/year																
PCE	0.71 [0.39 to 1.13]	0.84 [0.37 to 1.40]	0.12		0.60 [0.35 to 1.07]	0.70 [0.36 to 1.42]	0.08		0.72 [0.48 to 1.31]	0.80 [0.48 to 1.25]	0.95		0.81 [0.50 to 1.48]	0.76 [0.37 to 1.18]	0.04	
FRS	0.39 [0.18 to 0.81]	0.34 [0.18 to 0.69]	0.22		0.37 [0.18 to 0.73]	0.36 [0.22 to 0.76]	0.23		0.53 [0.32 to 0.98]	0.37 [0.20 to 0.69]	<0.001		0.57 [0.32 to 1.03]	0.34 [0.17 to 0.75]	<0.001	
Glucose change, mg/dL/year	0.82 [−1.73 to 3.20]	0.54 [−1.09 to 2.03]	0.03		−0.15 [−3.51 to 2.04]	0.38 [−0.92 to 1.77]	<0.001		0.79 [−3.08 to 3.35]	0.54 [−1.06 to 2.47]	0.61		0.70 [−3.18 to 3.45]	0.27 [−2.93 to 2.24]	0.06	
Creatinine change, mg/dL/year	−0.01 [−0.02 to 0.01]	0.00 [−0.02 to 0.01]	0.001		0.00 [−0.02 to 0.03]	−0.00 [−0.02 to 0.01]	<0.001		−0.01 [−0.03 to 0.02]	−0.00 [−0.02 to 0.02]	0.21		−0.01 [−0.03 to 0.02]	0.00 [−0.02 to 0.02]	0.003	

Note: Sex, statin use, liver cirrhosis, hepatocellular carcinoma, diabetes mellitus, and hypertension are represented by the number of patients and percentage, while the other values are represented by their median and IQR.

Abbreviatioins: ASCVD, atherosclerotic cardiovascular disease; ETV, entecavir; FRS, framingham risk score; HDL cholesterol, high density lipoprotein cholesterol; LDL cholesterol, low density lipoprotein cholesterol; OHA, oral hypoglycemic agent; PCE, pooled cohort equation; SMD, standardized mean difference; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

[a]Data presented in the manuscript.

TABLE 3 Results of linear regression model of each pair of groups (ETV-only vs. non-antiviral, TDF-only vs. non-antiviral, TAF-only vs. non-antiviral, and TAF-only vs. TDF-only) in the single-antiviral cohort.

	ETV-only versus non-antiviral	*p*	TDF-only versus non-antiviral	*p*	TAF-only versus non-antiviral	*p*	TAF-only versus TDF-only	*p*
Cholesterol change, mg/dL/year	−0.54 [−1.77 to 1.24]	0.56	−2.57 [−4.22 to −0.92][a]	0.002	2.88 [0.52 to 5.23][a]	0.02	4.80 [2.21 to 7.39][a]	<0.001
LDL cholesterol change, mg/dL/year	−0.25 [−1.01 to 0.51]	0.51	−0.46 [−1.15 to 0.22][a]	0.18	−1.28 [−2.77 to 0.21]	0.09	−1.03 [−3.21 to 1.15]	0.36
HDL cholesterol change, mg/dL/year	0.20 [−0.06 to 0.46]	0.14	−0.55 [−0.79 to −0.31][a]	<0.001	−0.29 [−0.78 to 0.20]	0.25	0.02 [−0.75 to 0.79]	0.96
Triglyceride change, mg/dL/year	2.18 [0.36 to 4.01]	0.02	0.41 [−3.14 to 3.96]	0.82	−1.07 [−4.36 to 2.23]	0.53	0.41 [−3.14 to 3.96]	0.82
Glucose change, mg/dL/year	0.08 [−1.61 to 1.77]	0.93	−1.31 [−2.29 to −0.33]	0.01	−2.20 [−5.40 to 0.99]	0.18	−0.24 [−4.38 to 3.89]	0.91
Creatinine change, mg/dL/year	−0.01 [−0.04 to 0.02]	0.61	0.02 [−0.01 to 0.05][a]	0.24	−0.01 [−0.04 to 0.02]	0.44	0.01 [−0.03 to 0.05]	0.58
10-year ASCVD risk change, %/year								
PCE	0.05 [−0.08 to 0.18]	0.42	0.41 [0.16 to 0.66]	0.001	0.38 [0.06 to 0.70]	0.02	0.59 [0.24 to 0.94][a]	0.001
FRS	0.09 [−0.02 to 0.19]	0.11	0.38 [0.19 to 0.58]	<0.001	0.44 [0.25 to 0.64]	<0.001	0.54 [0.33 to 0.74]	<0.001

Note: All values are represented by their median and IQR.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; ETV, entecavir; FRS, framingham risk score; HDL cholesterol, high density lipoprotein cholesterol; LDL cholesterol, low density lipoprotein cholesterol; PCE, pooled cohort equation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

[a]Data presented in the manuscript.

(IQR, −37.3 to 27.9) mg/dL/year] compared with the period preceding the switch [median, 67.1 (IQR, 4.1–121.1) mg/dL/year; $p = 0.70$].

Changes in serum creatinine levels were comparable between patients who switched from TDF to TAF [median, −0.003 (IQR, −0.028 to 0.045) mg/dL/year before switching to TAF, −0.022 (IQR, −0.148 to 0.037) mg/dL/year after switching to TAF, $p = 0.11$; Supporting Information: Figure 1]. Worsening renal function was the most common reason for switching from TDF to TAF, followed by hypophosphatemia and loss of bone mineral density (Supporting Information: Table 3).

3.3 | Sensitivity analysis

Patients included in the single-antiviral cohorts were subjected to a variety of sensitivity analyses to mitigate the potential effects of confounders. First, Data limited to within 3 years of NA treatment were utilized to estimate cholesterol changes, aiming to minimize the effects of different observation periods. The results on changes of total cholesterol were consistent to the main analysis (−2.96 mg/dL/year in the TDF-only group and +3.09 mg/dL/year in the TAF-only group; $p = 0.001$ and $p = 0.005$, respectively; Supporting Information: Figure 2) compare with the non-antiviral group.

Second, a sensitivity analysis was performed on patients who were treated or not treated with statins. In patients who were not treated with statins at the time of enrollment ($n = 24\,636$). Baseline characteristics of patients in the analysis were well balanced After PSM, with each SMD ≤ 0.1 (Supporting Information: Table 4). Consistent with the primary analysis, the TAF-only group had an increased level of total cholesterol [median, 1.16 (IQR, −8.93 to 9.60) mg/dL/year] compared with the non-antiviral group [median, −0.49 (IQR, −5.57 to 3.07) mg/dL/year; $p = 0.01$], whereas the TDF-only group showed decreased levels of total cholesterol [median, −2.55 (IQR, −9.36 to 2.50) mg/dL/year] compared with the non-antiviral group [median, −0.09 (IQR, −4.13 to 3.27) mg/dL/year; $p < 0.001$]. In addition, an increased proportion of patients with newly started statin treatment was noted in the TAF-only group compared with the TDF-only group [67 out of 589, 11.4% versus 28 out of 589, 4.8%; $p < 0.001$]. After adjusting for key variables, the TAF-only group exhibited increased total cholesterol level compared with the TDF-only group [median, 3.30 (IQR, 0.16–6.35) mg/dL/year; $p = 0.04$]. In addition, another sensitivity analysis was conducted using only patients who were prescribed statins at the center at the time of enrollment ($n = 2385$, Supporting Information: Table 5). Patients on statins were less likely to be prescribed TAF than those in the primary analysis (29 of 2,385, 1.2% vs. 670 of 28,762, 2.3%). A total of 56 patients analyzed after PSM had comparable total cholesterol levels [median, −5.05 (IQR, −13.41 to 6.81) mg/dL/year versus −3.36 (IQR, −10.60 to 1.59) mg/dL/year; $p = 0.80$] and 10-year ASCVD risk by PCE [median, +0.77 (IQR, 0.44–1.52) %/year versus 0.76 (IQR, 0.32–1.06) %/year; $p = 0.40$] between the TAF-only group and the TDF-only group.

Third, a sensitivity analysis was conducted with the start of statin use set at the end of the follow-up period. In line with the main

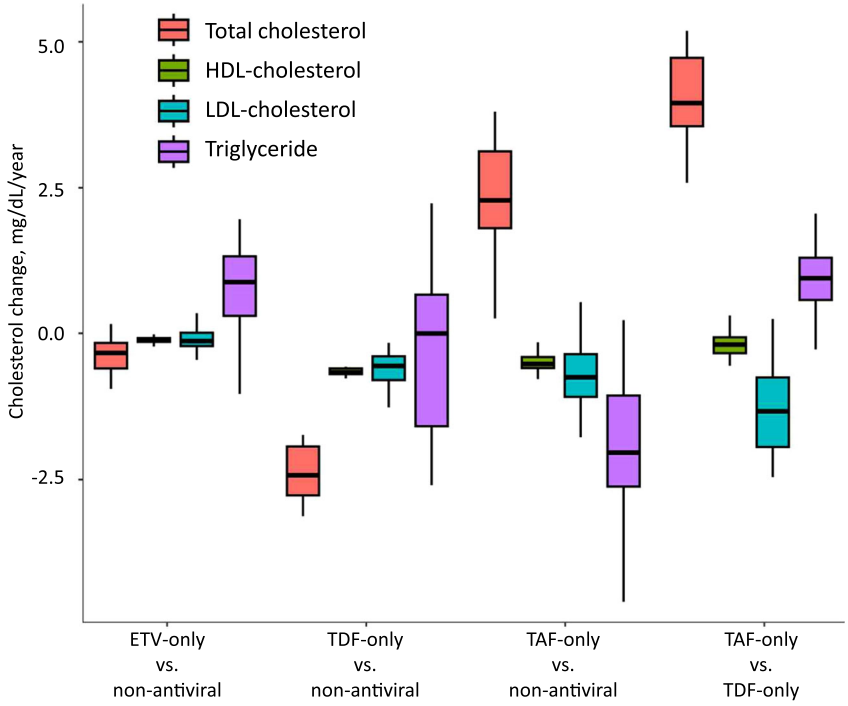

FIGURE 2 Changes in lipid profiles in each PS-matched pair of groups (ETV-only vs. non-antiviral, TDF-only vs. non-antiviral, TAF-only vs. non-antiviral, and TAF-only vs. TDF-only) in the single-antiviral cohort. ETV, entecavir; HDL cholesterol, high density lipoprotein cholesterol; LDL cholesterol, low density lipoprotein cholesterol; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

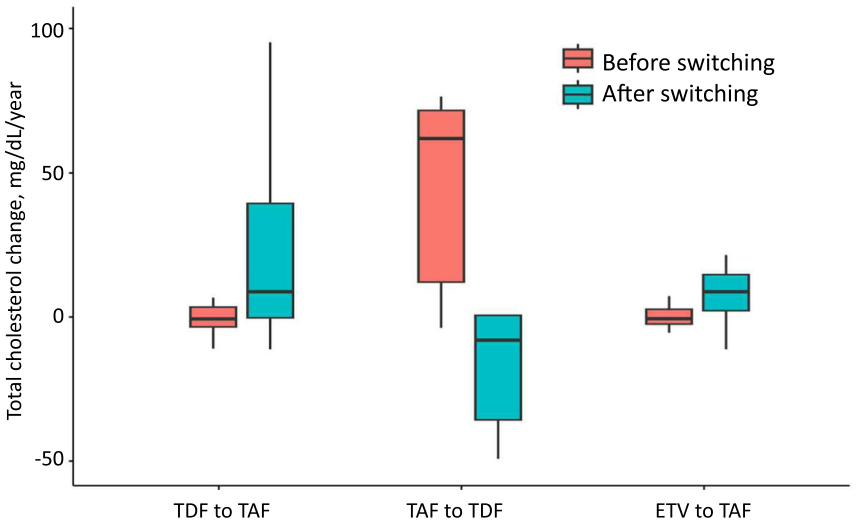

FIGURE 3 Changes in serum total cholesterol in each group (switching from TDF to TAF, from TAF to TDF and from ETV to TAF) in the switch-antiviral cohort. ETV, entecavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

analysis, the TAF-only group had an increased level of total cholesterol [median, 1.13 (IQR, −11.43 to 12.52) mg/dL/year] compared with the non-antiviral group [median, −0.91 (IQR, −6.17 to +4.91) mg/dL/year; $p = 0.002$]. Meanwhile, the TDF-only group showed decreased levels of total cholesterol [median, −3.09 (IQR, −10.52 to 3.31) mg/dL/year] compared with the non-antiviral group [median, 0.20 (IQR, −4.25 to 6.84) mg/dL/year; $p = 0.02$].

Finally, to minimize differences in the proportions of patients receiving NAs due to underlying liver diseases, a sensitivity analysis was conducted that included only patients without liver cirrhosis or a history of HCC at the time of enrollment. In the sensitivity analysis, groups well-balanced by PSM exhibited trends similar to those in the primary analysis (Supporting Information: Table 6).

4 | DISCUSSION

In this exhaustive study of all-comers with CHB involving 28 762 patients, we investigated the effect of the long-term use of high genetic barrier NAs on metabolic profiles using a variety of statistical analyses. In conclusion, the use of TAF is likely to increase serum total cholesterol levels, even after adjusting for body weight and statin use. The use of TDF was associated with decreased serum total cholesterol; however, the change was limited to a decrease in HDL cholesterol, which is associated with favorable clinical outcomes. These findings were consistent in the two primary studies and sensitivity analyses. Consequently, it could be stated that both TAF and TDF, particularly TAF, increase

the risk of ASCVD by altering lipid profiles, and the use of statins could mitigate this risk.

Our study is the first to include all patients with CHB at a specific research site and was comprehensively conducted by incorporating PSM with adjustments for key confounders of metabolic profiles, along with longitudinal pairwise analysis and various sensitivity analyses, and additional examination of the risk of ASCVD resulting from metabolic changes. PSM was adopted as the primary method in this single-antiviral cohort to mitigate potential selection bias introduced by the study design. Furthermore, a longitudinal pairwise analysis was performed in the switch-antiviral cohort to eliminate any possible bias from selecting patients who used only a single nucleoside analog throughout the observation period. Recent meta-analyses and large-scale studies involving CHB patients treated with TAF have reaffirmed the previously known lipid-elevating effects of TAF treatment in PWH.[11,17,18,23,24] Additionally, a recent prospective study reported increases in body weight and metabolic disturbances following a switch from TDF to TAF.[25] However, some limitations remain owing to the lack of key confounders and control groups. To overcome these limitations, we performed sensitivity analyses with only in-hospital statin users or nonstatin users to minimize the lipid-lowering effect of statins. In addition, a sensitivity analysis was performed to minimize the effects of rapidly declining cholesterol synthesis in patients with liver disease by excluding patients with severe liver diseases, such as liver cirrhosis or HCC. These results are consistent with the primary analyses.

Previous studies have thoroughly documented the effects of tenofovir-based regimens on the lipid profiles of PWH.[11,12,16,26] However, there were some differences between the studies involving PWH and other studies involving patients with CHB.[18,24,27] A recent multicenter Swiss study on PWH showed that switching from TDF to TAF was associated with weight gain and worsening of total cholesterol, LDL cholesterol, and HDL cholesterol levels. However, in this study, continued TDF use has been associated with weight gain which was a contradictory to the findings in patients with CHB. A possible explanation could be an association between sarcopenia and chronic liver disease.[19,28–30] In contrast, studies conducted on CHB patients yielded conflicting results regarding the impact of TDF and TAF.[15,17,18] However, these studies were limited by the fact that the control group was not CHB patients, and they did not adjust for important confounders such as weight change and statin use. The increased risk of cardiovascular disease (CVD) among PWH who switched from TDF to TAF was noteworthy, as in our study.[20,23,31–33] Worsening lipid profiles among CHB patients treated with tenofovir were critical issues to consider, and monitoring lipid profiles and effective treatment with statin might be necessary.[23,32,34–36] A recent study on PWH also showed that preserved lipid profiles in patients who were already treated with statin.[37] Considering that switching in the opposite direction from TAF to TDF, in PWH was likely to recover from weight gain and worsening lipid profiles,[13] it may be preferable to use other NAs instead of TAF in certain patients (i.e., patients with comorbidities) based on the risk-benefit profile of several key metabolic features.[38,39]

Although tenofovir-based regimens have been widely investigated in PWH, the plausible mechanisms underlying the contradictory results between TDF and TAF remain poorly understood. As similar effects were also observed in PWH, it could be assumed that HBV infection status had no effect on lipid profiles. A recent Japanese study illustrated one possible mechanism, namely the interaction between tenofovir and PPAR-α mediated signaling.[40] In this study, the dose-dependent effects of TDF on serum total cholesterol and its subsets were observed. Given that TAF is supposed to result in a lower serum level of tenofovir than TDF, this interaction might explain the difference in lipid profile effects.[40,41]

Our study had several limitations. First, as this was a single-center observational study, our results were susceptible to bias and confounding factors. Among these, the unreported use of statins may have been a major confounding factor in our study. Additionally, there may be a presence of selection bias when choosing the antiviral agent for initial treatment. Hence, we employed rigorous statistical methods, including PSM and longitudinal pairwise analyses, and conducted various sensitivity analyses. Despite the absence of routine body weight measurements, we incorporated baseline body weight into the propensity score and used body weight change as a key variable for adjustment to reduce the impact of body weight on lipid profiles. We also enrolled all patients with CHB at the center to evaluate the real-world impact of NAs on metabolic profiles. Therefore, we were able to include a relatively large number of patients with CHB who were followed up for a long period. Second, our study lacked data on the diagnosis of dyslipidemia, essential variables for assessing estimated ASCVD risk, such as smoking status and blood pressure measurements, and other lipid metabolites. Therefore, we performed sensitivity analyses and examined other variables affecting ASCVD risk assessment methods using two well-validated ASCVD risk estimates, PCE and FRS, both of which suggested consistent results. Clinicians tend to initiate statin treatment when their lipid profiles worsen before being diagnosed with dyslipidemia, and it is difficult to evaluate the long-term complications of tenofovir-induced dyslipidemia with proactive intervention. Therefore, a long-term investigation of the composite metabolic effects of TAF is warranted.

In conclusion, our comprehensive analysis, which included many patients with CHB, revealed that the long-term use of TAF was associated with increased total cholesterol, weight gain, and statin use. Additionally, long-term TDF use was associated with decreased total cholesterol levels; however, its effect was limited to HDL cholesterol, thereby increasing the risk of ASCVD. Further research is warranted to evaluate the clinical outcomes of tenofovir-induced dyslipidemia.

AUTHOR CONTRIBUTIONS

Hyunjae Shin: Conceptualization; methodology; software; formal analysis; data curation; investigation; writing—original draft preparation; writing—reviewing and editing; visualization. **Gyung Sun Lim**: Data curation; investigation. **Jae Woong Yoon**: Data curation; investigation. **Yunmi Ko**: Data curation; investigation. **Youngsu Park**: Data curation;

investigation. **Jeayeon Park**: Data curation; investigation. **Moon Haeng Hur**: Data curation; investigation. **Yuri Cho**: Resources. **Yun Bin Lee**: Resources. **Eun Ju Cho**: Resources. **Bohyun Kim**: Resources. **Jeong-Hoon Lee**: Resources. **Su Jong Yu**: Resources. **Jung-Hwan Yoon**: Resources. **Yoon Jun Kim**: Conceptualization; methodology; validation; resources; writing—reviewing and editing; supervision; project administration. All authors approved the final article.

DATA AVAILABILITY STATEMENT

The corresponding author, Yoon Jun Kim, had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

ORCID

Jeong-Hoon Lee https://orcid.org/0000-0002-0315-2080
Yoon Jun Kim http://orcid.org/0000-0001-9141-7773

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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