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ORIGINAL ARTICLE

Long-term virological and serologic responses of chronic hepatitis B virus infection to tenofovir disoproxil fumarate-containing regimens in patients with HIV and hepatitis B coinfection

Yu-Shan Huang[1] · Hsin-Yun Sun[1] · Sui-Yuan Chang[2,3] · Yu-Chung Chuang[1] · Aristine Cheng[1] · Sung-Hsi Huang[4,5] · Yi-Chia Huang[4] · Guan-Jhou Chen[6] · Kuan-Yin Lin[7] · Yi-Ching Su[1] · Wen-Chun Liu[1] · Chien-Ching Hung[1,5,8,9]

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Abstract

Background Data regarding the durability of HBV viral suppression with combination antiretroviral therapy (cART) containing tenofovir disoproxil fumarate (TDF) combined with lamivudine (3TC) or emtricitabine (FTC) in HIV/HBV-coinfected patients are scarce in hyperendemic areas of chronic HBV infection.

Methods Between 2004 and 2016, HIV/HBV-coinfected Taiwanese with available baseline HBV DNA load were retrospectively reviewed. Determinations of plasma HBV DNA load, HBV serologic markers (HBsAg, anti-HBs, HBeAg, and anti-HBe), and liver function were performed after initiation of cART. Factors associated with time to undetectable HBV DNA load were explored.

Results A total of 366 patients were included according to cART history: Group 1, 3TC as the only anti-HBV therapy ($n=73$); Group 2, TDF-containing cART as initial therapy ($n=127$); and Group 3, switch of 3TC-based to TDF-containing cART ($n=166$). At year 5, HBV suppression was achieved in 77.8%, 95.7%, and 95.7% of Groups 1, 2 and 3, respectively. In multivariate Cox regression analysis, TDF ($\pm$3TC or FTC) but not 3TC alone as initial anti-HBV therapy was significantly associated with HBV suppression (adjusted hazard ratio [aHR] 2.635; 95% CI 1.720–4.037), while HBeAg positivity at baseline was associated with failure to achieve HBV suppression (aHR 0.293; 95% CI 0.178–0.482). Loss of HBsAg occurred in 15 patients (4.1%), with 7 (1.9%) seroconversion to anti-HBs positivity, while HBeAg seroconversion occurred in 11 (16.9%) of 65 HBeAg-positive patients.

Conclusions TDF-containing cART achieved durable HBV viral suppression in HIV/HBV-coinfected patients and HBeAg positivity at baseline was associated with failure to achieve HBV suppression despite long-term TDF-containing cART.

Keywords Chronic hepatic complications · Liver fibrosis · Lamivudine · Emtricitabine · Tenofovir · Nucleotide reverse-transcriptase inhibitor

Introduction

Hepatitis B virus (HBV) coinfection in HIV-positive patients increases the risk of hepatitis flares and chronic hepatic complications. Without treatment, the course of chronic HBV infection is more aggressive in HIV/HBV-coinfected patients than those with HBV monoinfection [1]. Before the strategies for achieving functional and durable cure of chronic HBV infection are available, prevention of HBV-related hepatic complications relies on sustained viral suppression [2]. Prior studies suggest that patients with complete HBV viral suppression and/or HBV surface antigen (HBsAg) seroclearance are at lower risks of developing cirrhosis and hepatocellular carcinoma [3, 4]. In HIV/HBV-coinfected patients, early initiation of combination antiretroviral therapy (cART) in persons with higher CD4 counts has recently been shown to prevent liver fibrosis in the START trial [5].

Tenofovir disoproxil fumarate (TDF) is a potent nucleotide reverse-transcriptase inhibitor (NRTI) with antiviral activity against both HBV and HIV. TDF therapy leads

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✉ Chien-Ching Hung
hcc0401@ntu.edu.tw

Extended author information available on the last page of the article

to rapid decline of HBV replication and its propensity for selecting drug-resistant HBV is low [6]. For HIV/HBV-coinfected patients, TDF combined with lamivudine (3TC) or emtricitabine (FTC) are the recommended NRTI backbone of cART [7]. Unlike patients with HBV monoinfection, for whom the consensus among different guidelines of lifelong nucleos(t)ide analogue treatment is limited to decompensated cirrhosis [8], HIV/HBV-coinfected patients receive anti-HBV therapy early and indefinitely along with other antiretroviral agents for HIV, providing the opportunity to evaluate long-term effect of nucleos(t)ide analogues on HBV replication.

Currently, data regarding the durability of HBV suppression of TDF-containing cART in HIV/HBV-coinfected patients remain limited in areas with higher prevalence of chronic HBV infection. This study aimed to assess the long-term virological and serologic responses of HBV to TDF-containing cART in HIV-positive patients in Taiwan, where the prevalence of chronic HBV infection was estimated 15–20% in persons born before the implementation of nationwide neonatal HBV vaccination program in 1986.

Methods

Study setting and patient population

This retrospective observational study was conducted at the National Taiwan University Hospital (NTUH), a tertiary center for HIV care in Taiwan. All HIV/HBV-coinfected patients aged 20 years or greater who regularly sought HIV care at NTUH between 2004 and 2016 were consecutively included. According to their treatment history with cART, three groups of patients were defined: Group 1, patients who received 3TC as the only anti-HBV therapy (3TC group); Group 2, patients who initiated TDF-containing cART for both HIV and HBV infection (TDF group); and Group 3, patients who switched from coformulated zidovudine (AZT)/3TC- or abacavir (ABC)/3TC-based regimens to TDF and 3TC or coformulated TDF/FTC-based regimens (3TC-TDF group). Patients were excluded if they had no baseline HBV DNA testing before cART or no subsequent testing after cART, had been followed for less than 1 year, or ever received anti-HBV therapy including interferon, telbivudine, entecavir or adefovir; or loss of HBsAg had occurred before inclusion.

For patients in 3TC group and TDF group, baseline data were collected before the initiation of cART. For 3TC-TDF group, baseline data were collected when patients switched from AZT/3TC- or ABC/3TC-based regimens to TDF plus 3TC or TDF/FTC-based regimens. The observation duration of the patients in 3TC-TDF group before switching to TDF-based regimens was included in 3TC group, while that after switching to TDF-based regimens was included in 3TC-TDF group (Fig. 1).

In Taiwan, TDF and TDF/FTC had not been available in clinical care for HIV-positive patients until November 2011 and November 2014, respectively. TDF-containing cART was recommended for HIV/HBV-coinfected patients by the national HIV treatment guidelines when it became available in 2011. For patients with persistent HBV viral breakthrough while on TDF-containing cART despite good HIV viral suppression, entecavir would be considered as the add-on therapy if emergence of TDF-resistant HBV was suspected, as suggested by AASLD guidelines [9].

Our primary end-point was the proportion of patients who achieved undetectable plasma HBV DNA load before year 5, and the secondary end-points were the proportion of patients who had seroconversion of HBV envelope antigen (HBeAg) and that of patients with loss of HBsAg before year 5. The study was approved by the NTUH Research Ethics Committee (registration number, NTUH-201201028RIB), and the written or oral informed consent was waived.

Data collection and definitions

A standardized case record form was used to collect the clinical and laboratory data, which included CD4 lymphocyte count, plasma HIV RNA load, plasma HBV DNA load and serologic profiles of HBV at baseline and annually after initiation of 3TC-based or TDF-containing cART. Results of abdominal ultrasonography, resistance mutations of HBV, and HCV coinfection were documented, so were the numbers of patients with loss of HBsAg and HBsAg or HBeAg seroconversion.

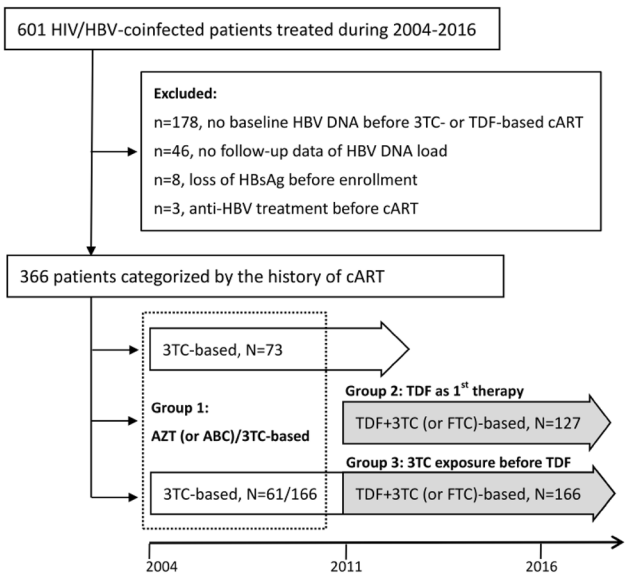

Fig. 1 Study flow

Chronic HBV infection was defined as the persistence of HBsAg for > 6 months, and undetectable plasma HBV DNA load was defined as having HBV DNA level < 128 copies/mL. HCV coinfection was defined as being positive for anti-HCV antibody. Virological breakthrough of HBV was defined as > 1 $\log_{10}$ increase in plasma HBV DNA load from nadir. Aspartate aminotransferase (AST)-to-platelet ratio index (APRI) was used for the noninvasive evaluation of liver fibrosis. Parenchymal liver disease or cirrhosis of the liver was documented by abdominal ultrasonography.

Laboratory investigations

CD4 count was determined using flow cytometry (BD FACS Calibur, Becton Dickinson and Coulter Epics XL, Beckman Coulter, CA, USA) and plasma HIV RNA load was quantified using the Cobas AmpliPrep/Cobas TaqMan HIV-1 test (version 2.0, Roche Molecular Systems, Inc.). HBV serologic markers (HBsAg, anti-HBs antibody, HBeAg, and anti-HBe antibody) and anti-HCV antibody were determined using enzyme immunoassay (Abbott Laboratories, Abbott Park, IL, USA). Plasma HBV DNA load was quantified using the Abbott Real Time HBV assay (Abbott Laboratories, Abbott Park, IL) with a lower detection limits of 15 IU/mL after 2.5 fold dilution of serum samples, and the results were stated as 1 IU/mL = 3.41 copies/mL. The HBV genotype was determined by constructing the phylogenetic trees using the neighbor-joining method and the Kimura 2-parameter distance matrix listed in the MEGA (molecular evolutionary genetics analysis) analytical package [10].

Statistical analysis

The distributions of patients' demographics and baseline characteristics were presented with descriptive statistics. Categorical variables were compared using Chi-square test or Fisher's exact test, and continuous variables using the Mann–Whitney *U* test. Univariate and multivariate Cox proportional hazards models were used to examine factors associated with undetectable plasma HBV DNA load before year 5. All *p* values were two-sided and a *p* value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

A total of 366 HIV/HBV-coinfected patients were included in the analysis (Fig. 1): 73 (19.9%) in 3TC group, 127 (34.7%) in TDF group, and 166 (45.4%) in 3TC-TDF group. Sixty-one (36.7%) patients in 3TC-TDF group had available plasma HBV DNA load before 3TC-based cART, and their follow-up during the treatment course with AZT/3TC- or ABC/3TC-based cART were included in the analysis of 3TC group (Fig. 1).

Baseline characteristics of the patients are shown in Table 1. The majority of the patients were middle-aged homosexual male. Genotype B (43.1%) was the predominant HBV subtype, followed by genotype C (13.8%). The overall prevalence of HBeAg positivity at baseline was 21.1% (65/308). The mean baseline plasma HBV DNA load of 3TC group and TDF group was 4.6 and 5.0 $\log_{10}$ copies/mL ($p = 0.179$), respectively, while the mean baseline plasma HBV DNA load of 3TC-TDF group (3.5 $\log_{10}$ copies/mL) was lower than those of the other two groups. The comparisons of 3TC and 3TC-TDF groups are shown in Supplementary Table 1.

Virological responses of HBV to different anti-HBV regimens

The mean plasma HBV DNA load of 3TC, TDF, and 3TC-TDF group was 2.9, 2.2, and 2.1 $\log_{10}$ copies/mL, respectively, at year 1, and 2.7, 2.1, and 2.1 $\log_{10}$ copies/mL, respectively, at year 5. The mean plasma HBV DNA level was similar between TDF group and 3TC-TDF group after 3 years of treatment (2.13 vs 2.12 $\log_{10}$ copies/mL, $p = 0.098$) (Fig. 2a). In the analysis only including patients with baseline plasma HBV DNA load ≥ 1000 copies/mL, the mean plasma HBV DNA load of TDF group was lower than that of 3TC-TDF group after 3 years of treatment (2.14 vs 2.17 $\log_{10}$ copies/mL, $p = 0.001$) (Fig. 2b).

The percentages of patients with undetectable HBV DNA in the three groups at each time point are shown in Fig. 3 and Supplementary Table 2. At year 5, the percentage of patients with undetectable plasma HBV DNA load in 3TC, TDF, and 3TC-TDF group was 77.8%, 95.7%, and 95.7%, respectively (Fig. 3a). The cumulative percentage of reaching undetectable HBV DNA at least once over the 5-year follow-up period was 88.9%, 100% and 100% of patients in 3TC, TDF, and 3TC-TDF groups, respectively, if they had not changed cART regimen earlier (Fig. 3b).

Among the patients receiving TDF-containing cART as the first-line or second-line anti-HBV treatment, 9.6% (28/293) had persistent HBV viremia after 1 year and 3.1% (9/293) after 2 years of therapy, and 10.6% (31/293) developed episodes of viral rebound after ever achieving an undetectable plasma HBV DNA level. The median peak HBV DNA level from nadir of 31 patients with HBV viral rebounds was 281 copies/mL (interquartile range, 171–879). The episodes of virological breakthrough in these patients were all associated with poor adherence to cART, as suggested by the rebounds of plasma HIV RNA load.

Table 1 Baseline clinical characteristics of 366 HIV/HBV-coinfected patients

	Group 1 3TC ($n=134$)*	Group 2 TDF ($n=127$)	Group 3 3TC to TDF ($n=166$)	p	
				Group 1 vs 2	Group 2 vs 3
Age, mean ± SD, years	36.6 ± 8.7	37.7 ± 8.7	41.5 ± 8.9	0.163	< 0.001
Male sex, *n* (%)	132 (98.5)	126 (99.2)	161 (97.0)		
Male who have sex with male, *n* (%)	110 (82.1)	111 (87.4)	136 (81.9)		
Year since HIV diagnosis, mean ± SD, years	2.4 ± 2.7	2.6 ± 2.9	8.0 ± 4.9	0.815	< 0.001
HBV genotype, *n* (%)					
B	69 (51.5)	42 (33.1)	73 (44.0)		
C	23 (17.2)	8 (6.3)	28 (16.9)		
No data	42 (31.3)	77 (60.6)	65 (39.2)		
Duration of prior 3TC use, mean ± SD, years	NA	NA	5.8 ± 4.6		
Document 3TC resistance, *n* (%)	NA	NA	47 (28.3)		
Positive HBeAg at baseline, *n*/*n* (%)	17/62 (27.4)	21/89 (23.6)	27/157 (17.2)	0.594	0.224
HBeAg level at baseline, S/CO	887.9 ± 604.6 ($n=13$)	753.2 ± 696.9 ($n=20$)	777.1 ± 520.8 ($n=22$)	0.580	0.999
HBsAg level at baseline, *n*/*n* (%)					
> 250 IU/mL	75/134 (56.0)	100/127 (78.7)	100/166 (60.2)	< 0.001	0.001
≤ 250 IU/mL	27/134 (20.1)	27/127 (21.3)	48/166 (28.9)	0.821	0.137
No data+	32/134 (23.9)	0/127 (0)	18/166 (10.8)		
Plasma HBV DNA level at baseline, mean ± SD, $\log_{10}$ copies/mL	4.6 ± 2.6	5.0 ± 2.5	3.5 ± 2.3	0.179	< 0.001
< 3 $\log_{10}$ copies/mL	46 (34.3)	34 (26.8)	102 (61.4)		
3–5 $\log_{10}$ copies/mL	43 (32.1)	39 (30.7)	31 (18.7)		
> 5 $\log_{10}$ copies/mL	45 (33.6)	54 (42.5)	33 (19.9)		
ALT at baseline, IU/L, mean ± SD	100 ± 209	55 ± 72	60 ± 90	0.912	0.703
APRI score at baseline, mean ± SD	1.1 ± 2.2	0.8 ± 1.6	0.5 ± 0.6	0.745	0.001
Liver cirrhosis at baseline, *n*/*n* (%)	3/127 (2.4)	3/114 (2.6)	8/159 (5.0)	0.999	0.369
Anti-HCV positivity at baseline, *n* (%)	6 (4.5)	12 (9.4)	11 (6.6)	0.133	0.373
CD4 count at baseline, mean ± SD, cells/μl	205 ± 172	250 ± 202	521 ± 307	0.063	< 0.001
Plasma HIV RNA load at baseline, mean ± SD, $\log_{10}$ copies/mL	4.6 ± 1.2	4.7 ± 0.9	1.9 ± 1.0	0.556	< 0.001
Follow-up duration, mean ± SD, years	3.6 ± 1.4	3.6 ± 1.4	4.0 ± 1.4	0.732	0.005

3TC lamivudine, *ALT* alanine aminotransferase, *APRI* AST-to-platelet ratio index, *AST*, aspartate aminotransferase, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *NA* not applicable, *SD* standard deviation, *TDF* tenofovir disoproxil fumarate

*61 patients were included both in group 1 (3TC group) and group 3 (3TC to TDF group)

+HBsAg reported as "positive" without quantitative data

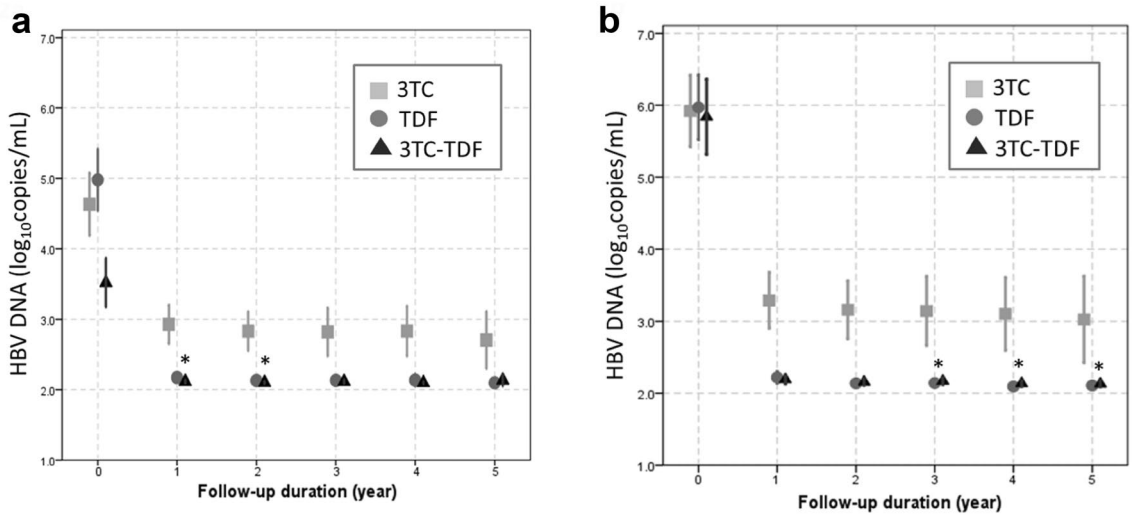

Fig. 2 Changes of plasma HBV DNA load in HIV/HBV-coinfected patients receiving 3TC-based cART (3TC group), TDF/3TC (or FTC)-containing cART (TDF group), or who switched from 3TC-based to TDF/FTC or TDF plus 3TC-containing cART (3TC-TDF group) with a baseline HBV DNA: **a** analysis of all patients; or **b** patients with baseline HBV DNA load ≥ 1000 copies/mL (*$p < 0.05$)

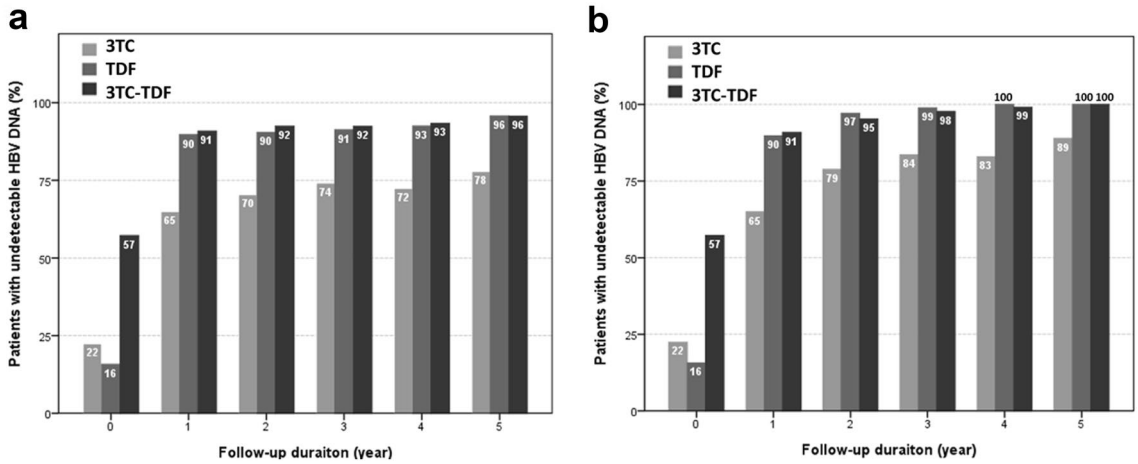

Fig. 3 Annual percentages of HIV/HBV-coinfected patients who achieved undetectable plasma HBV DNA load while receiving 3TC-based cART (3TC group), TDF/FTC or TDF plus 3TC-containing cART (TDF group), or switch from 3TC-based to TDF/FTC or TDF plus 3TC-containing cART (3TC-TDF group): **a** on-time analysis; **b** cumulative percentage

Thirteen patients with baseline HBeAg positivity had persistent HBV viremia during the study period: 11 in 3TC group who switched to TDF-based therapy with HBV suppression subsequently; and another 2 in TDF group, with 1 loss to follow-up and 1 subsequently switching to tenofovir alafenamide (TAF)-containing regimen. All, except the patient with loss to follow-up, survived without liver complications.

Thirty-four (25.4%) of 134 patients in 3TC group developed resistance to HBV, with 17 exhibiting YVDD mutation, 9 YIDD mutation, and 8 YMDD mutation. Five patients continued 3TC-based cART, while the other 29 switched to TDF-based cART. Of these patients, 2 patients who maintained on 3TC-based regimens died of pneumonia and lung cancer, respectively, 3 were lost to follow-up, and the other 29 continued to receive cART without complications.

Factors associated with HBV viral suppression

The Kaplan–Meier plots of HBV viral suppression among patients with baseline HBV DNA ≥ 1000 copies/mL are shown in Fig. 4a, b. Compared with TDF group, 3TC group had a significantly lower rate of HBV viral suppression (log rank $p < 0.001$). In contrast, the cumulative proportion of HBV viral suppression did not differ significantly between TDF group and 3TC-TDF group (log rank $p = 0.071$). In

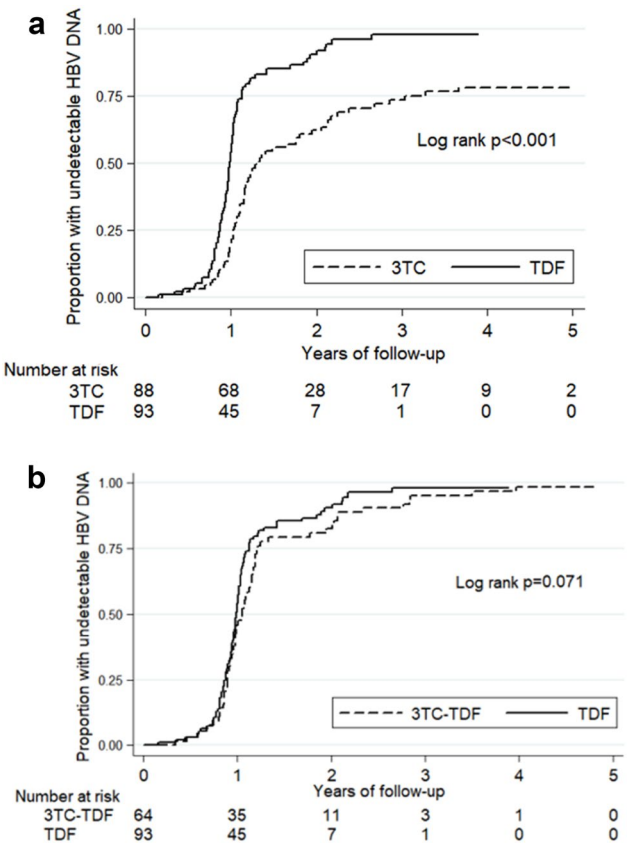

Fig. 4 Proportional curve for HIV/HBV-coinfected patients with a baseline HBV DNA ≥ 1000 copies/mL to achieve HBV viral suppression (< 128 copies/mL): **a** 3TC group vs TDF group (log rank $p < 0.001$); **b** TDF group vs 3TC-TDF group (log rank $p = 0.071$)

univariate analysis, age, baseline plasma HBV DNA and HIV RNA load, TDF vs 3TC as initial anti-HBV therapy, and baseline status of HBeAg were significantly associated with HBV viral suppression (Table 2). In multivariate analysis, TDF (± 3TC or FTC) but not 3TC alone as initial anti-HBV agent was more likely to be associated with HBV viral suppression (adjusted hazard ratio [aHR] 2.635; 95% CI 1.720–4.037), and HBeAg positivity at baseline were associated with failure to achieve HBV viral suppression (aHR 0.293; 95% CI 0.178–0.482; or aHR 0.318; 95% CI 0.206–0.491) (Table 2).

Serologic response of HBV

During the observation period, loss of HBeAg occurred in 23.5% (4/17), 33.3% (7/21), and 25.9% (7/27) in 3TC group, TDF group, and 3TC-TDF group, respectively. Overall, HBeAg seroconversion occurred in 11 (16.9%) of 65 patients of the 3 groups, and the rates were similar between TDF group and 3TC-TDF group (9.5% [2/21] vs 18.5% [5/27], $p = 0.45$). Of all patients, 5 (1.4%) tested positive for both HBsAg and anti-HBs; loss of HBsAg was observed in 15 (4.1%) after an average of 5.7 years of cART; and 7 (1.9%) also had seroconversion to anti-HBs.

During the study period, 16 patients had plasma HCV RNA testing; of them, 5 (31.3%) had undetectable HCV RNA level, and the mean plasma HCV RNA load of the other 11 was 6.78 $\log_{10}$ IU/mL (SD 0.7 $\log_{10}$ IU/mL). Thirteen patients had received anti-HCV therapy (3 in 3TC group, 4 TDF group, and 6 3TC-TDF group). Among them, 3 had received pegylated interferon and ribavirin (peg-IFN/RBV) before inclusion in this study, and 7 received peg-IFN/RBV and 3 received direct acting antivirals at an average of 2.9 years after inclusion with all having achieved undetectable HBV DNA levels prior to anti-HCV treatment. The results of the comparisons between groups did not change after excluding these three patients who had received peg-IFN/RBV before inclusion.

Discussion

In this cohort of HIV/HBV-coinfected patients in a hyperendemic country of chronic HBV infection, TDF-containing cART could achieve durable HBV viral suppression. HBeAg positivity at baseline was associated with failure to achieve HBV viral suppression after long-term TDF therapy, while presence of 3TC-resistant HBV or pre-treatment plasma HBV DNA load was not. Despite long-term HBV viral suppression, the rate of HBeAg seroconversion was 16.9% and that of HBsAg seroconversion was only 1.9%.

The potent effect of TDF-based dual therapy over 3TC monotherapy on HBV in HIV/HBV-coinfected patients has been demonstrated in previous studies with the case number ranging from 102 to 150 [11–14]. In our study, we included the largest number of HIV/HBV-coinfected patients ($n = 366$) with a longer follow-up period. A recently published meta-analysis involving 607 patients reported higher rates of undetectable HBV DNA, alanine aminotransferase (ALT) normalization, and loss of HBeAg in patients receiving TDF plus 3TC dual therapy than 3TC monotherapy for HIV/HBV coinfection, and their difference in rates of undetectable HBV DNA became more prominent over time [15], suggesting the durable virological effectiveness with dual therapy containing TDF. Moreover, the adverse impact of chronic HBV infection on the survival among HIV/HBV-coinfected patients could be significantly alleviated in the TDF era [16].

HBeAg positivity has been found to be associated with failure to achieve HBV viral suppression at 48 weeks of TDF therapy [17]. HBV genotype, HIV viremia while on cART, low CD4 count, and non-adherence have also been identified to correlate with HBV virological non-response [11, 18, 19].

Table 2 Factors associated with HBV viral suppression (< 128 copies/mL) within 5 years of anti-HBV therapy in patients with baseline HBV DNA ≥ 1000 copies/mL in Cox regression analysis

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
3TC group ($n=88$) vs TDF group ($n=93$)				
Age, per 1-year increase	1.022 (1.008–1.037)	0.003		
HBV genotype B vs genotype C	1.411 (0.832–2.394	0.202		
CD4 count at baseline, per 1-cell/μl increase	1.000 (0.999–1.001)	0.920		
Plasma HIV RNA load at baseline, per 1-$\log_{10}$ copies/mL increase	1.029 (0.851–1.245)	0.766		
Plasma HBV DNA load at baseline, per 1-$\log_{10}$ copies/mL increase	0.805 (0.745–0.869)	< 0.001		
TDF treatment vs 3TC treatment	2.839 (2.021–3.968	< 0.001	2.635 (1.720–4.037)	< 0.001
Positive HBeAg at baseline	0.309 (0.188–0.508	< 0.001	0.293 (0.178–0.482)	< 0.001
TDF group ($n=93$) vs 3TC to TDF group ($n=64$)				
Age, per 1-year increase	1.018 (1.003–1.034)	0.019		
HBV genotype B vs genotype C	1.046 (0.636–1.721)	0.860		
Presence of 3TC mutation	0.722 (0.501–1.040)	0.080		
CD4 count at baseline, per 1-cell/μl increase	1.000 (0.999–1.000)	0.221		
Plasma HIV RNA load at baseline, per 1-$\log_{10}$ copies/mL increase	1.111 (1.0051.228)	0.039		
Plasma HBV DNA load at baseline, per 1-$\log_{10}$ copies/mL increase	0.880 (0.816–0.950)	0.001		
No prior 3TC exposure	1.365 (0.972–1.891)	0.073		
Positive HBeAg at baseline	0.318 (0.206–0.491)	< 0.001	0.318 (0.206–0.491)	< 0.001

3TC lamivudine, *CI* confidence interval, *HBV* hepatitis B virus, *HBeAg* HBV envelope antigen, *HBsAg* HBV surface antigen, *TDF* tenofovir disoproxil fumarate

In our study, only HBeAg positivity at baseline could predict failure to achieve HBV viral suppression after long-term TDF-containing cART. Our findings suggest that patients with positive HBeAg were at higher risk of persistent HBV viremia despite TDF therapy and more frequent monitoring might be necessary. We did not find that 3TC exposure or occurrence of 3TC resistance compromised the effectiveness of TDF-containing cART on HBV viral suppression, which was in line with the findings of a meta-analysis including 550 HIV/HBV-coinfected patients [20].

All of our patients were infected with HBV genotype B or C. In contrast to the prior study that demonstrated genotype A was associated with delayed HBV response to TDF therapy [18], we found that genotype was not correlated with HBV suppression. Moreover, we did not find an association between pre-treatment CD4 count or plasma HIV RNA load and HBV suppression, which might have resulted from the longer follow-up duration in our study, in comparison with the 24 or 48 weeks of observation in previous studies [12, 19]. In our cohort, all anti-HCV-positive patients had HBV suppression during the follow-up period, which was in line with the findings of the study by Hafkin et al. that failed to identify HCV coinfection to be associated with incomplete HBV DNA suppression in 155 HIV/HBV-coinfected patients on TDF-based therapy [19].

Our results showed that 3.1% of the patients receiving TDF-containing cART had persistent HBV viremia after 2 years of treatment, and 10.6% experienced HBV viral rebounds from nadir. In a cohort of 111 HIV/HBV-coinfected patients undergoing TDF therapy, 13.5% of patients had persistent viremia after a median of 35 months of treatment and 10.4% had a transient blip of HBV DNA load [21]. Although a detectable HBV DNA load after long-term TDF-based therapy was not uncommon [22], the emergence of TDF resistance remained rare [21, 23]. In patients with persistent viremia or viral rebound, poor adherence was often cited as the main cause, as shown in our study [24]. However, in patients who had incomplete HBV viral suppression despite good adherence to cART with undetectable plasma HIV RNA load, the phenomenon might result from the genetic variability of HBV or a higher optimal adherence level might be required for HBV suppression [25]. Transient HBV viral blips might also represent random biological variations or assay variability [26]. Currently, the clinical impact of persistent low-level HBV viremia or frequent viral blips on the long-term outcomes among patients receiving TDF-containing therapy remains uncertain.

HBeAg seroconversion is an important milestone in the treatment of HBeAg-positive patients, with the rates ranging from 17 to 46% after 2–5 years of cART [11, 14, 27]. After an average of 5.1 years of anti-HBV therapy, HBeAg seroconversion occurred in 16.9% (11/65) in our study. In contrast, HBsAg loss was generally uncommon in HIV/HBV-coinfected patients and only 4.1% of

our patients lost their HBsAg and 1.9% achieved HBsAg seroconversion. A study by Kosi et al. showed the rate of HBsAg loss was estimated 30% in TDF-treated patients at year 5, which was much higher than that observed in our study [11]. Unlike the HBV-infected population in Taiwan where most of our patients were infected with HBV from mother-to-child transmission [28], only 3% of the patients in Kosi's study acquired HBV from vertical transmission. This might explain the discrepancy observed in response of HBsAg to anti-HBV therapy.

Our study has several limitations. First, due to the nature of retrospective study, data of HBV DNA load, genotype and serologic markers of HBV were incomplete. It is, therefore, that 40% of the patients with HIV/HBV coinfection were not included in the analyses (Fig. 1). Second, liver elastography or biopsies were not performed and we were unable to precisely evaluate the effect of long-term treatment on the evolution of liver fibrosis. Third, anti-HCV therapy might influence HBV DNA level and the evaluation of anti-HBV activity of 3TC- or TDF-based cART. However, only three of our patients had received anti-HCV therapy before inclusion. In the sensitivity analysis with the exclusion of these patients, the findings of our study were not changed. Fourth, we did not analyze the resistance mutations of HBV to TDF. Although most occasions of HBV virological breakthrough were likely associated with non-adherence to cART, the possibility of TDF resistance of HBV in the long-term warrants more follow-up studies. Finally, while TDF remains the most commonly used nucleotide reverse-transcriptase inhibitor in areas of high HBV endemicity, we were not able to examine the effectiveness in maintaining HBV suppression with TAF-containing cART. While TAF is as efficacious as TDF as the first-line anti-HBV therapy in HIV-negative patients [29], clinical experience with TAF in HIV/HBV-coinfected patients remains limited [30].

In conclusion, TDF-containing cART could maintain durable HBV viral suppression in HIV/HBV-coinfected patients and those with HBeAg positivity before treatment were less likely to achieve HBV viral suppression. Despite long-term TDF therapy with sustained suppression of HBV replication, seroconversion of HBsAg remained infrequent among HIV/HBV-coinfected patients in a country of hyperendemicity of HBV infection.

Compliance with ethical standards

Conflict of interest C.-C. H. has received research support from Gilead Sciences, Merck, and ViiV and speaker honoraria from Gilead Sciences and ViiV, and served on the advisory boards for Gilead Sciences and ViiV. Yu-Shan Huang, Hsin-Yun Sun, Sui-Yuan Chang, Yu-Chung Chuang, Aristine Cheng, Sung-Hsi Huang, Yi-Chia Huang, Guan-Jhou Chen, Kuan-Yin Lin, Yi-Ching Su, Wen-Chun Liu have no conflicts of interest.

Ethical approval The study was approved by the NTUH Research Ethics Committee (registration number, NTUH-201201028RIB).

Informed consent The written or oral informed consent was waived.

References

1. Thio CL, Seaberg EC, Skolasky R Jr, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet. 2002;360(9349):1921–6.
2. Tang LSY, Covert E, Wilson E, Kottilil S. Chronic hepatitis B infection: a review. JAMA. 2018;319(17):1802–13.
3. Nikolopoulos GK, Paraskevis D, Psichogiou M, Hatzakis A. HBV-DNA levels predict overall mortality in HIV/HBV coinfected individuals. J Med Virol. 2016;88(3):466–73.
4. Sheng WH, Kao JH, Chen PJ, et al. Evolution of hepatitis B serological markers in HIV-infected patients receiving highly active antiretroviral therapy. Clin Infect Dis. 2007;45(9):1221–9.
5. Dharan NJ, Neuhaus J, Rockstroh JK, et al. Benefit of early versus deferred antiretroviral therapy on progression of liver fibrosis among people with HIV in the START randomized trial. Hepatology. 2019;69(3):1135–50.
6. Sun HY, Sheng WH, Tsai MS, Lee KY, Chang SY, Hung CC. Hepatitis B virus coinfection in human immunodeficiency virus-infected patients: a review. World J Gastroenterol. 2014;20(40):14598–614.
7. Panel on Antiretroviral Guidelines for Adults and Adolescents (2018) Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Department of Health and Human Services. https://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Accessed 26 May 2019.
8. Chen GF, Wang C, Lau G. Treatment of chronic hepatitis B infection-2017. Liver Int. 2017;37(Suppl 1):59–66.
9. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67(4):1560–99.
10. Kumar S, Tamura K, Jakobsen IB, Nei M. MEGA2: molecular evolutionary genetics analysis software. Bioinformatics. 2001;17(12):1244–5.
11. Kosi L, Reiberger T, Payer BA, et al. Five-year on-treatment efficacy of lamivudine-, tenofovir- and tenofovir + emtricitabine-based HAART in HBV-HIV-coinfected patients. J Viral Hepat. 2012;19(11):801–10.
12. Thio CL, Smeaton L, Hollabaugh K, et al. Comparison of HBV-active HAART regimens in an HIV-HBV multinational cohort: outcomes through 144 weeks. AIDS. 2015;29(10):1173–82.
13. Kang M, Hollabaugh K, Pham V, et al. Virologic and serologic outcomes of mono versus dual HBV therapy and characterization of HIV/HBV coinfection in a US cohort. J Acquir Immune Defic Syndr. 2014;66(2):172–80.
14. de Vries-Sluijs TE, Reijnders JG, Hansen BE, et al. Long-term therapy with tenofovir is effective for patients co-infected with human immunodeficiency virus and hepatitis B virus. Gastroenterology. 2010;139(6):1934–41.
15. Luo A, Jiang X, Ren H. Lamivudine plus tenofovir combination therapy versus lamivudine monotherapy for HBV/HIV coinfection: a meta-analysis. Virol J. 2018;15(1):139.
16. Tsai WC, Hsu WT, Liu WD, et al. Impact of antiretroviral therapy containing tenofovir disoproxil fumarate on the survival of patients with HBV and HIV coinfection. Liver Int. 2019. https://doi.org/10.1111/liv.14059.
17. Huang YS, Chang SY, Sheng WH, et al. Virological response to tenofovir disoproxil fumarate in HIV-positive patients with

lamivudine-resistant hepatitis B virus coinfection in an area hyperendemic for hepatitis B virus infection. PLoS ONE. 2016;11(12):e0169228.
18. Bihl F, Martinetti G, Wandeler G, et al. HBV genotypes and response to tenofovir disoproxil fumarate in HIV/HBV-coinfected persons. BMC Gastroenterol. 2015;15:79.
19. Hafkin JS, Osborn MK, Localio AR, et al. Incidence and risk factors for incomplete HBV DNA suppression in HIV/HBV-co-infected patients initiating tenofovir-based therapy. J Viral Hepat. 2014;21(4):288–96.
20. Price H, Dunn D, Pillay D, et al. Suppression of HBV by tenofovir in HBV/HIV coinfected patients: a systematic review and meta-analysis. PLoS ONE. 2013;8(7):e68152.
21. Audsley J, Bent SJ, Littlejohn M, et al. Effects of long-term tenofovir-based combination antiretroviral therapy in HIV-hepatitis B virus coinfection on persistent hepatitis B virus viremia and the role of hepatitis B virus quasispecies diversity. AIDS. 2016;30(10):1597–606.
22. Matthews GV, Seaberg EC, Avihingsanon A, et al. Patterns and causes of suboptimal response to tenofovir-based therapy in individuals coinfected with HIV and hepatitis B virus. Clin Infect Dis. 2013;56(9):e87–94.
23. Kitrinos KM, Corsa A, Liu Y, et al. No detectable resistance to tenofovir disoproxil fumarate after 6 years of therapy in patients with chronic hepatitis B. Hepatology. 2014;59(2):434–42.
24. Hongthanakorn C, Chotiyaputta W, Oberhelman K, et al. Virological breakthrough and resistance in patients with chronic hepatitis B receiving nucleos(t)ide analogues in clinical practice. Hepatology. 2011;53(6):1854–63.
25. Boyd A, Gozlan J, Maylin S, et al. Persistent viremia in human immunodeficiency virus/hepatitis B coinfected patients undergoing long-term tenofovir: virological and clinical implications. Hepatology. 2014;60(2):497–507.
26. Liu Y, Corsa AC, Buti M, et al. No detectable resistance to tenofovir disoproxil fumarate in HBeAg+ and HBeAg- patients with chronic hepatitis B after 8 years of treatment. J Viral Hepat. 2017;24(1):68–74.
27. Boyd A, Maylin S, Gozlan J, et al. Use of hepatitis B surface and "e" antigen quantification during extensive treatment with tenofovir in patients co-infected with HIV-HBV. Liver Int. 2015;35(3):795–804.
28. Lin CL, Kao JH. Perspectives and control of hepatitis B virus infection in Taiwan. J Formos Med Assoc. 2015;114(10):901–9.
29. Agarwal K, Brunetto M, Seto WK, et al (2018) 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. J Hepatol 68(4):672–681
30. Gallant J, Brunetta J, Crofoot G, et al. Brief report: efficacy and safety of switching to a single-tablet regimen of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide in HIV-1/Hepatitis B-coinfected adults. J Acquir Immune Defic Syndr. 2016;73(3):294–8.

Affiliations

Yu-Shan Huang[1] · Hsin-Yun Sun[1] · Sui-Yuan Chang[2,3] · Yu-Chung Chuang[1] · Aristine Cheng[1] · Sung-Hsi Huang[4,5] · Yi-Chia Huang[4] · Guan-Jhou Chen[6] · Kuan-Yin Lin[7] · Yi-Ching Su[1] · Wen-Chun Liu[1] · Chien-Ching Hung[1,5,8,9]

1 Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, No.7 Chung-Shan South Road, Taipei 100, Taiwan

2 Department of Clinical Laboratory Sciences and Medical Biotechnology, National Taiwan University College of Medicine, Taipei, Taiwan

3 Department of Laboratory Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan

4 Department of Internal Medicine, National Taiwan University Hospital Hsin-Chu Branch, Hsin-Chu, Taiwan

5 Department of Tropical Medicine and Parasitology, National Taiwan University College of Medicine, Taipei, Taiwan

6 Department of Internal Medicine, National Taiwan University Hospital Yun-Lin Branch, Yun-Lin County, Taiwan

7 Department of Medicine, National Taiwan University Hospital Jin-Shan Branch, New Taipei City, Taiwan

8 Department of Medical Research, China Medical University Hospital, Taichung, Taiwan

9 China Medical University, Taichung, Taiwan