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Original Article

Evaluation of the Safety and Efficacy of SOF/VEL Treatment and Pre-treatment of TAF in Patients with Chronic Hepatitis B Virus/Hepatitis C Virus Coinfection: A Multicenter Study

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Abstract

Background and Aims: Hepatitis B virus (HBV) infection and hepatitis C virus (HCV) infection are among the leading causes of chronic liver diseases worldwide. Through the same transmission routes, HBV/HCV coinfection is widespread and aggravates liver damage. In this study, we aimed to assess the safety and efficacy of sofosbuvir/velpatasvir (SOF/VEL) and the pre-treatment of tenofovir alafenamide fumarate (TAF) on HBV reactivation in HBV/HCV coinfected patients. ***Methods:*** A multicenter, prospective, single-arm, open-label 12-week trial, followed by a 12/48-week observational clinical trial, was conducted. Ninety-six adults with chronic HBV/HCV coinfection were enrolled from May 2021 to December 2024 in thirteen centers in China. Seventy-seven non-cirrhotic patients were included in Group 1 and nineteen compensated cirrhotic patients in Group 2. All subjects were enrolled to receive SOF/VEL once daily for 12 weeks. Non-cirrhotic subjects received TAF once daily for 28 weeks, and compensated cirrhotic subjects received TAF once daily for 64 weeks simultaneously. Statistical significance was set at $P < 0.05$. ***Results:*** At the end of SOF/VEL treatment, the overall sustained virologic response was 97.9%, of which 100% was achieved in Group 2. HCV RNA, HBV DNA, and HBV RNA levels were substantially decreased in all patients. Alanine aminotransferase (ALT) (61.5 vs. 21.9, $P < 0.001$) and aspartate aminotransferase (AST) (50.8 vs. 25.7, $P < 0.001$) levels decreased, and albumin (ALB) (42.4 vs. 45.1, $P < 0.001$) level increased compared to pre-treatment in Group 1 at 12 weeks post-treatment. ALT (64.1 vs. 25.2, $P < 0.001$), AST (65.7 vs. 29.7, $P < 0.001$), alkaline phosphatase (ALP) (111.6 vs. 88.2, $P < 0.05$), and alpha-fetoprotein (AFP) (17.9 vs. 4.7, $P < 0.05$) levels decreased, and ALB (41.3 vs. 42.5, $P = 0.051$) and platelet count (PLT) (114.0 vs. 127.2, $P = 0.052$) levels showed a trend toward increase compared to pre-treatment in Group 2 at 48 weeks post-treatment. Liver stiffness measurement (LSM) (22.6 vs. 12.7, $P < 0.01$), aspartate aminotransferase to platelet ratio index (APRI) (1.6 vs. 0.6, $P < 0.001$), and fibrosis-4 index (FIB-4) (4.7 vs. 2.6, $P < 0.05$) significantly decreased after treatment in Group 2. Two patients in Group 1 with genotype 3 showed HBV reactivation and HCV relapse, respectively. No drug-related adverse events were observed in the study. ***Conclusions:*** SOF/VEL effectively achieves a sustained virologic response and improves liver function, with an acceptable safety profile in chronic HBV/HCV coinfected patients, including those with compensated cirrhosis, who achieved modest improvement in non-invasive fibrosis indices. Pre-administration of TAF may mitigates the risk of HBV reactivation in this population.

Keywords: Hepatitis B virus; HBV; Hepatitis C virus; HCV; Sofosbuvir/velpatasvir; SOF/VEL; Safety; Efficacy..

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Introduction

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections represent major etiological factors contributing to chronic liver disease globally. According to the Report of the World Health Organization, more than 296 million people worldwide are infected with HBV,[1] and 58 million people with HCV.[2] Because HBV and HCV share common transmission routes, co-infection is frequently observed and aggravates severe liver damage. Epidemiologic studies suggest that approximately 10% to 15% of patients with hepatitis C infection are co-infected with HBV.[3] Given the lack of large-scale studies, these numbers may underestimate the actual number of patients coinfected with HBV and HCV.

HBV/HCV coinfection refers to the simultaneous presence of HBV and HCV in the same individual, with both viruses potentially affecting the same organs or tissue types. HBV/HCV coinfection exhibits greater clinical and virological complexity compared to mono-infection with either HBV or HCV alone. In chronic HBV/HCV coinfection, HBV interacts with HCV, but which virus has the dominant inhibitory status may be related to the sequence of viral infection in the body.[4] In general, the virus that infects subsequently suppresses the one that infected first; coinfection will aggravate liver damage and lead to more severe disease outcomes.[5,6] HCV infection is the dominant driver of chronic hepatitis activity. It can suppress HBV replication, potentially leading to the inactivation of concurrent HBV infection or even occult infection, characterized by undetectable serum HBsAg and/or HBV DNA. Studies have shown that HCV inhibits the replication of HBV in patients with HBV/HCV coinfection through core protein, NS2 protein, and NS5A protein, leading to HBV infection being inactive or occult.[7,8] HBV can also inhibit HCV, but it is not as obvious as HCV inhibiting HBV.[9]

Currently, direct-acting antiviral agents (DAAs), characterized by short treatment courses, high sustained virologic response (SVR) rates, and low incidence of adverse events (AEs), have created a new era in the treatment of chronic hepatitis C.[10] However, DAA therapy for HCV can lead to upregulation of HBV replication and protein expression, increasing the risk of HBV reactivation. A meta-analysis revealed that the HBV reactivation rate in HBV/HCV co-infected patients who received DAAs was 12.2%.[11]

In this study, we assessed the safety and efficacy of sofosbuvir/velpatasvir (SOF/VEL) and the pre-treatment of tenofovir alafenamide fumarate (TAF) on HBV reactivation in HBV/HCV coinfected patients from the thirteen centers in China.

Methods

Study design and patients

A multicenter, prospective, single-arm, open-label 12-week trial followed by a 12/48-week observational clinical trial (ChiCTR2000033390) was conducted in thirteen centers in China from May 2021 to December 2024. Patients with chronic HBV/HCV (GT1–6) coinfection were enrolled: 1) Age ≥ 18 years, male or non-pregnant/non-lactating female; 2) treatment-naive for both HBV and HCV; 3) HBsAg positive and HCV RNA positive for ≥6 months. Patients were excluded if they had: 1) a history of malignant tumors within 5 years prior to screening, except for specific cancers that have been cured by surgical resection, or were suspected of having malignant tumors; 2) a current or previous history of a major medical condition or any other major medical disorder that may interfere with the individual's treatment, assessment, or compliance program; 3) HIV or HDV infection; 4) chronic liver disease other than HCV pathogens. Patients with chronic liver diseases other than HBV/HCV coinfection were strictly excluded, including alcoholic liver disease, non-alcoholic fatty liver disease, drug-induced liver injury, autoimmune liver disease, and genetic metabolic liver diseases, to avoid confounding bias and ensure the homogeneity of the study cohort.

Non-cirrhotic patients and/or compensated cirrhotic patients were enrolled to receive SOF/VEL once daily for 12 weeks. Compensated cirrhosis is defined by evidence of cirrhosis on clinical, laboratory, endoscopic, imaging, or histological assessments. The diagnosis requires meeting one of the following four criteria:[12] 1) histological confirmation of cirrhosis; 2) endoscopic evidence of esophagogastric varices or ectopic gastrointestinal varices, with non-cirrhotic portal hypertension ruled out; 3) imaging findings from ultrasound, liver stiffness measurement (LSM), CT, or MRI suggestive of cirrhosis or portal hypertension, such as splenomegaly, portal vein diameter ≥1.3 cm, with LSM ≥7.3 kPa[13]; 4) in the absence of histological, endoscopic, or imaging evidence, the presence of cirrhosis is suggested by abnormalities in at least two of the following indicators: PLT $<100\times10^9$/L, with no other explanatory causes; serum ALB <35 g/L, excluding malnutrition, protein-losing enteropathy, or renal disease; INR >1.3 or prolonged PT (after discontinuing thrombolytic or anticoagulant drugs for at least seven days); adult aspartate aminotransferase-to-platelet ratio index (APRI) score >2. Patients diagnosed with decompensated cirrhosis were excluded. This condition was characterized by the presence of cirrhosis, corroborated by clinical, laboratory, endoscopic, imaging, or histological assessments, and the manifestation of at least one severe complication linked to portal hypertension, including ascites, esophageal variceal bleeding, hepatorenal syndrome, or hepatic encephalopathy.[12] All patients with confirmed cirrhosis underwent standardized upper gastrointestinal endoscopy at baseline to screen for esophageal and gastric varices, and the severity and related signs of varices were recorded in detail.

Non-cirrhotic patients received TAF once daily for 28 weeks, and compensated cirrhotic patients received TAF once daily for 64 weeks simultaneously. The following study visits were completed: screening, Day 1 (starting with TAF), at the end of Week 4 (starting with SOF/VEL), Weeks 8, 12, 16 (at the end of SOF/VEL), 12 weeks post-treatment (end of TAF use in non-cirrhotic patients), and 48 weeks post-treatment (end of TAF use in patients with cirrhosis) (Fig. 1).

Each SOF/VEL (EPCLUSA) tablet contains 400 mg of sofosbuvir and 100 mg of velpatasvir. Each TAF (VEMLIDY) tablet contains 25 mg of tenofovir alafenamide. SOF/VEL (400 mg/100 mg tablet) was administered orally once daily with or without food. TAF (25 mg tablet) was administered orally once daily with food. Each patient was given instructions to maintain approximately the same daily dosing interval between study drug doses. For GT3 cirrhotic patients, ribavirin was added simultaneously with SOF/VEL for 12 weeks. For patients weighing <75 kg, the dose was 500 mg twice daily; for patients weighing ≥75 kg, the dose was 600 mg twice daily.

Assessments

Screening assessments included physical examination, medical history, height, weight, vital signs, 12-lead ECG, AEs related to screening procedures, concomitant medications, safety laboratory tests (including hematology, chemistry,

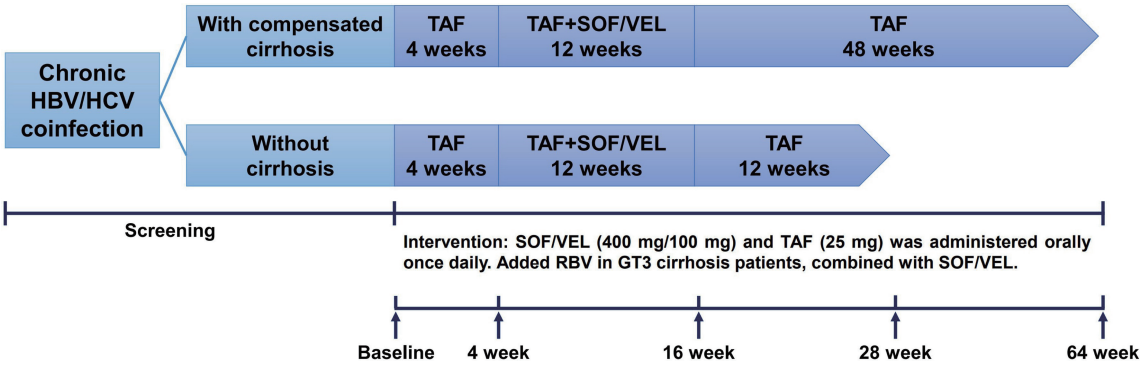

Fig. 1. Study design. HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; TAF, tenofovir alafenamide fumarate; SOF/VEL, sofosbuvir/velpatasvir.

and coagulation), HCV RNA (cobas® HCV, Shanghai Roche Diagnostics Co., Ltd.), HBV DNA (cobas® HBV, Shanghai Roche Diagnostics Co., Ltd.), serology (HIV, HCV, HDV), hemoglobin A1c, assessment of the presence or absence of cirrhosis, screening for hepatocellular carcinoma for subjects with cirrhosis, serum β-hCG (females of childbearing potential only), HCV genotyping, and urinalysis. Serum samples were collected for HBV RNA (Hepatitis B Virus RNA Assay Kit, Beijing Hotgen Biotech Co., Ltd.) detection at baseline, Week 16 during treatment, and Week 28 after treatment. Serologic testing, APRI, fibrosis-4 score (FIB-4), and LSM were evaluated during the screening, on-treatment, and post-treatment periods. APRI was calculated as [(AST/ULN) × 100/PLT (10^9/L)], and FIB-4 was calculated as:

$$\frac{\text{age} \times \text{AST}}{\text{PLT } (10^9/\text{L}) \times \sqrt{\text{ALT}}}.$$

LSM was performed using FibroScan®, a device based on vibration-controlled transient elastography technology.

At each center, LSM measurements were performed by radiologists with more than 10 years of experience who were blinded to the patients' group assignments. All study data were collected by independent data collectors. The final data analysis was conducted by two analysts who were blinded to both the patients' group assignments and the timing of treatment to reduce subjective bias.

Study endpoints

The primary efficacy endpoint was SVR12 (Sustained Virologic Response at 12 weeks, HCV RNA < the lower limit of quantification (LLOQ) 12 weeks after cessation of therapy) in the full analysis set population. The primary safety endpoint was any AE leading to permanent discontinuation of study drug(s). AE classification was based on Common Terminology Criteria for Adverse Events (CTCAE) standards. HBV reactivation was defined as an increase in HBV DNA levels of more than 2 $\log_{10}$ (100-fold) IU/mL compared with baseline; an HBV DNA level of ≥1,000 IU/mL in a person with a previously undetectable HBV DNA level; or an HBV DNA level of ≥10,000 IU/mL if no baseline HBV DNA level is available.[14] In our study, the LLOQ was 20 IU/mL for HBV DNA, 100 copies/mL for HBV RNA, and 15 IU/mL for HCV RNA.[15] Secondary endpoints included the following: 1) changes in HBV DNA, HCV RNA, and HBV RNA levels from baseline; 2) changes in serological indices from baseline; 3) changes in indicators of liver fibrosis from baseline.

Analysis

Data were shown as mean ± standard deviation or median (IQR) for normally and non-normally distributed continuous variables. Group t-tests or Mann–Whitney U tests were used for comparisons between groups. Paired-samples t-tests or nonparametric tests were used for comparisons within groups before and after treatment. Mann–Whitney U tests and Kruskal–Wallis tests, coupled with post hoc comparisons, were used to test the differences in continuous variables between groups. A sample size of 96 subjects provided more than 75% power to detect the SVR12 rate using a two-sided exact one-sample binomial test at a significance level of 0.05. Statistical analyses were performed using SPSS 29.0 (IBM SPSS, Chicago, IL, USA). Statistical significance was set at $P < 0.05$.

Results

Baseline characteristics

The study included 96 patients with HBV/HCV coinfection, with a median age of 50.5 (16.5) years (range 21–87 years), and a median HCV RNA level of 5.7 (1.7) log10 IU/mL (range 2.2–7.8 log10 IU/mL). Of these, 77 non-cirrhotic patients were included in Group 1 and 19 compensated cirrhosis patients in Group 2. At baseline, HCV RNA levels were 5.8 (1.2) and 5.5 (1.3) in the two groups, respectively, with no statistical differences. AST, ALP, TBIL, AFP, APRI, FIB-4, and LSM were higher in Group 2 than in Group 1, and ALB levels and PLT counts were lower than in Group 1 (Table 1). The HCV genotype distribution of the patients is shown in Figure 2. Genotype 1 was the most prevalent across the whole cohort, accounting for 29.2%. Genotype 2 was less frequent, accounting for 13.6% (Fig. 2).

SVR12

All patients demonstrated good adherence to treatment and took their medication as prescribed. HCV RNA was tested after cessation of anti-HCV therapy, and two patients with genotype 3 did not achieve SVR in Group 1. After confirmation via viral genotyping or resistance testing, these patients underwent retreatment. At 12 weeks after cessation of therapy, the overall SVR12 rate was 97.9% (94/96), with 97.4% (75/77) in Group 1 and 100% (19/19) in Group 2 (Fig. 3). Stratified by HCV genotype, genotype 3 patients had a lower SVR12 rate of 90.0% (18/20), while genotypes 1, 2, and 6 all achieved 100% SVR12.

Changes in HBV DNA, HCV RNA, and HBV RNA

At 28 weeks, the HBV/HCV coinfected patients without cirrhosis had finished the treatment. At this time, changes in

Table 1. Baseline characteristics

Characteristic	Group 1 (n = 77)	Group 2 (n = 19)	Total (n = 96)	*P*-value
Age, years	50.7 (17.5)	49.6 (8.0)	50.5 (16.5)	0.622
Sex, n (%)				0.260
Male	48 (62.3)	13 (68.4)	61 (63.5)	
Female	29 (37.7)	6 (31.6)	35 (36.5)	
HCV genotype, n(%)				0.973
1	20 (26.0)	8 (42.1)	28 (29.2)	
2	11 (14.3)	2 (10.5)	13 (13.6)	
3	18 (23.4)	2 (10.5)	20 (20.8)	
6	16 (20.8)	4 (21.0)	20 (20.8)	
NA	12 (15.6)	3 (15.8)	15 (15.6)	
HCV RNA (log10 IU/mL)	5.8 (1.2)	5.5 (1.3)	5.7 (1.7)	0.278
HBV DNA (log10 IU/mL)	3.2 (1.7)	2.8 (0.8)	3.1 (1.7)	0.815
ALT (IU/L)	61.5 (39.2)	64.1 (48.0)	62.0 (36.6)	0.149
AST (IU/L)	50.8 (31.8)	65.7 (40.4)	53.8 (32.8)	0.014
ALP (IU/L)	84.8 (39.3)	111.6 (81.0)	90.4 (39.9)	0.019
TBIL (μmol/L)	15.3 (9.2)	20.6 (8.8)	16.3 (7.4)	0.008
ALB (g/L)	43.0 ± 3.5	39.2 ± 5.8	42.2 ± 4.3	0.014
PLT (*10^9/L)	175.4 ± 61.7	106.0 ± 39.6	162.7 ± 64.0	<0.001
AFP (ng/mL)	7.8 (3.8)	17.9 (19.0)	9.7 (6.5)	<0.001
LSM (kPa)	8.1 (4.2)	22.6 (16.4)	11.1 (6.5)	<0.001
APRI	0.8 (0.8)	1.6 (1.2)	1.0 (1.0)	<0.001
FIB-4	2.1 (1.6)	4.8 (5.2)	2.5 (1.9)	<0.001

Qualitative data are shown as n (%). Quantitative data are shown as mean ± standard deviation or median (interquartile range) for normally and non-normally distributed continuous variables. Results were compared by group t-test or Mann-Whitney U test (Group 1 vs. Group 2). Mann-Whitney U-test and Kruskal-Wallis test, coupled with post hoc comparisons, were used to test the differences in continuous variables between groups. Group 1, HBV/HCV coinfection patients without cirrhosis; Group 2, HBV/HCV coinfection patients with compensated cirrhosis. NA, not available. Normal reference ranges: ALT 9–50 IU/L; AST 15–40 IU/L; ALP 45–125 IU/L; TBIL 1.7–20 μmol/L; ALB 40–55 g/L; PLT 125–350 × 10^9/L; AFP < 10.9 ng/mL; LSM < 7.3 kPa; APRI < 0.5; FIB-4 < 1.3. HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; ALP, Alkaline Phosphatase; TBIL, Total Bilirubin; ALB, Albumin; PLT, Platelet Count; AFP, Alpha-fetoprotein; LSM, Liver Stiffness Measurement; APRI, Aspartate Aminotransferase to Platelet Ratio Index; FIB-4, Fibrosis-4 Index.

the levels of HBV DNA and HCV RNA across the whole cohort were analyzed. A significant reduction was observed both HCV RNA and HBV DNA levels. Serum specimens were collected from a cohort of 28 patients for the purpose of evaluating HBV RNA levels. Throughout the treatment regimen, a reduction in HBV RNA levels was observed. However, this

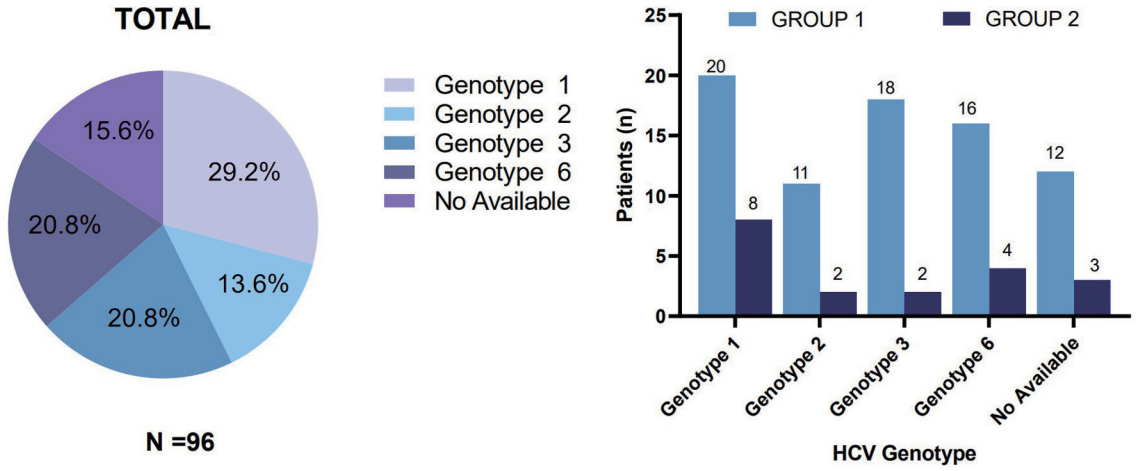

Fig. 2. Prevalence of HCV genotype. Group 1, HBV/HCV coinfection patients without cirrhosis (n = 77); Group 2, HBV/HCV coinfection patients with compensated cirrhosis (n = 19). HBV, Hepatitis B Virus; HCV, Hepatitis C Virus.

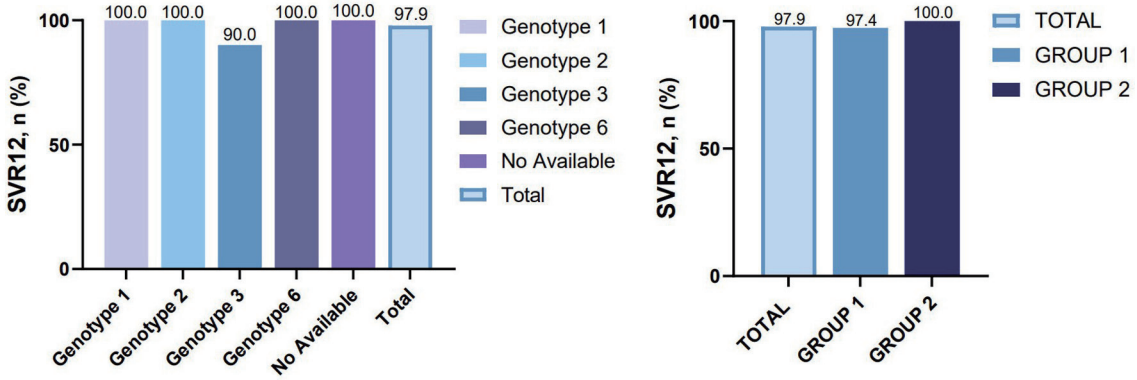

Fig. 3. SVR12 across genotypes and groups. SVR12, Sustained Virologic Response at 12 weeks. Group 1, HBV/HCV coinfection patients without cirrhosis (n = 77); Group 2, HBV/HCV coinfection patients with compensated cirrhosis (n = 19). HBV, Hepatitis B Virus; HCV, Hepatitis C Virus.

decline was notably less significant when compared to the reduction in HBV DNA levels (Fig. 4, Table 2). Five patients demonstrated elevated HBV RNA levels during the administration of SOF/VEL (Table 3).

Changes in ALT, AST, ALP, TBIL, ALB, PLT, and AFP

Serological changes before and after treatment within the two groups were compared. At 12 weeks post-treatment, ALT (61.5 vs. 21.9, $P < 0.001$) and AST (50.8 vs. 25.7, $P < 0.001$) levels decreased, while ALB (42.4 vs. 45.1, $P < 0.001$) levels increased compared to pre-treatment in Group 1 (Table 4). No significant differences were observed in ALP and TBIL levels or PLT counts before and after treatment. At 48 weeks post-treatment, ALT (64.1 vs. 25.2, $P < 0.001$), AST (65.7 vs. 29.7, $P < 0.001$), ALP (111.6 vs. 88.2, $P < 0.05$), and AFP (17.9 vs. 4.7, $P < 0.05$) levels decreased, while ALB (41.3 vs. 42.5, $P = 0.051$) and PLT (114.0 vs. 127.2, $P = 0.052$) levels showed a trend toward increase. Compared to pre-treatment in Group 2 (Table 4). TBIL levels fluctuated during treatment with a downward trend, but the difference was not statistically significant. Changes in serological indicators across study visits are shown in Figure 5 and Table 4.

Changes in indicators of liver fibrosis

LSM values, APRI, and FIB-4 calculation algorithms based on serological indices were used to indicate the degree of liver fibrosis. APRI (0.8 vs. 0.5, $P < 0.001$) levels decreased in Group 1. LSM (22.6 vs. 12.7, $P < 0.01$), APRI (1.6 vs. 0.6, $P < 0.001$), and FIB-4 (4.7 vs. 2.6, $P < 0.05$) significantly decreased after treatment in Group 2 (Table 4, Fig. 6).

HBV reactivation

A patient in Group 1 with genotype 3 experienced HBV reactivation, with HBV DNA levels below the LLOQ at baseline and after four weeks of TAF therapy. The HBV DNA level increased to 2.15 log10 (100-fold) IU/mL at the end of SOF/VEL treatment but reverted to below the LLOQ at 12 weeks post-therapy (Fig. 7). The findings indicated that the incidence of HBV reactivation among patients receiving SOF/VEL and pre-used TAF was 1%.

HCV relapse

A patient in Group 1 with genotype 3 experienced HCV relapse. Baseline HCV RNA was 7.23 log10 IU/mL, which declined to below the LLOQ following 12 weeks of SOF/VEL therapy. However, HCV RNA rebounded to 7.02 log10 IU/mL at 20 weeks post-therapy (Fig. 8). The incidence of HCV relapse in the cohort was 1%.

Safety

During the study, six patients experienced the following AEs: skin rash, abnormal uterine bleeding, fracture, malignant lung tumor, hospitalization due to chest pain attack, and hepatocellular carcinoma. Among these, the patient hospital-

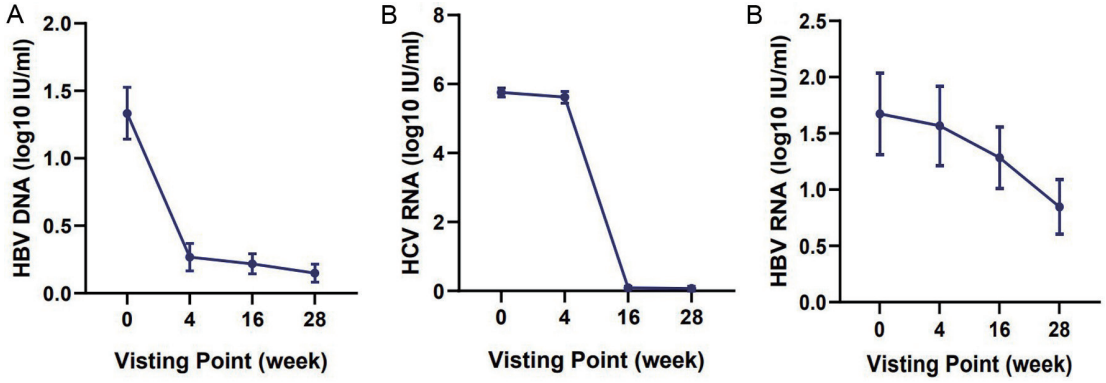

Fig. 4. Changes in HBV DNA, HCV RNA, and HBV RNA at the end of SOF/VEL treatment. HBV DNA and HCV RNA were decreased in HBV/HCV coinfection patients (n = 96) at the end of SOF/VEL treatment. (A) HBV DNA; (B) HCV RNA; (C) HBV RNA. HBV, Hepatitis B Virus; HCV, Hepatitis C Virus.

Table 2. Baseline and longitudinal changes of key virological, serological, and fibrosis markers between two groups

Parameters	Reference range	Group 1, Baseline/ Week 16/Week 28	Group 2, Baseline/ Week 28/Week 64
HBV DNA (log10 IU/mL)	LLOQ<20 IU/mL	3.2/<LLOQ/<LLOQ	2.8/<LLOQ/<LLOQ
HCV RNA (log10 IU/mL)	LLOQ<15 IU/mL	5.8/<LLOQ/<LLOQ	5.5/<LLOQ/<LLOQ
ALT (IU/L)	9–50	61.5/23.3/21.9	64.1/25.6/25.2
AST (IU/L)	15–40	50.8/25.4/25.7	65.7/37.5/29.7
ALP (IU/L)	45–125	84.8/81.0/82.6	111.6/105.8/88.2
TBIL (μmol/L)	1.7–20	15.3/13.4/14.3	20.6/19.7/15.7
ALB (g/L)	40–55	43.0/44.7/45.2	39.2/41.5/43.5
PLT (*10^9/L)	125–350	175.4/178.2/186.7	106.0/109.8/132.7
AFP (ng/mL)	<10.9	7.8/7.7/8.0	17.9/27.0/4.7
LSM (kPa)	<7.3	8.1/7.8/7.5	22.6/16.3/12.7
APRI	<0.5	0.8/0.5/0.5	1.6/1.0/0.6
FIB-4	<1.3	2.1/2.0/2.0	4.8/4.7/2.6

Quantitative data are shown as mean or median for normally and non-normally distributed continuous variables. Group 1, HBV/HCV coinfection patients without cirrhosis; Group 2, HBV/HCV coinfection patients with compensated cirrhosis. NA, not available. HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; ALP, Alkaline Phosphatase; TBIL, Total Bilirubin; ALB, Albumin; PLT, Platelet Count; AFP, Alpha-fetoprotein; LSM, Liver Stiffness Measurement; APRI, Aspartate Aminotransferase to Platelet Ratio Index; FIB-4, Fibrosis-4 Index.

ized for chest pain attack discontinued the study. No laboratory abnormalities or drug-related AEs were observed during the study (Table 5).

Discussion

With the extensive adoption of DAA regimens, an increasing number of patients with HCV infection are achieving SVR. However, despite the high efficacy rates in managing chronic hepatitis C with DAA therapy, several critical challenges persist, including HCV coinfection with other hepatotropic viruses such as HBV, as well as instances of antiviral treatment failure. In this study, we assessed the safety and efficacy of SOF/VEL and the pre-treatment of tenofovir alafenamide fumarate (TAF) on HBV reactivation in HBV/HCV coinfected patients from the thirteen centers in China.[16]

SOF/VEL was used for HCV antiviral therapy and TAF for HBV antiviral therapy. Phase 2 and 3 evaluations of SOF/VEL demonstrated that co-administration of the single agents for 12 weeks was well tolerated and resulted in high SVR rates across a broad range of HCV genotypes. In the Phase 3 study, administration of SOF 400 mg/VEL 100 mg for 12 weeks to treatment subjects without cirrhosis with genotype 1a, 1b, 2, 4, 5, or 6 HCV infection resulted in SVR12 rates of 98% (206/210), 99% (117/118), 100% (104/104), 100% (116/116), 97% (34/35), and 100% (41/41), respectively.[2,3,17] TAF is a prodrug of tenofovir that more efficiently delivers tenofovir into lymphoid cells and tissues than tenofovir disoproxil fumarate. It is a HBV nucleoside analog reverse transcriptase inhibitor and is indicated for the treatment of chronic HBV infection in adults with compensated liver disease. HBV/HCV co-infected patients were treated with TAF for 4 weeks prior to HCV treatment to assess HBV reactivation. The rationale for initiating TAF 4 weeks prior to DAA therapy was based on pharmacokinetic, pharmacodynamic, and clinical evidence. TAF achieves steady-state intracellular levels of its active metabolite, tenofovir diphosphate, within approximately 4 weeks of daily administration, ensuring sufficient hepatic drug exposure to effectively inhibit HBV cccDNA (covalently closed circular DNA, cccDNA) transcription and reduce viral load before the immune perturbations associated with rapid HCV clearance.[18] Prior studies in chronic hepatitis B patients have shown that, after TAF antiviral therapy, the rate of patients who achieved HBV DNA <20 IU/mL at 4 weeks was 77.1%.[19] The clinical evidence supports a 4-week pretreatment window as a clinically effective interval for HBV prophylaxis. Although current clinical guidelines uniformly recommend pre-DAA HBV prophylaxis, they do not specify an optimal pretreatment duration.[20,21] Direct comparisons of shorter (2 weeks), longer (6 weeks), and concurrent initiation strategies remains limited. Future randomized controlled studies are warranted to define the most effective and safe timing for prophylactic NAs in HBV/HCV coinfected patients undergoing DAA therapy.

Table 3. Patients with elevated HBV RNA during DAAs therapy for HCV

HBV RNA (log10 IU/mL)	0w	4w	16w	28w
Patient 1	2.36	1.44	2.17	1.77
Patient 2	0	0	2.82	0
Patient 3	2.07	0	1.73	0
Patient 4	1.40	0	1.96	0
Patient 5	0	0	1.52	0

HBV, Hepatitis B Virus; HCV, Hepatitis C Virus.

Our study enrolled 96 patients with HBV and HCV coinfection, including 77 patients without cirrhosis and 19 patients with compensated cirrhosis. At baseline, there were no significant differences between compensated cirrhotic and non-cirrhotic patients in age, sex, genotype distribution, HBV DNA levels, HCV RNA levels, and ALT levels. Cirrhotic patients exhibited higher levels of AST, ALP, TBIL, AFP, ALT, APRI, and FIB-4 compared to non-cirrhotic patients, while PLT counts and ALB levels were lower in cirrhotic patients. At 12 weeks after cessation of SOF/VEL treatment, the overall SVR was 97.9%. Only genotype 3 patients achieved an SVR rate of 90%, while patients with genotypes 1, 2, 6, and some unknown genotypes all achieved an SVR rate of 100%. Our findings align with other studies indicating that antiviral efficacy in genotype 3 patients is acceptable but remains lower than

Table 4. Changes in serological indices and indicators of liver fibrosis

	Total (n = 96)		
	Baseline	**Week 28**	***P*-value**
ALT (IU/L)	62.0 (36.6)	22.8 (10.0)	<0.001[a]
AST (IU/L)	53.8 (32.8)	28.6 (9.3)	<0.001[a]
ALP (IU/L)	90.4 (39.9)	88.1 (37.0)	0.671[a]
TBIL (μmol/L)	16.3 (7.4)	15.6 (8.6)	0.223[a]
ALB (g/L)	42.2 ± 4.3	44.4 ± 4.0	<0.001[a]
PLT (*10^9/L)	162.7 ± 64.0	168.2 ± 70.8	0.568[a]
AFP (ng/mL)	9.7 (6.5)	12.8 (2.5)	0.006[a]
LSM (kPa)	11.1 (6.5)	9.4 (5.6)	0.342[a]
APRI	1.0 (1.0)	0.6 (0.4)	<0.001[a]
FIB-4	2.5 (1.9)	2.5 (2.0)	0.394[a]

	Group 1 (n = 77)		
	Baseline	**Week 28**	***P*-value**
ALT (IU/L)	61.5 (39.2)	21.9 (8.0)	<0.001[a]
AST (IU/L)	50.8 (31.8)	25.7 (11.3)	<0.001[a]
ALP (IU/L)	84.8 (39.3)	82.6 (29.3)	0.560[a]
TBIL (μmol/L)	15.3 (9.2)	14.3 (6.4)	0.232[a]
ALB (g/L)	43.0 ± 3.5	45.2 ± 2.7	<0.001[a]
PLT (*10^9/L)	175.4 ± 61.7	186.7 ± 67.4	0.262[a]
AFP (ng/mL)	7.8 (3.8)	8.0 (1.8)	0.960[a]
LSM (kPa)	8.1 (4.2)	7.5 (2.7)	0.288[a]
APRI	0.8 (0.8)	0.5 (0.3)	<0.001[a]
FIB-4	2.1 (1.6)	2.0 (1.3)	0.168[a]

	Group 2 (n = 19)				
	Baseline	**Week 28**	***P*-value**	**Week 64**	***P*-value**
ALT (IU/L)	64.1 (48.0)	25.6 (17.7)	<0.001[a]	25.2 (12.7)	<0.001[b]
AST (IU/L)	65.7 (40.4)	37.5 (13.1)	<0.001[a]	29.7 (15.0)	<0.001[b]
ALP (IU/L)	111.6 (81.0)	105.8 (43.0)	0.708[a]	88.2 (24.2)	0.043[b]
TBIL (μmol/L)	20.6 (8.8)	19.7 (13.9)	0.624[a]	15.7 (11.5)	0.110[b]
ALB (g/L)	39.2 ± 5.8	41.5 ± 6.0	0.234[a]	43.5 ± 5.9	0.051[b]
PLT (*10^9/L)	106.0 ± 39.6	109.8 ± 45.7	0.975[a]	132.7 ± 32.2	0.052[b]
AFP (ng/mL)	17.9 (19.0)	27.0 (6.1)	0.070[a]	4.7 (4.6)	0.012[b]
LSM (kPa)	22.6 (16.4)	16.3 (12.5)	0.135[a]	12.7 (8.6)	0.009[b]
APRI	1.6 (1.2)	1.0 (0.9)	0.015[a]	0.6 (0.4)	<0.001[b]
FIB-4	4.8 (5.2)	4.7 (4.5)	0.820[a]	2.6 (2.3)	0.016[b]

Data are shown as mean ± standard deviation or median (interquartile range) for normally and non-normally distributed continuous variables. Results were compared by paired-samples t-test and paired-samples nonparametric test. Mann-Whitney U-test and Kruskal-Wallis test, coupled with post hoc comparisons, were used to test the differences in continuous variables between groups. [a](Baseline vs. Week 28) [b](Baseline vs. Week 64). Normal reference ranges: ALT 9–50 IU/L; AST 15–40 IU/L; ALP 45–125 IU/L; TBIL 1.7–20 μmol/L; ALB 40–55 g/L; PLT 125–350 × 10^9/L; AFP < 10.9 ng/mL; LSM < 7.3 kPa; APRI < 0.5; FIB-4 < 1.3. HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; ALP, Alkaline Phosphatase; TBIL, Total Bilirubin; ALB, Albumin; PLT, Platelet Count; AFP, Alpha-fetoprotein; LSM, Liver Stiffness Measurement; APRI, Aspartate Aminotransferase to Platelet Ratio Index; FIB-4, Fibrosis-4 Index.

in other genotypes.[22] Compensated cirrhosis did not affect the efficacy of antiviral therapy. During treatment, HBV DNA, HCV RNA, ALT, and AST levels significantly decreased, and ALB levels increased across the whole cohort. These findings indicate that antiviral treatment diminishes hepatitis activity and mitigates hepatocellular injury in patients with HBV/HCV

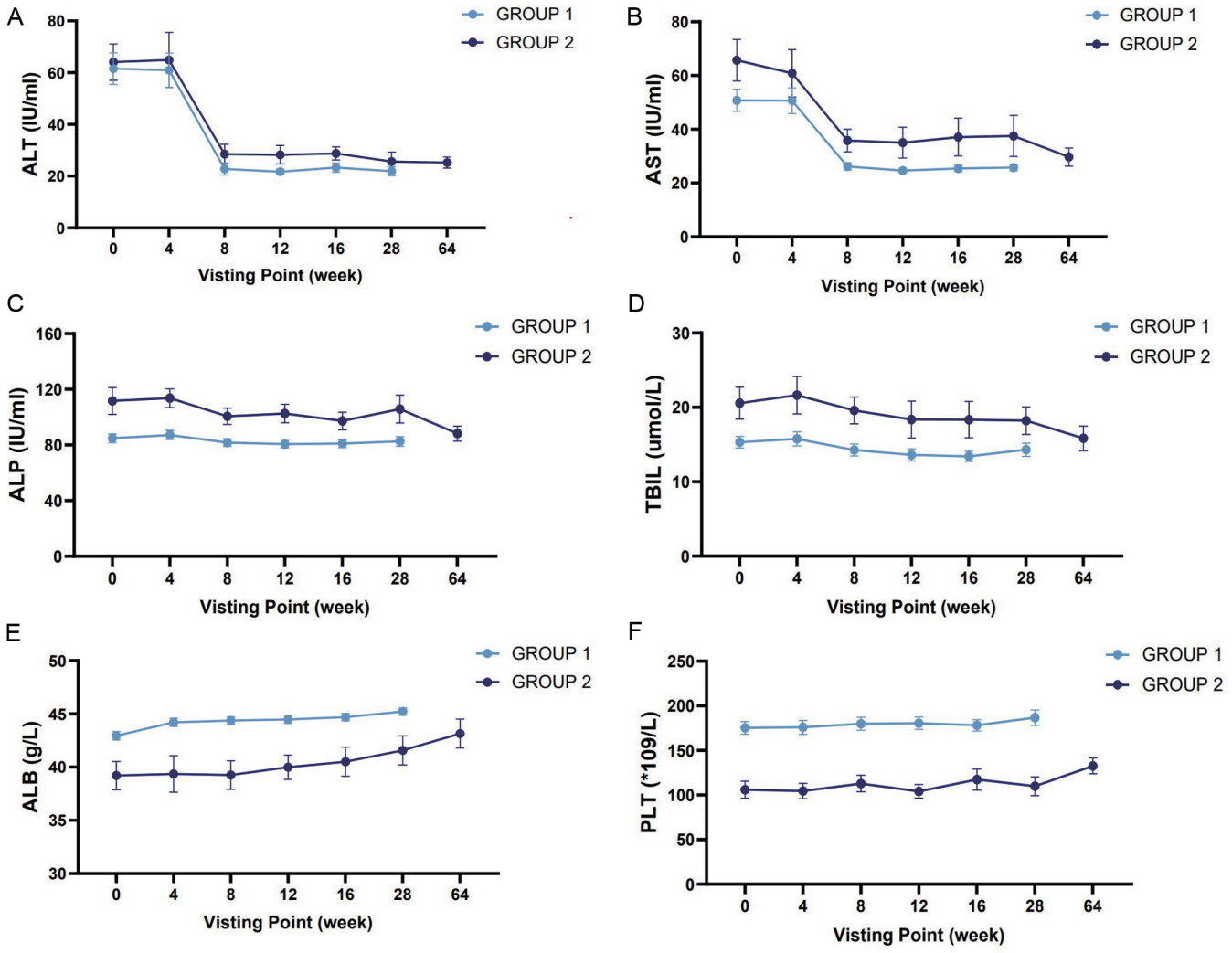

Fig. 5. Changes in ALT, AST, ALP, TBIL, ALB, and PLT. (A) ALT; (B) AST; (C) ALP; (D) TBIL; (E) ALB; (F) PLT. Normal reference ranges: ALT 9–50 IU/L; AST 15–40 IU/L; ALP 45–125 IU/L; TBIL 1.7–20 μmol/L; ALB 40–55 g/L; PLT 125–350 × 10^9/L. ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; ALP, Alkaline Phosphatase; TBIL, Total Bilirubin; ALB, Albumin; PLT, Platelet Count.

coinfection.[23] In contrast to non-cirrhotic patients, individuals with cirrhosis experienced a reduction in ALP levels and an elevation in PLT counts during the treatment period. In addition, TBIL levels in cirrhotic patients fluctuated during the course of treatment and gradually declined. Changes in serological indices following antiviral therapy may improve the prognosis of patients with compensated cirrhosis.[24,25]

LSM, APRI, and FIB-4 scores are important non-invasive biomarkers for the assessment and prediction of cirrhosis. APRI is recognized for its ability to predict liver fibrosis, with a cut-off of 0.5 indicating significant fibrosis and 1.5 for cirrhosis.[26] Elevated FIB-4 index values significantly correlate with increased risks of cirrhosis and liver-related mortality in chronic HBV patients.[17] A real-world, single-center study demonstrated that, following DAA therapy, the APRI score in patients with chronic hepatitis C decreased from 0.701 to 0.328, and the FIB-4 index declined from 2.355 to 1.860, indicating potential improvement in liver fibrosis markers.[27] Our previous study demonstrated significant improvement in LSM among patients with hepatitis C-related cirrhosis following DAA therapy, with a 3.6 kPa reduction observed in F3/F4 patients. Furthermore, APRI and FIB-4 scores exhibited significant decreases, from 0.64 to 0.35 and from 2.53 to 1.87, respectively, suggesting a considerable regression of liver fibrosis.[28] In this study, patients with compensated cirrhosis had a pre-treatment APRI score of 1.6 and a FIB-4 score of 4.7, and post-treatment APRI and FIB-4 scores of 0.6 and 2.6, respectively, suggesting that antiviral therapy has a modest improvement in liver fibrosis in patients with compensated cirrhosis.

Hepatitis B reactivation was observed in our study in a patient with HBV/HCV coinfection who tested positive for HBsAg. The patient was interviewed via a standardized medication adherence questionnaire, and both self-reported adherence and pharmacy refill records confirmed 100% medication compliance (no missed doses). A comprehensive review of the patient's concomitant medications (no other antiviral, immunosuppressant, or hepatotropic drugs) and pharmacokinetic data confirmed no known drug–drug interactions between TAF and SOF/VEL. The patient reported no gastrointestinal symptoms (e.g., diarrhea, nausea, vomiting) during the entire treatment and follow-up period, and routine blood tests

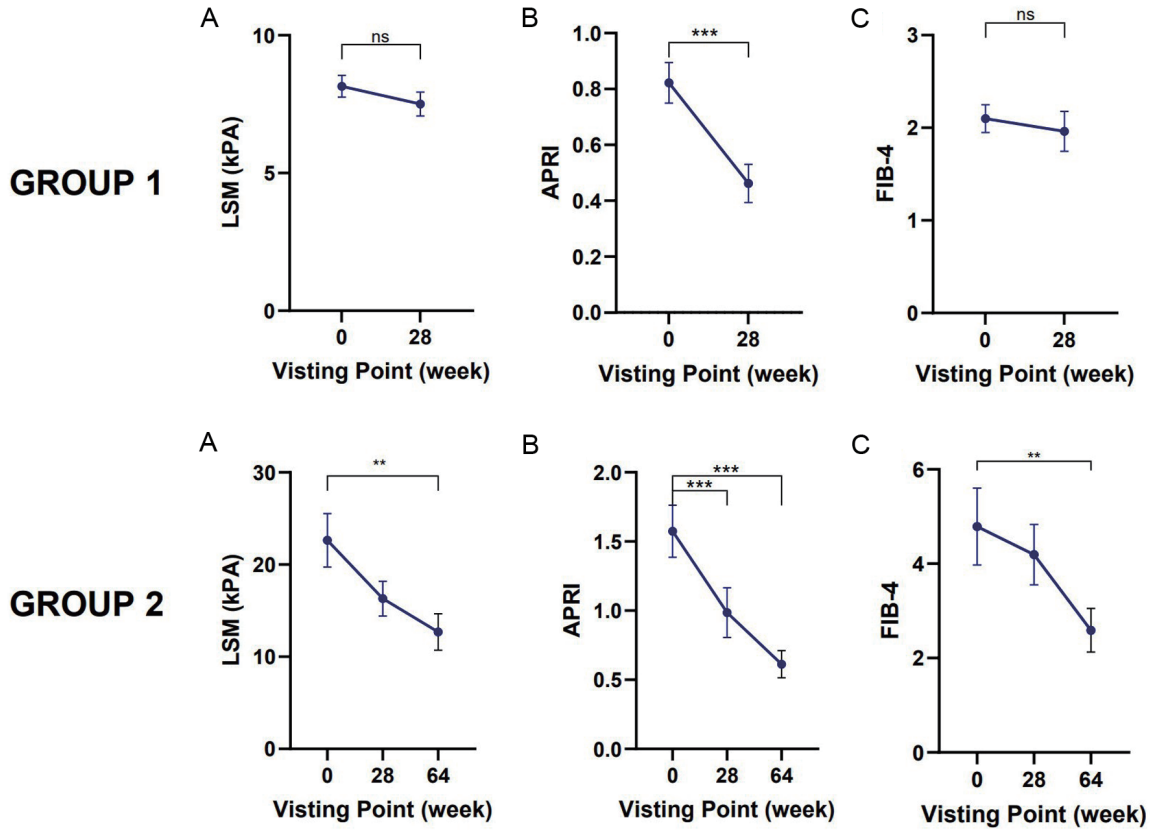

Fig. 6. Changes in indicators of liver fibrosis. (A) LSM; (B) APRI; (C) FIB-4. Results were compared by paired-samples nonparametric test. Mann-Whitney U-test and Kruskal-Wallis test, coupled with post hoc comparisons, were used to test the differences in continuous variables between groups. *P < 0.05, **P < 0.01, ***P < 0.001. Normal reference ranges: LSM < 7.3 kPa; APRI < 0.5; FIB-4 < 1.3. LSM, Liver Stiffness Measurement; APRI, Aspartate Aminotransferase to Platelet Ratio Index; FIB-4, Fibrosis-4 Index.

showed normal intestinal absorption-related indices (e.g., albumin, prealbumin). Thus, impaired drug absorption was not a factor. The HBV DNA test was repeated twice to verify the results. False-positive results due to laboratory variability were ruled out. We hypothesize that the transient HBV reactivation may be attributed to HCV clearance-induced immune reconstitution.[29] Rapid HCV suppression by SOF/VEL leads to a shift in the intrahepatic immune response from HCV-dominated to HBV-targeted, accompanied by a transient increase in pro-inflammatory cytokines (e.g., interferon-γ, Tumor Necrosis Factor-α). These cytokines can transiently upregulate HBV cccDNA transcriptional activity by activating the cccDNA promoter,[30] leading to a small, temporary elevation of HBV DNA. This phenomenon is consistent with prior reports that HCV clearance diminishes the hepatic interferon response, which in turn triggers HBV reactivation in HBV/HCV coinfected patients, even with concurrent antiviral prophylaxis for HBV.[31] Recent trials have used DAAs for the clearance of HCV in co-infected patients. Reactivation of HBV has been observed in patients following therapeutic intervention, with

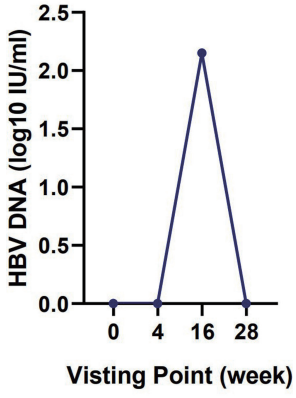

Fig. 7. HBV reactivation. HBV, Hepatitis B Virus.

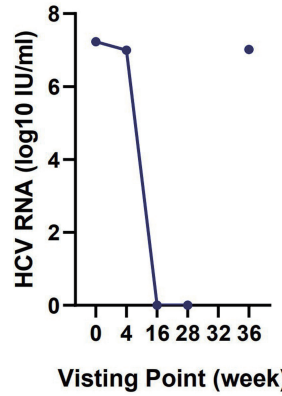

Fig. 8. HCV recurrence. HCV, Hepatitis C Virus.

Table 5. Adverse events

Adverse events	Patients, n	Grade	Relationship to study drugs	Study drug management
Skin rash	1	1	NO	Continue
Abnormal uterine bleeding	1	2	NO	Continue
Fracture	1	2	NO	Continue
Malignant tumors of the lung	1	3	NO	Continue
Hospitalization for chest pain attack	1	3	NO	Discontinue
Hepatocellular carcinoma	1	3	NO	Continue

increased incidence and earlier onset observed in individuals previously treated for HCV infection with DAAs compared to those treated with pegylated interferon-based regimens.[32] In another cohort study, HBV reactivation was observed in 2% to 57% of patients with detectable HBsAg during DAA treatment.[33] Advance treatment with nucleos(t)ide analogs is recommended during DAA therapy. Our research indicates that, following a four-week pre-treatment regimen of TAF, the hepatitis B reactivation rate was 1%. This finding implies that pre-treatment of TAF may significantly mitigate the risk of hepatitis B reactivation. In summary, regardless of the therapy regimen, close monitoring of HBV DNA levels is necessary for patients with HBV/HCV coinfection, even in cases of good adherence and the absence of drug interactions.

Our study also tested changes in HBV RNA levels during treatment among 28 patients. It has recently been shown that serum HBV RNA is a non-invasive biomarker that reflects cccDNA transcriptional activity.[34] HBV RNA levels decline at a slower rate than HBV DNA levels. Transient elevations in HBV RNA levels were observed in five patients during DAA therapy for HCV, with peak elevations occurring at week 16 in most cases, followed by spontaneous decline to undetectable levels by week 28, without concurrent HBV DNA reactivation or virological breakthrough. These findings are consistent with prior evidence that transient HBV RNA reactivation can occur in HBV/HCV co-infected patients during HCV DAA treatment, driven by HCV suppression and subsequent immune reconstitution.[29] Some patients with undetectable HBV DNA levels still exhibited detectable HBV RNA during testing. This phenomenon illustrates that HBV RNA is a complementary biomarker of intrahepatic viral activity than HBV DNA, capable of capturing subclinical cccDNA transcriptional reactivation that is missed by standard HBV DNA testing. Such dynamics highlight the potential utility of HBV RNA as an early indicator of low-level intrahepatic cccDNA activity, which could guide optimized treatment and reduce the risk of HBV reactivation in patients with HBV/HCV coinfection receiving long-term antiviral therapy.[30] HBV DNA and HBV RNA assays should be concurrently employed to assess viral replication activity in patients during clinical monitoring. There is no established definition for HBV RNA-associated hepatitis B reactivation, and further research is required.

Hepatitis C relapse is a significant concern. In patients achieving SVR with DAAs, the relapse rate is low at 0.89/1,000 person-years for low-risk individuals, but significantly higher at 29.37/1,000 person-years for high-risk populations.[35] However, there is a paucity of data regarding the relapse rate of HCV in patients with HBV/HCV coinfection. In this study, a patient with genotype 3 presented with hepatitis C relapse. To our knowledge, the patient does not have high-risk factors for hepatitis C reinfection during the course of treatment. The patient had a baseline HCV RNA of 7.23 log10 IU/mL and a controlled attenuation parameter (CAP) of 336 dB/m. CAP is a quantitative indicator measured by transient elastography that is used to assess hepatic steatosis by detecting ultrasound attenuation in the liver parenchyma, and elevated CAP values reflect the presence and degree of hepatic steatosis.[36] It was reported that steatosis was identified as an independent predictor of relapse in patients with HCV genotype 3. Steatosis was associated with a higher rate of relapse, especially in patients with high viral loads, whereas patients without steatosis did not experience relapse.[37] The mechanism by which steatosis influences treatment outcome in HCV genotype 3 infection is not fully understood. We hypothesize that hepatic steatosis impairs the uptake and metabolism of DAA in hepatocytes and creates a microenvironment conducive to HCV replication, both of which contribute to reduced treatment efficacy.[37] The cause of relapse in this patient may be related to his genotype and hepatic steatosis. Further research is required to substantiate this correlation.

This study has several key limitations. First, the study adopted a single-arm design, which represents a major methodological limitation. Previous research indicates that patients with HBV/HCV coinfection are at increased risk of HBV reactivation following hepatitis C treatment.[11,32,33] Although ethical considerations preclude the establishment of a control group receiving SOF/VEL alone, the absence of comparator groups with different TAF initiation time points significantly weakens the causal inference of our conclusion. Notably, while all the aforementioned authoritative guidelines uniformly recommend initiating antiviral prophylaxis before exposure to medications associated with HBV reactivation risk, none provide specific recommendations on the optimal time window for TAF pretreatment.[20,21] Second, the small overall sample size (especially the limited cirrhosis subgroup) reduces statistical power for stratified analyses and subgroup validation, and the lack of uniform baseline CAP assessment and standardized steatosis stratification introduces population heterogeneity, hindering exploration of steatosis and HCV relapse correlation. Third, the predefined follow-up duration (64 weeks for cirrhotic, 28 weeks for non-cirrhotic patients) limits long-term outcome assessment; extended follow-up is ongoing to collect data on hepatocellular carcinoma, hepatic decompensation, and long-term HCV recurrence. Fourth, the study lacked detailed collection and stratification of comorbid conditions in the enrolled patients, which may have contributed to the relatively high SVR rates reported. This gap in comorbidity data may introduce potential selection bias and limit the generalizability of the findings to populations with complex comorbidities. Fifth, although detailed adherence records confirmed that all patients demonstrated good medication adherence as prescribed, and the predictable pharmacokinetic properties of TAF have been well established in prior literature,[18,38] we did not perform direct real-time plasma TAF concentration quantification. Subtle drug exposure bias cannot be excluded. Finally, HBV RNA

detection was not initially included, and poor serum storage left only 28 patients with usable samples, resulting in incomplete longitudinal HBV RNA data and hindering in-depth analysis of cccDNA activity and HBV RNA as a biomarker. Future research directions to address these limitations include: conducting large-sample, multicenter RCTs with different TAF initiation time points; expanding the cirrhosis subgroup sample size; extending follow-up beyond 2 years; implementing uniform baseline CAP measurement and steatosis stratification; integrating real-time TAF concentration monitoring and prospective HBV RNA detection; and recording detailed missed dose information to optimize preventive strategies for HBV/HCV co-infected patients receiving DAA therapy.

Pre-treatment of TAF for 4 weeks, followed by a 12-week treatment regimen with SOF/VEL single-tablet combination, demonstrated efficacy in most patients with HBV/HCV coinfection. Although HBV reactivation and HCV recurrence were observed in patients infected with HCV genotype 3, these events were not associated with significant changes in serological indices or clinical symptoms. Among the AEs recorded during the study, no drug-related adverse reactions or nonspecific symptoms such as malaise or headache—commonly reported in the literature—were identified. Overall, patients exhibited a favorable response to this therapeutic regimen. The findings of this study indicate that pre-administration of TAF may effectively reduce the risk of HBV reactivation in co-infected individuals. Continuous monitoring for signs of HBV reactivation and HCV recurrence during and after treatment is recommended, with therapeutic intervention guided by current clinical guidelines.

Conclusions

SOF/VEL effectively achieves SVR and improves liver function with an acceptable safety profile in chronic HBV/HCV co-infected patients, including those with compensated cirrhosis who achieved modest improvement in non-invasive fibrosis indices. Pre-administration of TAF may mitigates the risk of HBV reactivation in this population.

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Conflict of interest

HY and YN have been Editorial Board Members of *Journal of Clinical and Translational Hepatology* since 2021 and 2022. The other authors have no conflict of interests related to this publication.

Author contributions

Conception and design (YY, XX), provision of study materials or patients (DZ, ZH, MS, JG, ZW, SX, XL, HY, LZ, JS, LZ, YN, BW, CL, YJ), collection and assembly of data (QK, HC, ZZ), data analysis and interpretation (YH, NL), manuscript writing (YH, NL), and final approval of manuscript (XX). All authors have approved the final version and publication of the manuscript.

Ethical statement

The studies involving human participants were performed in accordance with the Declaration of Helsinki (as revised in 2024), and were reviewed and approved by the Ethics Committee of Peking University First Hospital (ChiCTR2000033390). The patients/participants provided their written informed consent to participate in this study.

Data sharing statement

The original contributions presented in this study are included in the article; further inquiries can be directed to the corresponding authors.

References

[1] WHO. Guidelines for the Prevention, Diagnosis, Care, and Treatment for People With Chronic Hepatitis B Infection. 2024. Available from: https://www.who.int/publications/i/item/9789240090903.
[2] WHO. WHO publishes updated guidance on hepatitis C infection - with new recommendations on treatment of adolescents and children, simplified service delivery and diagnostics. 2022. Available from: https://www.who.int/news/item/24-06-2022-WHO-publishes-updated-guidance-on-hepatitis-C-infection.
[3] Abdelaal R, Yanny B, El Kabany M. HBV/HCV Coinfection in the Era of HCV-DAAs. Clin Liver Dis 2019;23(3):463–472. doi:10.1016/j.cld.2019.04.003, PMID:31266620.
[4] Liaw YF, Yeh CT, Tsai SL. Impact of acute hepatitis B virus superinfection on chronic hepatitis C virus infection. Am J Gastroenterol 2000;95(10):2978–2980. doi:10.1111/j.1572-0241.2000.02337.x, PMID:11051381.
[5] Lee LP, Dai CY, Chuang WL, Chang WY, Hou NJ, Hsieh MY, *et al*. Comparison of liver histopathology between chronic hepatitis C patients and chronic hepatitis B and C-coinfected patients. J Gastroenterol Hepatol 2007;22(4):515–517. doi:10.1111/j.1440-1746.2006.04547.x, PMID:17376043.
[6] Mücke MM, Backus LI, Mücke VT, Coppola N, Preda CM, Yeh ML, *et al*. Hepatitis B virus reactivation during direct-acting antiviral therapy for hepatitis C: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2018;3(3):172–180. doi:10.1016/S2468-1253(18)30002-5, PMID:29371017.
[7] Elbaz T, El-Kassas M, Esmat G. New era for management of chronic hepatitis C virus using direct antiviral agents: A review. J Adv Res 2015;6(3):301–310. doi:10.1016/j.jare.2014.11.004, PMID:26257927.
[8] Eyre NS, Phillips RJ, Bowden S, Yip E, Dewar B, Locarnini SA, *et al*. Hepatitis B virus and hepatitis C virus interaction in Huh-7 cells. J Hepatol 2009;51(3):446–457. doi:10.1016/j.jhep.2009.04.025, PMID:19596477.
[9] Maqsood Q, Sumrin A, Iqbal M, Younas S, Hussain N, Mahnoor M, *et al*. Hepatitis C virus/Hepatitis B virus coinfection: Current prospectives. Antivir Ther 2023;28(4):13596535231189643. doi:10.1177/13596535231189643, PMID:37489502.
[10] Ji F, Tran S, Ogawa E, Huang CF, Suzuki T, Wong YJ, *et al*. Real-world

Effectiveness and Tolerability of Interferon-free Direct-acting Antiviral for 15,849 Patients with Chronic Hepatitis C: A Multinational Cohort Study. J Clin Transl Hepatol 2024;12(7):646–658. doi:10.14218/JCTH.2024.00089, PMID:38993510.
[11] Chen G, Wang C, Chen J, Ji D, Wang Y, Wu V, *et al*. Hepatitis B reactivation in hepatitis B and C coinfected patients treated with antiviral agents: A systematic review and meta-analysis. Hepatology 2017;66(1):13–26. doi:10.1002/hep.29109, PMID:28195337.
[12] Xu X, Ding H, You H, Guan Y, Xu J, Li W, *et al*. Chinese Guidelines for Clinical Diagnosis, Treatment, and Management of Cirrhosis (2025). J Clin Transl Hepatol 2026;14(1):96–115. doi:10.14218/JCTH.2025.00517, PMID:41659997.
[13] Chinese Society of Hepatology Chinese Medical Association, Chinese Society of Gastroenterology Chinese Medical Association, Chinese Society of Infectious Diseases, Chinese Medical Association. [Consensus on the diagnosis and therapy of hepatic fibrosis in 2019]. Zhonghua Gan Zang Bing Za Zhi 2019;27(9):657–667. doi:10.3760/cma.j.issn.1007-3418.2019.09.001, PMID:31594088.
[14] Ghany MG, Pan CQ, Lok AS, Feld JJ, Lim JK, Wang SH, *et al*. AASLD ISDA Practice Guideline on treatment of chronic hepatitis B. Hepatology 2026;83(4):974–997. doi:10.1097/HEP.0000000000001549, PMID:41186418.
[15] Bhattacharya D, Aronsohn A, Price J, Lo Re V, AASLD-IDSA HCV Guidance Panel. Hepatitis C Guidance 2023 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Clin Infect Dis 2023. doi:10.1093/cid/ciad319, PMID:37229695.
[16] De Monte A, Courjon J, Anty R, Cua E, Naqvi A, Mondain V, *et al*. Direct-acting antiviral treatment in adults infected with hepatitis C virus: Reactivation of hepatitis B virus coinfection as a further challenge. J Clin Virol 2016;78:27–30. doi:10.1016/j.jcv.2016.02.026, PMID:26967675.
[17] Tseng TC, Liu CJ, Su TH, Yang WT, Chen CL, Yang HC, *et al*. Fibrosis-4 index predicts cirrhosis risk and liver-related mortality in 2075 patients with chronic HBV infection. Aliment Pharmacol Ther 2018;47(11):1480–1489. doi:10.1111/apt.14619, PMID:29601647.
[18] Podany AT, Bares SH, Havens J, Dyavar SR, O'Neill J, Lee S, *et al*. Plasma and intracellular pharmacokinetics of tenofovir in patients switched from tenofovir disoproxil fumarate to tenofovir alafenamide. AIDS 2018;32(6):761–765. doi:10.1097/QAD.0000000000001744, PMID:29334548.
[19] Gao WK, Shu YY, Chen Y, Ai Y, Yang XQ, Du F, *et al*. Effectiveness of Tenofovir Alafenamide in Chronic Hepatitis B Patients with Normal Alanine Aminotransferase and Positive Hepatitis B Virus DNA. J Clin Transl Hepatol 2022;10(1):112–119. doi:10.14218/JCTH.2021.00131, PMID:35233379.
[20] Ali FS, Nguyen MH, Hernaez R, Huang DQ, Wilder J, Piscoya A, *et al*. AGA Clinical Practice Guideline on the Prevention and Treatment of Hepatitis B Virus Reactivation in At-Risk Individuals. Gastroenterology 2025;168(2):267–284. doi:10.1053/j.gastro.2024.11.008, PMID:39863345.
[21] European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2025;83(2):502–583. doi:10.1016/j.jhep.2025.03.018, PMID:40348683.
[22] Kowdley KV, Nelson DR, Lalezari JP, Box T, Gitlin N, Poleynard G, *et al*. On-treatment HCV RNA as a predictor of sustained virological response in HCV genotype 3-infected patients treated with daclatasvir and sofosbuvir. Liver Int 2016;36(11):1611–1618. doi:10.1111/liv.13165, PMID:27188960.
[23] Jia JD, Cheng LF, Chinese Society of Hepatology of Chinese Medical Association, Chinese Society of Gastroenterology of Chinese Medical Association. [Consensus on the clinical significance and evaluation of common liver biochemistry tests]. Zhonghua Gan Zang Bing Za Zhi 2010;18(5):387–393, Chinese. PMID:20665994.
[24] Mallik M, Singhai A, Khadanga S, Ingle V. The Significant Morbidity and Mortality Indicators in Patients of Cirrhosis. Cureus 2022;14(1):e21226. doi:10.7759/cureus.21226, PMID:35174029.
[25] Han YF, Xu XY. Clinical research progress in 2025 for hepatic fibrosis, cirrhosis, and portal hypertension. Zhonghua Gan Zang Bing Za Zhi 2026;34(1):7–9. doi:10.3760/cma.j.cn501113-20251205-00517, PMID:41629071.
[26] De Matteis C, Cariello M, Graziano G, Battaglia S, Suppressa P, Piazzolla G, *et al*. AST to Platelet Ratio Index (APRI) is an easy-to-use predictor score for cardiovascular risk in metabolic subjects. Sci Rep 2021;11(1):14834. doi:10.1038/s41598-021-94277-3, PMID:34290320.
[27] Lee SH, Shin HP, Lee JI. Real-world single-center experience with direct-acting antivirals for improvement of the liver fibrosis after chronic hepatitis C treatment. Antivir Chem Chemother 2020;28:2040206620974835. doi:10.1177/2040206620974835, PMID:33215505.
[28] Kang Q, Xu J, Luo H, Tan N, Chen H, Cheng R, *et al*. Direct antiviral agent treatment leads to rapid and significant fibrosis regression after HCV eradication. J Viral Hepat 2021;28(9):1284–1292. doi:10.1111/jvh.13558, PMID:34105867.
[29] Cheng X, Uchida T, Xia Y, Umarova R, Liu CJ, Chen PJ, *et al*. Diminished hepatic IFN response following HCV clearance triggers HBV reactivation in co-infection. J Clin Invest 2020;130(6):3205–3220. doi:10.1172/JCI135616, PMID:32163375.
[30] Yu X, Pfefferkorn M, van Bömmel F, Zhang X, Berg T. Clinical applications of circulating HBV RNA as a potential surrogate biomarker for intrahepatic cccDNA transcriptional activity. Gut 2024;73(4):563–566. doi:10.1136/gutjnl-2023-331217, PMID:38123992.
[31] Balagopal A, Thio CL. When viruses collide: hepatitis B virus reactivation after hepatitis C treatment. J Clin Invest 2020;130(6):2823–2826. doi:10.1172/JCI137477, PMID:32420916.
[32] Shih YF, Liu CJ. Hepatitis C Virus and Hepatitis B Virus Co-Infection. Viruses 2020;12(7):741. doi:10.3390/v12070741, PMID:32664198.
[33] Pisaturo M, Macera M, Alessio L, Calò F, Coppola N. Hepatitis B Virus (HBV) Reactivation Following Pharmacological Eradication of Hepatitis C Virus (HCV). Viruses 2019;11(9):850. doi:10.3390/v11090850, PMID:31540223.
[34] Tian Y, Yu H, Chen J. Emerging Serum Biomarkers for Chronic Hepatitis B: Focus on Serum HBV RNA and HBcrAg. J Clin Transl Hepatol 2025;13(9):766–775. doi:10.14218/JCTH.2025.00064, PMID:40951536.
[35] Huang P, Wang Y, Yue M, Ge Z, Xia X, Jeyarajan AJ, *et al*. The risk of hepatitis C virus recurrence in hepatitis C virus-infected patients treated with direct-acting antivirals after achieving a sustained virological response: A comprehensive analysis. Liver Int 2021;41(10):2341–2357. doi:10.1111/liv.14976, PMID:34051040.
[36] European Association for the Study of the Liver. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. J Hepatol 2021;75(3):659–689. doi:10.1016/j.jhep.2021.05.025, PMID:34166721.
[37] Restivo L, Zampino R, Guerrera B, Ruggiero L, Adinolfi LE. Steatosis is the predictor of relapse in HCV genotype 3- but not 2-infected patients treated with 12 weeks of pegylated interferon-α-2a plus ribavirin and RVR. J Viral Hepat 2012;19(5):346–352. doi:10.1111/j.1365-2893.2011.01555.x, PMID:22497814.
[38] Yager JL, Brooks KM, Castillo-Mancilla JR, Nemkov C, Morrow M, Peterson S, *et al*. Tenofovir-diphosphate in peripheral blood mononuclear cells during low, medium and high adherence to emtricitabine/tenofovir alafenamide vs. emtricitabine/tenofovir disoproxil fumarate. AIDS 2021;35(15):2481–2487. doi:10.1097/QAD.0000000000003062, PMID:34482350.