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Original Article

Longitudinal Lipid Changes During 144-week PegIFNα-based Therapy in Chronic Hepatitis B: A Retrospective Cohort Study

Rehman Shahab[1#], Siyao Wang[2#], Ahmad Faiza[1], Keyang Dong[2], Liping Zuo[3], Zhan Qu[2], Li Ma[2], Fangfang Li[2,4], S. Abdulaziz Abdulgani[5], Jing Li[2], Feng Ye[2*] and Yi Liu[1*]

[1]*Department of Traditional Chinese Medicine, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China;* [2]*Department of Infectious Disease, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China;* [3]*Department of Gastroenterology, The Fifth Hospital of Xi'an, Xi'an, Shaanxi, China;* [4]*Emergency Department, Xidian Group Hospital, Xi'an, Shaanxi, China;* [5]*Department of Gastroenterology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China*

[#]*These authors contributed equally to this work.*

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Abstract

Background and objectives: Pegylated interferon alpha (PegIFNα) has been associated with altered lipid metabolism, but long-term lipid trajectories in chronic hepatitis B remain poorly characterized. We evaluated lipid profiles and virological parameters during 144 weeks of PegIFNα-based therapy.

Methods: This single-center retrospective cohort study included 129 patients with chronic hepatitis B who completed 144 weeks of PegIFNα monotherapy, PegIFNα plus tenofovir alafenamide, or PegIFNα plus entecavir. Serum lipids, hepatitis B surface antigen (HBsAg), hepatitis B e antigen, and hepatitis B virus DNA were assessed at baseline and weeks 24, 48, 72, 96, and 144. Within-patient changes were analyzed with paired tests. Associations between early lipid changes and on-treatment HBsAg seroclearance at week 144 were examined with logistic regression.

Results: From baseline to week 144, mean high-density lipoprotein cholesterol (HDL-C) increased by 0.10 ± 0.25 mmol/L (95% confidence interval, 0.06 to 0.15; $P < 0.001$) and mean total cholesterol decreased by 0.15 ± 0.41 mmol/L (95% confidence interval, −0.22 to −0.08; $P < 0.001$). Changes in triglycerides, low-density lipoprotein cholesterol, and the triglyceride-to-HDL-C ratio were not significant. HDL-C declined early and later recovered above baseline. At week 144, 37 patients (28.7%) achieved on-treatment HBsAg seroclearance (≤ 0.05 IU/mL). Of the 34 patients with HBsAg seroclearance at week 96, 13 had detectable HBsAg again at week 144. Early lipid changes were not associated with this endpoint.

Conclusions: HDL-C shows an early decline followed by recovery above baseline, whereas total cholesterol decreases modestly, with no significant net changes in triglycerides, low-density lipoprotein cholesterol, or the triglyceride-to-HDL-C ratio. Early lipid changes are not significantly associated with on-treatment HBsAg seroclearance. The durability of HBsAg loss requires post-treatment follow-up.

Keywords: Chronic hepatitis B; Pegylated interferon alpha; High-density lipoprotein cholesterol; Triglyceride-to-HDL-C ratio; HBsAg seroclearance; Lipid metabolism; Nucleos(t)ide analogues; Tenofovir alafenamide.

***Correspondence to:** Yi Liu, Department of Traditional Chinese Medicine, The First Affiliated Hospital of Xi'an Jiaotong University, 277 Yanta West Road, Xi'an, Shaanxi 710061, China. ORCID: https://orcid.org/0000-0001-6874-4709. Tel: +86-18991232576, E-mail: Liuyi.jiaotong@163.com; Feng Ye, Department of Infectious Disease, The First Affiliated Hospital of Xi'an Jiaotong University, 277 Yanta West Road, Xi'an, Shaanxi 710061, China. ORCID: https://orcid.org/0000-0003-1418-7980. Tel: +86-18991232860, E-mail: Yefeng.jiaotong@163.com

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Introduction

Persistent hepatitis B virus (HBV) infection can result in chronic hepatitis B (CHB) and progressive liver disease, including fibrosis, cirrhosis, hepatic decompensation, and hepatocellular carcinoma.[1,2] Recent estimates indicate that approximately 254 million people worldwide live with chronic HBV infection. HBV-related cirrhosis and hepatocellular carcinoma account for approximately 1.1 million deaths annually.[2] Treatment of CHB therefore aims to achieve sustained viral suppression, promote serological responses, and reduce liver-related complications.[3]

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The main antiviral treatments for CHB are nucleos(t)ide analogues (NAs) and pegylated interferon alpha (PegIFNα).[3,4] NAs potently and durably suppress HBV DNA, but most patients require prolonged therapy, during which hepatitis B surface antigen (HBsAg) seroclearance remains uncommon.[2,5] PegIFNα offers a distinct combination of antiviral and immunomodulatory effects. Although PegIFNα suppresses HBV DNA less rapidly and profoundly than potent NAs, it can induce hepatitis B e antigen (HBeAg) seroconversion and reduce quantitative HBsAg levels. In appropriately selected patients, a small proportion ultimately achieve HBsAg seroclearance.[6] Both the early decline and on-treatment level of quantitative HBsAg are associated with subsequent virological and serological responses.[7,8] These measures may therefore inform response prediction and treatment decisions.

Dyslipidemia is a major risk factor for atherosclerotic cardiovascular disease and frequently coexists with obesity, insulin resistance, diabetes mellitus, and hepatic steatosis.[9,10] In patients with CHB, these metabolic abnormalities may further increase the risks of fibrosis progression, liver-related events, and hepatocellular carcinoma.[11,12] Monitoring lipid profiles during antiviral therapy may therefore help characterize metabolic changes observed during treatment and inform long-term hepatic and cardiovascular risk assessment.

The liver plays a central role in lipid synthesis, transport, and clearance. Accordingly, serum lipid profiles may be influenced by HBV infection, liver disease activity, and antiviral therapy.[13,14] Previous studies of interferon alpha (IFNα) or PegIFNα reported increased triglyceride (TG) levels and reduced total cholesterol (TC). Reductions in high-density lipoprotein cholesterol (HDL-C) or low-density lipoprotein cholesterol (LDL-C) were also reported. However, findings have been inconsistent, and some evidence was derived from patients with chronic hepatitis C or other diseases.[15-17]

Studies in patients with CHB further suggest that baseline lipid levels and early treatment-related changes may be associated with HBeAg seroconversion or HBsAg seroclearance. However, the implicated lipid components, directions of association, and clinical endpoints have varied across studies.[18,19] Individual NAs, including tenofovir disoproxil fumarate, tenofovir alafenamide (TAF), and entecavir (ETV), may also have distinct effects on lipid profiles. Evaluations of lipid changes observed during PegIFNα-based therapy should therefore account for exposure to specific NAs, whether concomitant or prior.[20]

Previous studies have focused largely on the first 24–48 weeks of PegIFNα therapy, leaving long-term lipid trajectories during extended treatment poorly characterized. We selected the change in HDL-C from baseline to week 144 as the primary outcome because prior interferon-based studies have most consistently reported reductions in HDL-C, because HDL-C is a clinically relevant cardiometabolic marker, and because findings for TC, TG, LDL-C, and the TG/HDL-C ratio have been more heterogeneous. We therefore conducted a retrospective study of patients with CHB receiving PegIFNα-based therapy, with follow-up through week 144. We characterized longitudinal changes in TC, TG, HDL-C, LDL-C, and the TG/HDL-C ratio. We concurrently evaluated changes in HBsAg, HBeAg, and HBV DNA and examined whether lipid parameters were associated with HBsAg seroclearance.

Materials and methods

Study design and participants

This single-center retrospective cohort study included patients with chronic HBV infection treated at the First Affiliated Hospital of Xi'an Jiaotong University. The report was prepared with reference to the STROBE statement for observational cohort studies. PegIFNα-based therapy was initiated between September 1, 2020 and June 18, 2023. All included patients completed 144 weeks of on-treatment follow-up before the final data cutoff in April 2026. Eligible patients initiated PegIFNα-based therapy during the specified study period and completed the 144-week treatment course. Lipid measurements at the prespecified time points were also required.

Patients were eligible if they met all the following criteria: (1) Age ≥ 18 years. (2) Serum HBsAg positivity for at least 6 months. (3) Initiation of PegIFNα-based therapy during the specified enrollment period and completion of 144 weeks of treatment. (4) Availability of lipid measurements at baseline and the prespecified follow-up points required for the primary analysis. (5) Complete or traceable records of antiviral treatment.

Patients were excluded for any of the following reasons: (1) Coinfection with hepatitis C virus, hepatitis D virus, or human immunodeficiency virus. (2) Decompensated cirrhosis. (3) Previous liver or other solid-organ transplantation. (4) Autoimmune liver disease, drug-induced liver injury, alcohol-related liver disease, or another chronic liver disease substantially affecting liver function. (5) Active malignancy. (6) Use of systemic glucocorticoids, immunosuppressants, or other medications substantially affecting immune responses during treatment. (7) Pregnancy or breastfeeding. (8) Severe thyroid disease, uncontrolled diabetes mellitus, nephrotic syndrome, or another condition substantially affecting lipid levels. (9) Missing clinical or laboratory data that precluded the primary analysis.

Because completion of the full 144-week PegIFNα course was required for inclusion, patients who discontinued early were not represented. Potential reasons for early discontinuation include poor tolerability, virological failure, adverse events, and loss to follow-up. This completer-only design may introduce attrition-related selection bias. A formal a priori sample-size calculation was not performed. The cohort comprised consecutive patients meeting eligibility criteria during the study window (a convenience sample). The number of patients who initiated PegIFNα-based therapy but were excluded could not be reliably reconstructed from the available records. A quantitative screening flow diagram with exact denominators could therefore not be provided. Potential confounders of lipid trajectories considered a priori included age, sex, baseline body mass index, baseline dyslipidemia or hepatic steatosis, treatment regimen, and prior or concomitant NA exposure. Longitudinal weight, lipid-lowering therapy, and complete prior-NA timelines were incompletely captured. Residual confounding therefore remains possible.

Treatment regimens and follow-up

PegIFNα-2a was administered subcutaneously at 180 μg once weekly. PegIFNα-2b was administered subcutaneously at 1.5 μg/

kg once weekly. Overall, 40 patients received PegIFNα-2a and 89 received PegIFNα-2b.

Patients were classified according to their treatment regimen at PegIFNα initiation. The PegIFNα monotherapy group included 90 patients. The combination-treatment groups comprised 26 patients receiving tenofovir alafenamide (TAF; 25 mg once daily) and 13 receiving entecavir (ETV; 0.5 mg once daily). Thus, 39 of 129 patients (30.2%) received concomitant NA therapy at PegIFNα initiation. Treating physicians selected regimens according to previous antiviral therapy, virological and liver disease status, drug tolerability, and patient preference; regimen comparisons were therefore exploratory and non-randomized. Where available, previous NA exposure (agent and approximate duration) and subsequent on-treatment regimen changes were abstracted from medical records; however, complete lifetime NA timelines were not uniformly documented for all patients.

Clinical and laboratory data were extracted from electronic medical records at baseline and treatment weeks 24, 48, 72, 96, and 144. Baseline was defined as the most recent assessment performed within 7 days before the first PegIFNα dose. Data on adverse events, temporary treatment interruptions, dose modifications, and treatment adherence were also collected. For patients previously treated with NAs, the specific agent, treatment duration, and HBV DNA level at PegIFNα initiation were recorded. Subsequent changes in antiviral medication were also documented. Longitudinal body weight or body mass index (BMI) after baseline and use of lipid-lowering medications (e.g., statins or fibrates) were not systematically recorded in the available retrospective dataset and therefore could not be analyzed.

Clinical and laboratory assessments

At each follow-up visit, venous blood was collected after fasting for at least 8 hours and before that week's scheduled PegIFNα injection. Quantitative HBsAg and HBeAg were measured by chemiluminescent microparticle immunoassay using the Alinity system. HBV DNA was quantified by fluorescent probe-based real-time polymerase chain reaction using an ABI 7500 system. The assay had a lower detection limit of 10 IU/mL. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured kinetically using a LABOSPECT 008 AS automated biochemical analyzer.

TC, TG, HDL-C, and LDL-C were measured in the institutional laboratory. The TG/HDL-C ratio was calculated by dividing TG by HDL-C. All laboratory analyses were performed by the Department of Laboratory Medicine at the First Affiliated Hospital of Xi'an Jiaotong University.

Hepatic steatosis was assessed by abdominal ultrasonography and defined as hepatic parenchymal echogenicity greater than that of the renal cortex. Patients were classified according to the presence or absence of hepatic steatosis (binary ultrasound-based definition). Neither liver biopsy nor controlled attenuation parameter–based quantification was performed. Validated noninvasive continuous scores such as the Hepatic Steatosis Index (HSI) or Fatty Liver Index (FLI) were not applied because key required variables (including waist circumference and γ-glutamyltransferase for FLI, and complete diabetes phenotyping for HSI) were not systematically available in the retrospective records. Examinations were performed by the Department of Ultrasound Medicine at the same institution. Images were interpreted by physicians holding the rank of associate chief physician or higher.

Outcomes and definitions

The primary outcome was the change in HDL-C from baseline to week 144. Secondary lipid outcomes included changes in TC, TG, LDL-C, and the TG/HDL-C ratio during treatment.

Virological and serological outcomes included changes in quantitative HBsAg, on-treatment HBsAg seroclearance, HBeAg status among those positive at baseline, and virological response. In this study, HBsAg seroclearance was defined as an on-treatment HBsAg level ≤ 0.05 IU/mL at week 144 of PegIFNα-based therapy. This endpoint denotes HBsAg loss assessed while patients were still receiving treatment and should not be interpreted as sustained HBsAg seroclearance after treatment discontinuation.

Among patients positive for HBeAg at baseline (HBeAg ≥ 1.0 cutoff index (COI)), HBeAg clearance was defined as HBeAg < 1.0 COI at week 144. Virological response was defined as an HBV DNA level ≤ 10 IU/mL at week 144 (aligned with the assay reporting floor used in this cohort; values reported as 10 IU/mL were treated as being at the detection limit). Anti-HBs seroconversion and HBeAg seroconversion (anti-HBe appearance) were not uniformly available in the retrospective laboratory extracts and were therefore not analyzed as endpoints.

Patients were classified by their week-144 HBsAg response according to quantitative HBsAg values. Complete response (CR) was defined as on-treatment HBsAg seroclearance at week 144 (HBsAg ≤ 0.05 IU/mL; not off-treatment sustained seroclearance). Partial response (PR) was defined as a decrease from baseline while HBsAg remained detectable (> 0.05 IU/mL) at week 144. No response (NR) was defined as no decrease in HBsAg from baseline.

Biochemical response was defined as ALT normalization to the sex-specific upper limit of normal: 40 U/L for men and 35 U/L for women. Baseline dyslipidemia was defined as a clinician-documented diagnosis of dyslipidemia or hyperlipidemia in the medical records available at admission, including previously diagnosed patients receiving lipid-lowering therapy. This classification was based on documented clinical diagnoses rather than isolated baseline lipid measurements. For reference, the 2023 Chinese guideline for lipid management provides the following lipid thresholds: TC ≥5.2 mmol/L, TG ≥1.7 mmol/L, LDL-C ≥3.4 mmol/L, and HDL-C <1.0 mmol/L for both men and women.[21]

Statistical analysis

Continuous variables were summarized as mean ± standard deviation (SD) or median with interquartile range (IQR), as appropriate, and categorical variables as counts (percentages). For primary and secondary lipid endpoints, mean changes from baseline to week 144 are reported with 95% confidence intervals (CIs). HBsAg values of 0 IU/mL were assigned a value of 0.05 IU/mL before $\log_{10}$ transformation. HBV DNA values below or at the laboratory reporting limit of 10 IU/mL were analyzed as 10 IU/mL for the binary virological response endpoint (≤ 10 IU/mL) and as half the detection limit (5 IU/mL) for $\log_{10}$-transformed continuous summaries when a numerical value below the limit was required. For the baseline-to-week-144 comparisons reported in Table 1, continuous variables were analyzed using two-sided

Table 1. Changes in virological markers during PegIFNα-based therapy

Parameter	Baseline	Week 96	Week 144	Change (W144 – W0)	*P* value
HBsAg, log_{10} IU/mL	2.62 ± 1.30	1.03 ± 1.82	1.14 ± 1.88	−1.48 ± 1.64	< 0.001
HBsAg, IU/mL, median (IQR)	637.2 (125.5–3506.0)	17.5 (0.0–346.3)	66.0 (0.0–498.8)	−398.0 (−1850.2 to −41.1)	< 0.001
HBV DNA, log_{10} IU/mL	2.42 ± 1.89	1.12 ± 0.42	1.12 ± 0.41	−1.29 ± 1.87	< 0.001
HBV DNA, IU/mL, median (IQR)	73 (20–639)	10 (10–10)	10 (10–10)	−27 (−614 to 0)	0.028
HBeAg, COI	93.00 ± 329.47	1.21 ± 3.51	3.35 ± 25.90	−89.66 ± 329.23	0.002
HBeAg, COI, median (IQR)	0.40 (0.36–0.85)	0.35 (0.32–0.43)	0.37 (0.33–0.44)	−0.05 (−0.39 to 0.02)	0.002
Binary endpoints, *n*/*N* (%)					
HBeAg positive (≥ 1.0 COI)	31/129 (24.0)	13/129 (10.1)	10/129 (7.8)	−16.3 pp	< 0.001
HBV DNA ≤ 10 IU/mL	29/129 (22.5)	112/129 (86.8)	108/129 (83.7)	+61.2 pp	< 0.001
On-treatment HBsAg loss (≤ 0.05 IU/mL)	0/129 (0.0)	34/129 (26.4)	37/129 (28.7)	+28.7 pp	< 0.001

Data are presented as mean ± SD or median (IQR) for continuous variables and as *n*/N (%) for categorical variables. Change was defined as the week 144 value minus the baseline value. *P values* compare Week 144 with baseline. Two-sided paired *t-tests* were used for all continuous variables, including those presented as median (IQR), and McNemar tests were used for paired binary endpoints. For variables reported on both the original and log_{10}-transformed scales, *P values* were calculated separately on the corresponding scales. COI, cutoff index; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B virus DNA; IQR, interquartile range; n, number of patients meeting the endpoint; N, total number of patients; pp, percentage points; SD, standard deviation; W0, baseline (week 0); W144, week 144.

paired *t*-tests, and paired binary endpoints were analyzed using McNemar tests. For other within-patient continuous comparisons, paired *t*-tests or Wilcoxon signed-rank tests were used, as appropriate. Between-group comparisons of continuous variables used analysis of variance or the Kruskal–Wallis test, as appropriate; categorical variables used the chi-square test or Fisher's exact test. Comparisons among treatment regimens were prespecified as exploratory. Associations between lipid changes at weeks 24 and 48 and on-treatment HBsAg seroclearance at week 144 were examined using binary logistic regression. Univariable models were followed by exploratory multivariable models adjusting for age, sex, baseline log_{10} HBsAg, treatment regimen (PegIFNα plus NA versus monotherapy), and baseline dyslipidemia. Effect estimates are reported as odds ratios (ORs) with 95% CIs. All tests were two-sided, with $P < 0.05$ considered statistically significant. Analyses were performed using IBM SPSS Statistics version 27.0.1 (IBM, Chicago, IL, USA).

Results

Study population and baseline characteristics

The study included 129 patients with a mean age of 39.4 ± 8.8 years, of whom 75 (58.1%) were male. The mean body mass index was 25.4 ± 6.0 kg/m². At baseline, 37 patients (28.7%) had hepatic steatosis and 51 (39.5%) had dyslipidemia. Mean TC, TG, HDL-C, and LDL-C levels were 4.19 ± 0.76, 1.17 ± 0.65, 1.65 ± 0.35, and 2.57 ± 0.51 mmol/L, respectively, and the mean TG/HDL-C ratio was 0.74 ± 0.44. Median HBsAg and HBV DNA levels were 637.2 IU/mL (IQR, 125.5–3506.0) and 73 IU/mL (IQR, 20–639), respectively. Median ALT and AST levels were 26 U/L (IQR, 16–46) and 23 U/L (IQR, 19–32), respectively. Additional baseline characteristics are presented in Table 2.

Changes in lipid levels during 144 weeks of treatment

From baseline to week 144, mean TC decreased by 0.15 ± 0.41 mmol/L (95% CI, −0.22 to −0.08; $P < 0.001$), whereas mean HDL-C increased by 0.10 ± 0.25 mmol/L (95% CI, 0.06 to 0.15; $P < 0.001$). In contrast, changes in TG (0.10 ± 0.67 mmol/L; 95% CI, −0.02 to 0.21; $P = 0.105$), LDL-C (−0.07 ± 0.65 mmol/L; 95% CI, −0.19 to 0.04; $P = 0.211$), and the TG/HDL-C ratio (−0.01 ± 0.43; 95% CI, −0.08 to 0.07; $P = 0.893$) were not statistically significant. Notably, mean HDL-C initially decreased from 1.65 ± 0.35 mmol/L at baseline to 1.17 ± 0.31 mmol/L at week 24 ($P < 0.001$), remained below baseline through week 96, and subsequently increased to 1.75 ± 0.23 mmol/L at week 144. This pattern was descriptive, as nonlinear temporal trends were not formally tested. Longitudinal mean trajectories across weeks 0, 24, 48, 72, 96, and 144 are shown in Figure 1.

Changes in virological markers from baseline to week 144

After 144 weeks of PegIFNα therapy, HBsAg, HBeAg, and HBV DNA levels were significantly reduced from baseline. Mean HBsAg decreased from 2.62 ± 1.30 to 1.14 ± 1.88 log_{10} IU/mL (mean change, −1.48 ± 1.64 log_{10} IU/mL; 95% CI, −1.77 to −1.19; $P < 0.001$), with a median change of −398.0 IU/mL (IQR, −1850.2 to −41.1) on the raw scale. Mean HBV DNA decreased from 2.42 ± 1.89 to 1.12 ± 0.41 log_{10} IU/mL (mean change, −1.29 ± 1.87 log_{10} IU/mL; $P < 0.001$), corresponding to a median raw-scale change of −27 IU/mL (IQR, −614 to 0). HBeAg levels also declined significantly (mean change, −89.66 ± 329.23 COI; median change, −0.05 COI [IQR, −0.39 to 0.02]; $P = 0.002$). Among 31 patients who were HBeAg-positive at baseline, 21 (67.7%) achieved HBeAg clearance at week 144. ALT normalization increased from 84/129 (65.1%) at baseline to 117/129 (90.7%) at week 144. Correspondingly, the proportions of patients who were HBeAg-positive decreased, whereas those

Table 2. Baseline demographics and clinical characteristics of 129 patients with chronic hepatitis B

Characteristic	Total (*N* = 129)
Demographics	
Age, years	39.4 ± 8.8
Male	40.1 ± 7.4
Female	38.4 ± 10.4
Sex, *n* (%)	
Male	75 (58.1)
Female	54 (41.9)
Height, cm	168.5 ± 9.8
Weight, kg	71.6 ± 15.1
BMI, kg/m²	25.4 ± 6.0
Treatment regimen, *n* (%)	
PegIFNα monotherapy	90 (69.8)
PegIFNα + TAF	26 (20.2)
PegIFNα + ETV	13 (10.1)
Hepatic steatosis, *n* (%)	37 (28.7)
Dyslipidemia at baseline, *n* (%)	51 (39.5)
Virologic and serologic markers	
HBsAg, $\log_{10}$ IU/mL	2.62 ± 1.30
HBsAg, IU/mL, median (IQR)	637.2 (125.5–3506.0)
HBeAg positive (≥ 1 COI), *n* (%)	31 (24.0)
HBeAg, COI, median (IQR)	0.40 (0.36–0.85)
HBV DNA, $\log_{10}$ IU/mL	2.42 ± 1.89
HBV DNA, IU/mL, median (IQR)	73 (20–639)
Liver biochemistry	
AST, U/L, median (IQR)	23 (19–32)
ALT, U/L, median (IQR)	26 (16–46)
Lipid profile	
Total cholesterol, mmol/L	4.19 ± 0.76
Triglycerides, mmol/L	1.17 ± 0.65
HDL-C, mmol/L	1.65 ± 0.35
LDL-C, mmol/L	2.57 ± 0.51
TG/HDL-C ratio	0.74 ± 0.44
Hematology	
Platelets, $\times 10^9$/L	179 ± 55
WBC, $\times 10^9$/L	5.46 ± 1.77
On-treatment HBsAg response at week 144, *n* (%)	
Complete response	37 (28.7)
Partial response	83 (64.3)
No response	9 (7.0)

Data are presented as mean ± SD, unless otherwise specified as median (IQR); categorical variables as *n* (%). HBeAg positivity was defined as HBeAg ≥ 1.0

COI at baseline (week 0). HBsAg and HBV DNA levels are presented on both the log_{10}-transformed and original scales. A total of 129 patients with chronic hepatitis B (CHB) who received PegIFNα-based therapy were included. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CHB, chronic hepatitis B; COI, cutoff index; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B virus DNA; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; N, total number of patients; PegIFNα, pegylated interferon alpha; SD, standard deviation; TAF, tenofovir alafenamide; TG, triglycerides; WBC, white blood cells.

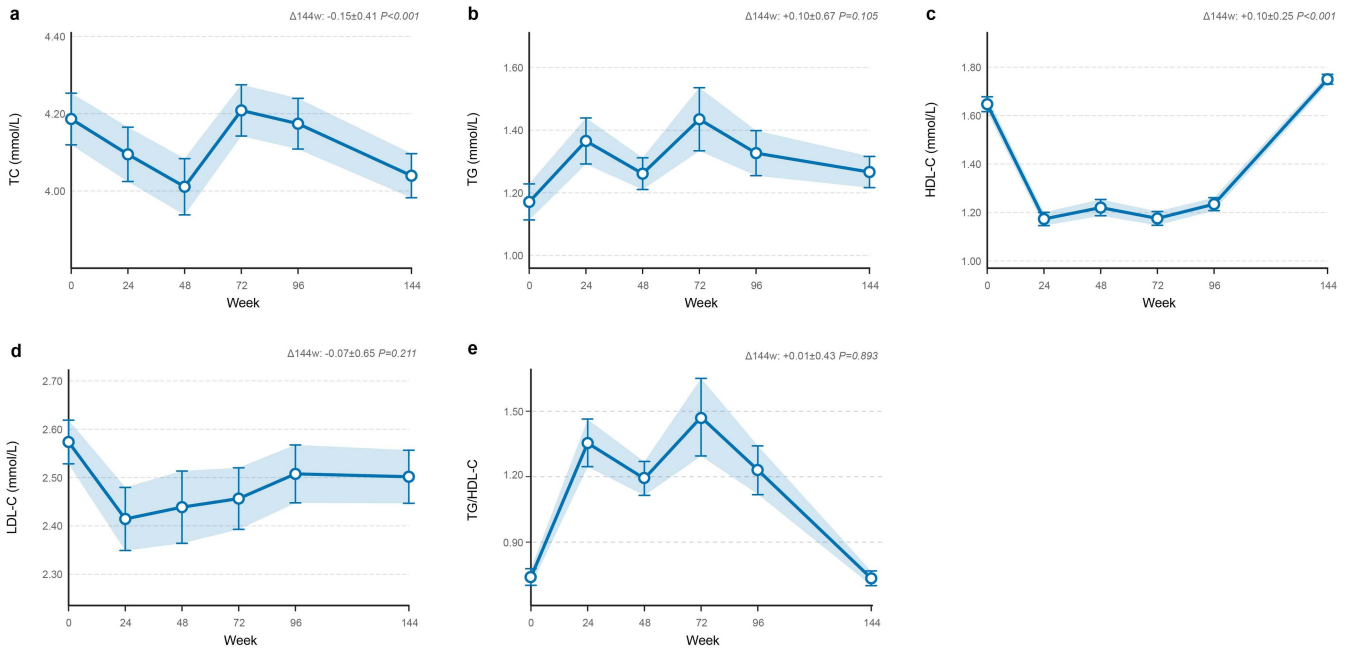


Fig. 1. Longitudinal lipid trajectories during 144 weeks of PegIFNα-based therapy. (a) TC; (b) TG; (c) HDL-C; (d) LDL-C; and (e) TG/HDL-C ratio. Values are shown as means at baseline and weeks 24, 48, 72, 96, and 144. Error bars and shaded areas represent the standard error of the mean (SEM). Δ144w values are presented as the mean change from baseline to week 144 ± standard deviation (SD), with the corresponding *P* value. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PegIFNα, pegylated interferon alpha; SD, standard deviation; SEM, standard error of the mean; TC, total cholesterol; TG, triglycerides; Δ144w, change from baseline to week 144.

achieving HBV DNA ≤ 10 IU/mL and on-treatment HBsAg loss at week 144 increased (Table 1; all binary comparisons $P < 0.001$). These serological outcomes reflect status during continued PegIFNα-based therapy rather than sustained responses after treatment cessation. Of note, verification against the source dataset confirmed that the median raw HBsAg level rose from 17.5 IU/mL (IQR, 0.0–346.3) at week 96 to 66.0 IU/mL (IQR, 0.0–498.8) at week 144, while the mean log_{10} HBsAg also increased slightly (1.03 to 1.14). This pattern is explained by within-patient dynamics rather than a calculation error: 13 patients who had HBsAg ≤ 0.05 IU/mL at week 96 rebounded to detectable levels at week 144, whereas 16 other patients newly achieved HBsAg loss between weeks 96 and 144 (net increase from 34 [26.4%] to 37 [28.7%]).

HBsAg response at week 144

Based on quantitative HBsAg values at week 144 and the prespecified definitions above, 37 patients (28.7%) achieved a complete response (on-treatment HBsAg ≤ 0.05 IU/mL), 83 (64.3%) a partial response, and 9 (7.0%) no response. Thus, a complete or partial response was observed in 120 patients (93.0%) (Fig. 2). Complete response indicates on-treatment HBsAg seroclearance at week 144 and does not represent durable off-treatment HBsAg seroclearance. These counts are consistent with the on-treatment HBsAg-loss endpoint reported in Table 1.

Outcomes according to baseline metabolic status

Patients were stratified according to baseline hepatic steatosis and dyslipidemia status, and between-group differences were assessed using Mann–Whitney U tests (Fig. 3).

At baseline, patients with hepatic steatosis had higher AST ($P < 0.001$), ALT ($P < 0.001$), TG ($P = 0.011$), and TG/HDL-C ratios ($P = 0.026$) than those without steatosis, whereas HBsAg, HBeAg, HBV DNA, TC, HDL-C, and LDL-C levels were comparable between groups (all $P > 0.05$) (Fig. 3a). Patients with dyslipidemia had higher TC ($P < 0.001$), TG ($P < 0.001$), and TG/HDL-C ratios ($P < 0.001$) than those without dyslipidemia, while HBsAg, HBeAg, HBV DNA, AST, ALT, HDL-C, and LDL-C levels did not differ significantly between groups (all $P > 0.05$) (Fig. 3b).

From baseline to week 144, decreases in AST and ALT were greater in patients with hepatic steatosis ($P < 0.001$ and $P = 0.001$, respectively), whereas changes in lipid and virological parameters were comparable between steatosis groups (all $P > 0.05$). Among patients stratified by baseline dyslipidemia status (51/129, 39.5%),

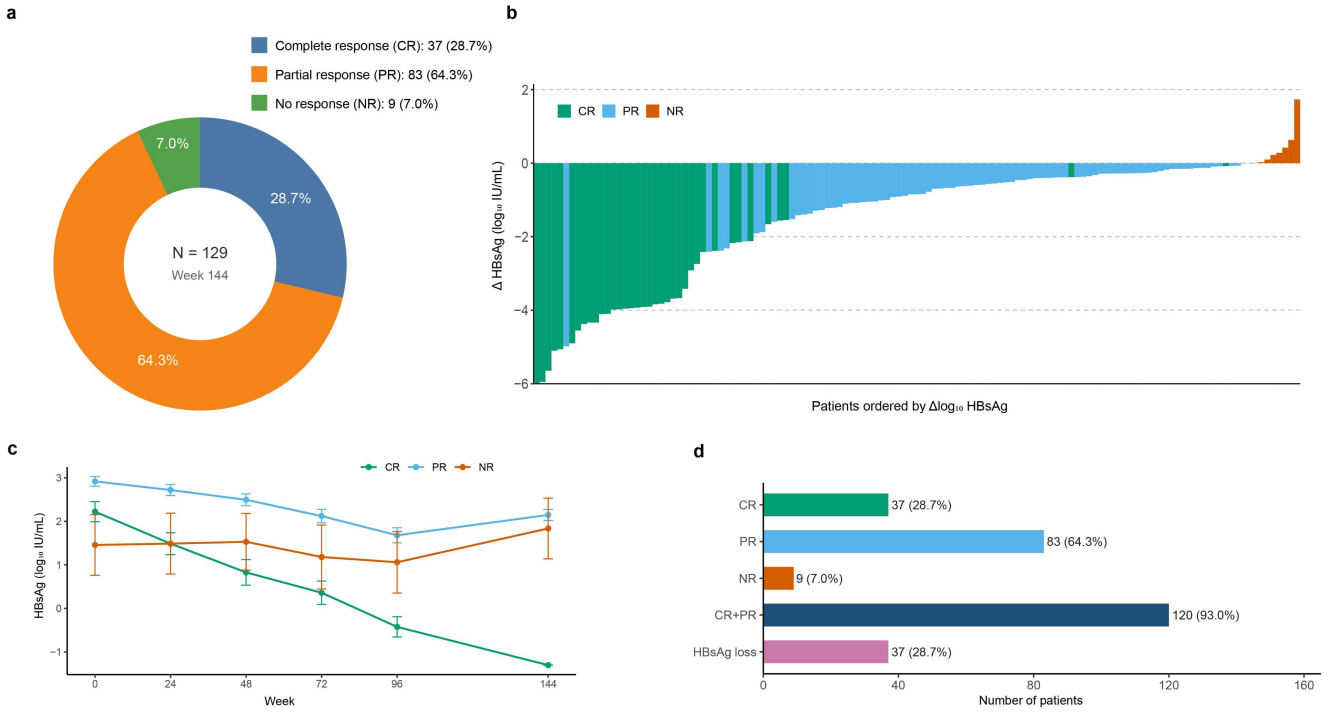


Fig. 2. HBsAg responses at week 144 of PegIFNα-based therapy. (a) Distribution of complete response (CR), partial response (PR), and no response (NR); (b) patient-level changes in $\log_{10}$ HBsAg from baseline to week 144, ordered by magnitude of change; (c) longitudinal HBsAg levels according to week-144 response group; and (d) response categories and on-treatment HBsAg loss at week 144. CR was defined as week-144 HBsAg ≤ 0.05 IU/mL; PR as a decrease from baseline with week-144 HBsAg > 0.05 IU/mL; and NR as no decrease from baseline. HBsAg, hepatitis B surface antigen; PegIFNα, pegylated interferon alpha.

TG and TG/HDL-C ratio decreased in those with dyslipidemia but increased in those without dyslipidemia, resulting in significant between-group differences in both changes (both $P < 0.001$). Changes in TC, HDL-C, LDL-C, AST, ALT, and virological parameters did not differ significantly between the two dyslipidemia groups (all $P > 0.05$). On-treatment HBsAg seroclearance at week 144 occurred in 15 of 51 patients with baseline dyslipidemia (29.4%) and in 22 of 78 patients without baseline dyslipidemia (28.2%), with no significant between-group difference ($P = 0.88$).

Lipid changes across treatment regimens and HBsAg response groups

In exploratory comparisons across the non-randomized treatment groups, the change in HDL-C from baseline to week 144 differed significantly among regimens ($P = 0.037$). Mean HDL-C changes were 0.10 ± 0.26 mmol/L with PegIFNα monotherapy ($n = 90$), 0.04 ± 0.26 mmol/L with PegIFNα plus TAF ($n = 26$), and 0.25 ± 0.18 mmol/L with PegIFNα plus ETV ($n = 13$). Given the small ETV subgroup and unequal group sizes, this finding should be interpreted cautiously. After excluding the ETV subgroup, the difference between PegIFNα monotherapy and PegIFNα plus TAF was no longer significant ($P = 0.26$). Changes in TC, TG, LDL-C, HBsAg, and HBeAg did not differ among regimens (all $P > 0.05$). Longitudinal lipid profiles by treatment regimen are shown in Figure 4.

Changes in lipid parameters, AST, ALT, and HBeAg did not differ among the CR ($n = 37$), PR ($n = 83$), and NR ($n = 9$) groups (all $P > 0.05$). The percentage change in HBsAg differed among response groups ($P < 0.001$), as expected because HBsAg change defined the response categories.

Associations between early lipid changes and complete HBsAg response

Binary logistic regression was used to assess the associations of lipid changes from baseline to weeks 24 and 48 with on-treatment complete response at week 144 (HBsAg ≤ 0.05 IU/mL; 37/129 patients). In univariable models, changes in TC, TG, HDL-C, and LDL-C were not significantly associated with complete response at either time point (all $P > 0.05$; Fig. 5). In separate exploratory multivariable models adjusted for age, sex, baseline $\log_{10}$ HBsAg, treatment regimen (PegIFNα plus NA versus monotherapy), and baseline dyslipidemia, the adjusted ORs (95% CIs) per 1-mmol/L change at week 24 were 0.94 (0.54–1.62) for TC, 0.95 (0.57–1.58) for TG, 0.62 (0.25–1.55) for HDL-C, and 1.11 (0.69–1.79) for LDL-C. The corresponding estimates at week 48 were 1.35 (0.81–2.26), 1.65 (0.77–3.50), 0.72 (0.32–1.64), and 1.08 (0.69–1.69), respectively. None of the adjusted associations was statistically significant (all $P > 0.05$), and the wide confidence intervals indicated limited precision.

Discussion

In this retrospective study of 129 patients with chronic HBV infec-

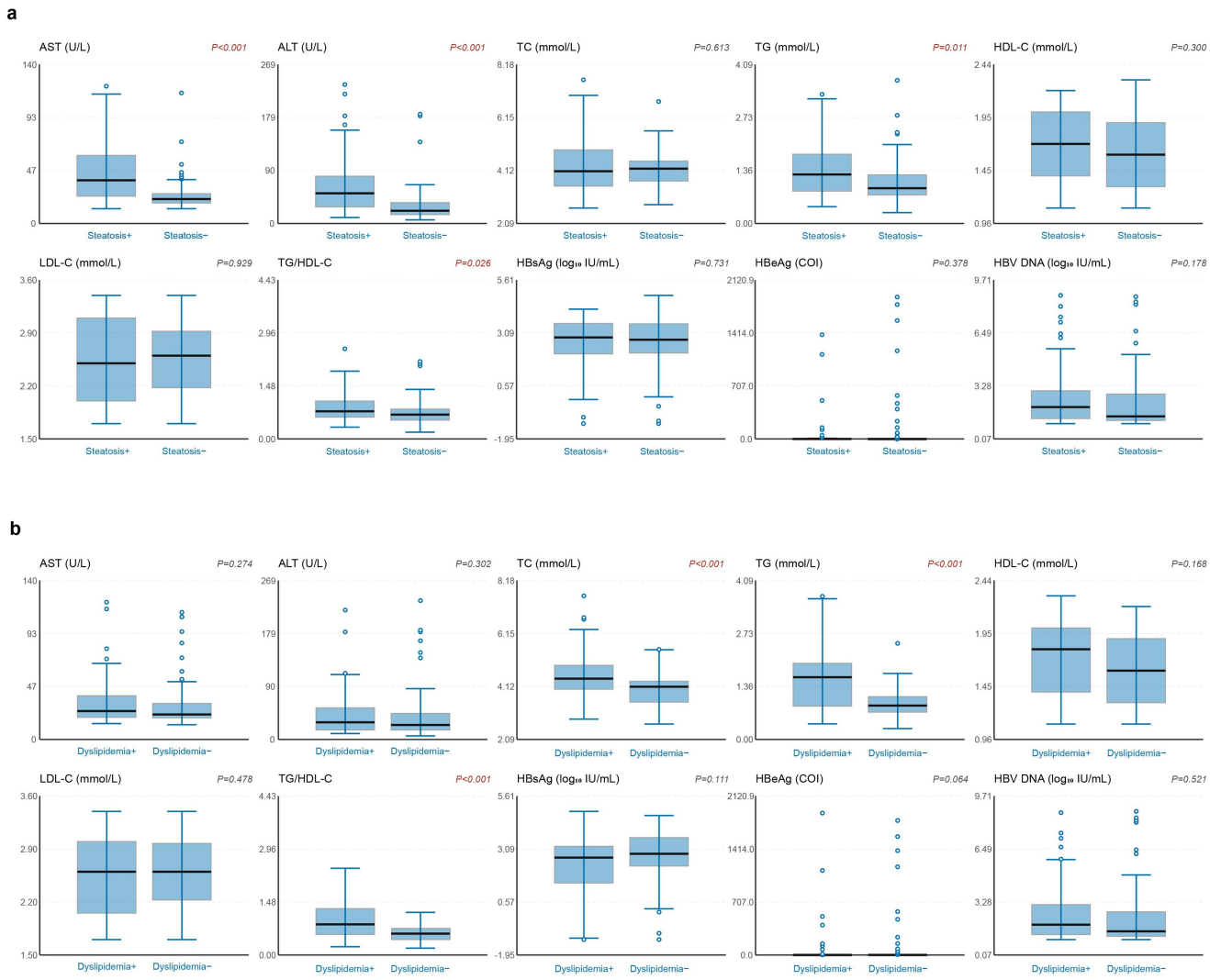


Fig. 3. Baseline comparisons according to hepatic steatosis and dyslipidemia status. (a) Comparisons between patients with and without hepatic steatosis; (b) comparisons between patients with and without baseline dyslipidemia. Between-group differences were assessed using Mann–Whitney U tests. ALT, alanine aminotransferase; AST, aspartate aminotransferase; COI, cutoff index; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B virus DNA; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

tion who completed 144 weeks of PegIFNα-based therapy, lipid parameters showed distinct changes over time. During follow-up, HDL-C was observed to decline early and subsequently recover above baseline by week 144. Total cholesterol was modestly lower at week 144 than at baseline, whereas triglycerides, LDL-C, and the TG/HDL-C ratio showed no significant net differences. Early changes in lipid parameters were not significantly associated with on-treatment HBsAg seroclearance at week 144. These observational findings indicate that lipid changes recorded during the early phase of PegIFNα-based treatment may not necessarily reflect longer-term patterns and should not be interpreted as establishing a causal effect of PegIFNα on lipid metabolism.

Previous studies have suggested that IFNα or PegIFNα therapy may be associated with alterations in several lipid components.[17] However, much of the available evidence has been derived from relatively short treatment periods or from populations other than patients with chronic hepatitis B.[22] The early decline in HDL-C observed in our cohort was broadly consistent with previous reports, whereas its subsequent recovery by week 144 suggests that measurements obtained during the first 24–48 weeks may not fully represent longer-term changes. Because nonlinear time effects were not formally evaluated using longitudinal models, this pattern should be considered descriptive rather than evidence of a confirmed biphasic trajectory. Importantly, an increase in HDL-C concentration should not be interpreted as evidence of cardiovascular benefit, because HDL-C concentration alone does not reflect the composition or functional properties of HDL particles.[23,24] HDL function—including cholesterol efflux capacity and anti-

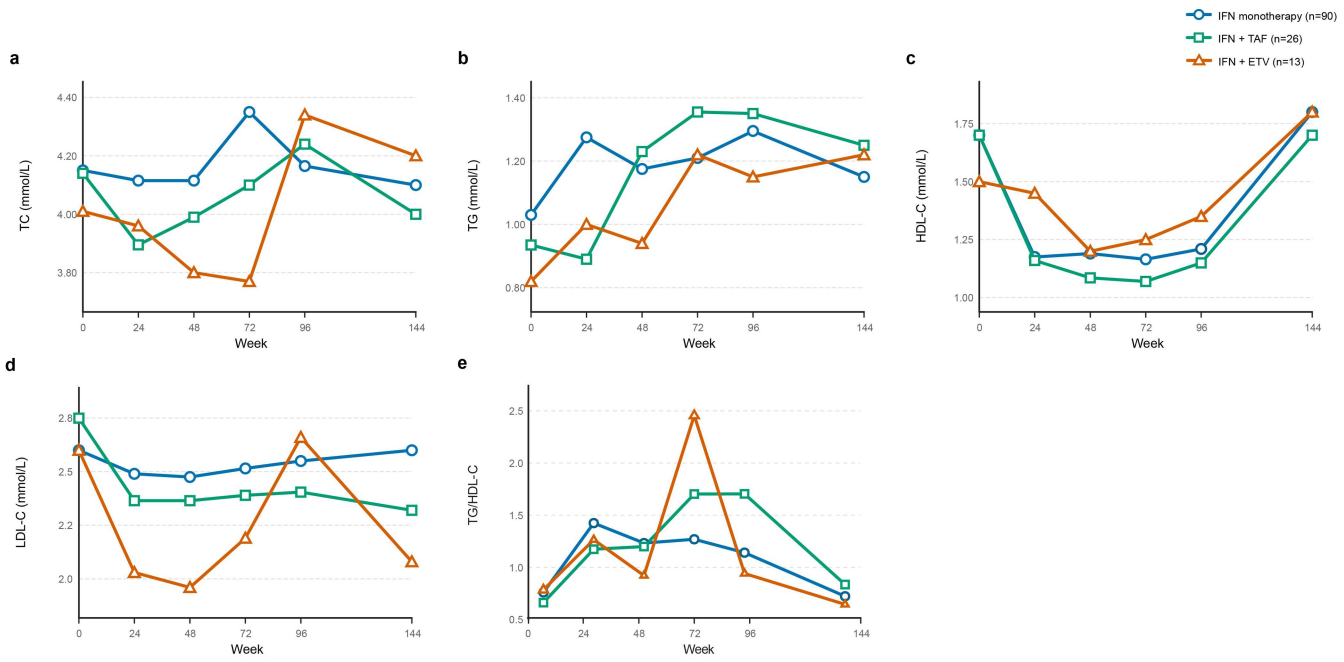


Fig. 4. Longitudinal lipid profiles according to treatment regimen during 144 weeks of PegIFNα-based therapy. (a) TC; (b) TG; (c) HDL-C; (d) LDL-C; and (e) TG/HDL-C ratio. Treatment groups comprised PegIFNα monotherapy, PegIFNα plus TAF, and PegIFNα plus ETV. ETV, entecavir; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PegIFNα, pegylated interferon alpha; TAF, tenofovir alafenamide; TC, total cholesterol; TG, triglycerides.

inflammatory activity—may be more clinically informative than HDL-C concentration alone; functional HDL assays were not performed in this study. Moreover, LDL-C and the TG/HDL-C ratio showed no significant net improvement at week 144. The metabolic implications of these findings should therefore be interpreted across multiple lipid parameters rather than on the basis of HDL-C alone.

Previous studies indicate that hepatic steatosis in CHB is more strongly associated with host metabolic factors, including obesity, insulin resistance, and elevated TG levels. By contrast, its associations with alanine aminotransferase and aspartate aminotransferase levels have been inconsistent.[25-27] In our cohort, hepatic steatosis was ascertained by ultrasonography as a binary variable; quantitative indices such as HSI or FLI could not be calculated from the available data. Patients with baseline hepatic steatosis had higher aminotransferase levels, TG levels, and TG/HDL-C ratios than those without steatosis. However, longitudinal lipid changes did not differ significantly between the two groups.

Changes in TG levels and TG/HDL-C ratios differed in direction across subgroups defined by baseline lipid status. These subgroup patterns may reflect regression to the mean or unmeasured changes in body weight,[28] lipid-lowering therapy, and concomitant medications. Previous studies have shown that changes in body weight, insulin resistance, and lipid profiles may occur concurrently after modification of antiviral regimens.[29] Individual NAs may also have distinct effects on lipid profiles.[30-32] Analyses of lipid changes during PegIFNα-based therapy should therefore account for both the type and timing of concomitant or previous NA exposure.

More broadly, contemporary systems-biology and endocrine frameworks underscore that antiviral therapy–associated metabolic changes are embedded in interconnected glucose–lipid regulatory networks. Network pharmacology approaches have been used to map metabolic pathways relevant to diabetes and systemic metabolic remodeling[33]; incretin-axis biology provides a mechanistic lens on hormonal regulation of glucose and lipid metabolism[34]; and proteomic analyses of circulating exosomes have identified transition signatures across metabolic complications of chronic disease.[35] Although these approaches were not applied in the present retrospective lipid analysis, they provide useful methodological and mechanistic context for interpreting PegIFNα-associated metabolic observations and for designing future biomarker studies.

Among patients who completed 144 weeks of follow-up, 28.7% achieved on-treatment HBsAg seroclearance at week 144, exceeding the proportions typically reported after conventional 48-week PegIFNα therapy.[36] Several factors likely contributed to this relatively high rate. First, baseline HBsAg and HBV DNA levels in this cohort were comparatively low (median HBsAg 637.2 IU/mL; median HBV DNA 73 IU/mL). This distribution is consistent with enrichment for patients with lower pretreatment HBsAg levels, including those below approximately 3000 IU/mL, a profile that has been associated with a greater likelihood of treatment response and HBsAg loss.[37,38] Lower pretreatment antigen and viremia burdens may be associated with an increased probability of HBsAg loss. Second, 39 patients (30.2%) were receiving concomitant NA therapy (TAF or ETV) at PegIFNα initiation, and prior or ongoing NA exposure may facilitate subsequent serological responses to PegIFNα. Third, restriction of the analytic cohort to patients who completed the full 144-week course

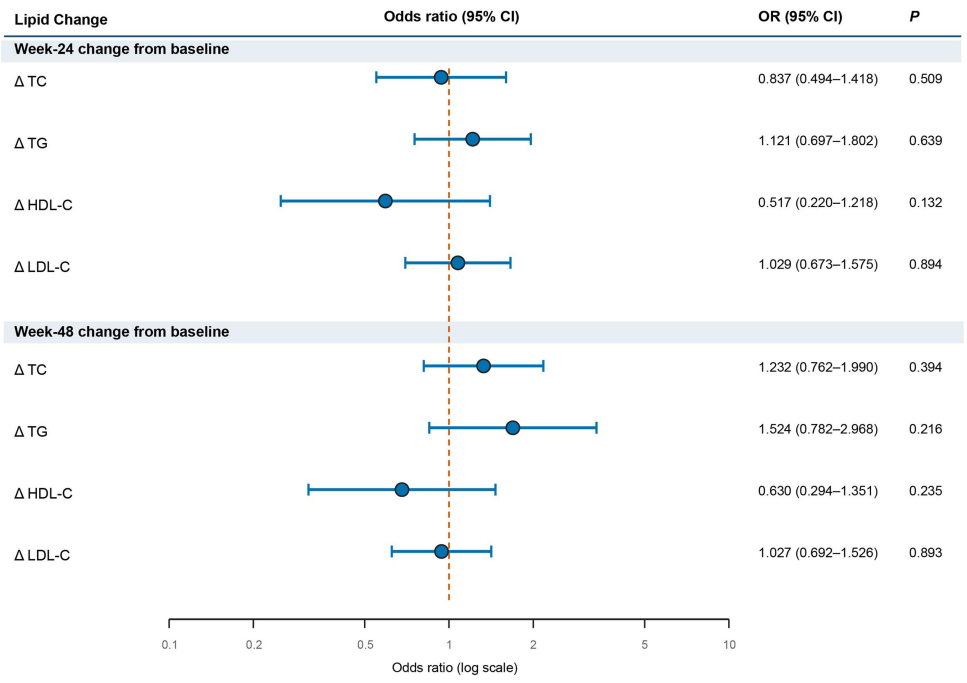


Fig. 5. Univariable associations of early lipid changes with complete response at week 144. Associations of changes in TC, TG, HDL-C, and LDL-C from baseline to weeks 24 and 48 with complete response at week 144 were evaluated using univariable logistic regression. ORs are expressed per 1-mmol/L increase in lipid change; horizontal lines indicate 95% CIs, and the vertical dashed line indicates an OR of 1. Complete response was defined as on-treatment HBsAg ≤ 0.05 IU/mL at week 144. CI, confidence interval; HBsAg, hepatitis B surface antigen; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; TC, total cholesterol; TG, triglycerides.

excludes those who stopped early for intolerance, adverse events, or suboptimal response, thereby introducing attrition-related selection bias that can inflate apparent response rates. Accordingly, this on-treatment HBsAg seroclearance rate cannot be attributed solely to extending PegIFNα therapy to 144 weeks, nor should it be equated with durable functional cure after treatment discontinuation.

Changes in lipid parameters were not significantly associated with on-treatment HBsAg seroclearance (complete response) at week 144. However, the limited number of seroclearance events precluded exclusion of smaller, threshold-dependent, or nonlinear associations. Furthermore, the study assessed on-treatment seroclearance at week 144 rather than sustained seroclearance after treatment discontinuation. Because HBsAg may reappear after treatment cessation,[38,39] the durability of this response requires confirmation through long-term post-treatment follow-up.

A key strength of this study was the 144-week follow-up, with repeated measurements of lipid and virological parameters at multiple time points. This design enabled preliminary characterization of their long-term trajectories during PegIFNα-based therapy. Several limitations should be considered. First, this was a single-center retrospective study without a concurrent control group, which limits causal inference and generalizability; observed lipid changes during PegIFNα-based therapy should therefore be interpreted as associations rather than treatment effects. Second, eligibility required completion of 144 weeks of PegIFNα treatment, thereby excluding patients who discontinued early because of poor tolerability, virological failure, adverse events, or loss to follow-up. This completer-only sampling frame constitutes attrition-related selection bias and may overestimate serological response rates and distort lipid trajectories relative to an intention-to-treat population. The number of patients screened or treated but not included because they did not complete 144 weeks could not be determined from the available retrospective records. Furthermore, detailed information on adverse events, temporary treatment interruptions, dose adjustments, and treatment adherence was not systematically available in the retrospective records, precluding a comprehensive assessment of treatment tolerability and adherence. Third, treatment regimens were heterogeneous, and the relatively small and unequal treatment subgroups (particularly PegIFNα plus ETV, n = 13) limited meaningful comparisons among PegIFNα monotherapy and combination regimens; the between-regimen difference in HDL-C change (P = 0.037) was not robust in a sensitivity analysis excluding the ETV subgroup. Previous and concomitant nucleos(t)ide analogue exposure may also have been associated with differences in lipid profiles. Fourth, potentially relevant metabolic factors were incompletely captured: longitudinal body weight or body mass index after baseline, use of statins/fibrates or other lipid-modifying agents, dietary changes, and new-onset diabetes mellitus were not systematically available in the retrospective records and could not be analyzed; residual confounding of lipid trajectories is therefore possible. Fifth, although lipid parameters were measured repeatedly during follow-up, we did not fit formal mixed-effects models with time as a continuous or categor-

ical predictor, nor could we adjust for time-varying metabolic covariates that were unavailable retrospectively; the apparent biphasic HDL-C trajectory should therefore be regarded as descriptive. Future analyses using mixed-effects models could more rigorously evaluate nonlinear time trends. Finally, cardiovascular outcomes were not assessed, and changes in individual lipid parameters should not be interpreted as evidence of altered cardiovascular event risk. In keeping with STROBE recommendations, we note that incomplete reconstruction of the screening denominator and limited multivariable adjustment for time-varying metabolic confounders constrain causal interpretation of lipid trajectories.

Conclusions

Among patients with chronic HBV infection who complete 144 weeks of PegIFNα-based therapy, HDL-C shows a descriptive early decline followed by recovery above baseline. This pattern remains unconfirmed by formal longitudinal models and does not establish a causal effect of PegIFNα. At week 144, TC is modestly lower than at baseline, whereas TG, LDL-C, and the TG/HDL-C ratio show no significant net changes. Changes in lipid parameters show no significant association with on-treatment HBsAg seroclearance at week 144.

Acknowledgments

During the preparation of this manuscript, the authors used ChatGPT for language editing, grammatical correction, and improving the clarity and readability of the manuscript. ChatGPT was not used for study design, data collection, statistical analysis, interpretation of the results, or generation of scientific conclusions. In addition, the revised manuscript underwent a thorough author-led language and typographical review. All authors have carefully reviewed and edited the AI-assisted text, approved the final version of the manuscript, and take full scientific responsibility for its accuracy, integrity, and content.

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Conflict of interest

FY serves as an Editorial Board Member of the *Journal of Translational Gastroenterology*. The authors declare no other conflicts of interest related to this work.

Author contributions

Conceptualization (AF, JL), methodology (SW), software (KD), validation (LZ), formal analysis (ZQ), investigation (LM), resources (FL), data curation (RS), writing the original draft (RS), reviewing and editing the manuscript (SW), visualization (SAA), supervision (FY, YL), project administration (FY, YL), funding acquisition (JL). All authors have approved the final version and publication of the manuscript.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2024) and was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (protocol code XJTU1AF2020LSL-024), which covers the present retrospective analysis of patients receiving 144 weeks of PegIFNα-based therapy. All data were de-identified before analysis. As this was a retrospective observational study, prospective clinical trial registration was not required. The requirement for written informed consent was waived by the Ethics Committee because this retrospective study involved the analysis of previously collected clinical data.

Data sharing statement

The data supporting the findings of this study were collected from the First Affiliated Hospital of Xi'an Jiaotong University and are not publicly available due to patient privacy and ethical restrictions. Data are available from the corresponding author upon reasonable request, subject to ethical restrictions.

References

[1] Seto WK, Lo YR, Pawlotsky JM, Yuen MF. Chronic hepatitis B virus infection. Lancet 2018;392(10161):2313–2324. DOI: 10.1016/S0140-6736(18)31865-8, PMID: 30496122.

[2] Jeng WJ, Yip TC, Lok AS. Hepatitis B: A Review. JAMA 2026;335(21):1879–1892. DOI: 10.1001/jama.2026.6070, PMID: 42081318.

[3] European Association For The Study Of The Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 2012;57(1):167–185. DOI: 10.1016/j.jhep.2012.02.010, PMID: 22436845.

[4] You H, Wang F, Li T, Xu X, Sun Y, Nan Y, *et al*. Guidelines for the Prevention and Treatment of Chronic Hepatitis B (version 2022). J Clin Transl Hepatol 2023;11(6):1425–1442. DOI: 10.14218/JCTH.2023.00320, PMID: 37719965.

[5] Hsu YC, Yeh ML, Wong GL, Chen CH, Peng CY, Buti M, *et al*. Incidences and Determinants of Functional Cure During Entecavir or Tenofovir Disoproxil Fumarate for Chronic Hepatitis B. J Infect Dis 2021;224(11):1890–1899. DOI: 10.1093/infdis/jiab241, PMID: 33999179.

[6] Lau GK, Piratvisuth T, Luo KX, Marcellin P, Thongsawat S, Cooksley G, *et al*. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. N Engl J Med 2005;352(26):

2682–2695. DOI: 10.1056/NEJMoa043470, PMID: 15987917.

[7] Rijckborst V, Hansen BE, Cakaloglu Y, Ferenci P, Tabak F, Akdogan M, *et al*. Early on-treatment prediction of response to peginterferon alfa-2a for HBeAg-negative chronic hepatitis B using HBsAg and HBV DNA levels. Hepatology 2010;52(2):454–461. DOI: 10.1002/hep.23722, PMID: 20683945.

[8] Sonneveld MJ, Rijckborst V, Boucher CA, Hansen BE, Janssen HL. Prediction of sustained response to peginterferon alfa-2b for hepatitis B e antigen-positive chronic hepatitis B using on-treatment hepatitis B surface antigen decline. Hepatology 2010;52(4):1251–1257. DOI: 10.1002/hep.23844, PMID: 20830787.

[9] Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, *et al*. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 2023;77(5):1797–1835. DOI: 10.1097/HEP.0000000000000323, PMID: 36727674.

[10] European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines on the Management of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). Obes Facts 2024;17(4):374–444. DOI: 10.1159/000539371, PMID: 38852583.

[11] van Kleef LA, Choi HSJ, Brouwer WP, Hansen BE, Patel K, de Man RA, *et al*. Metabolic dysfunction-associated fatty liver disease increases risk of adverse outcomes in patients with chronic hepatitis B. JHEP Rep 2021;3(5):100350. DOI: 10.1016/j.jhepr.2021.100350, PMID: 34557660.

[12] Patmore LA, Katwaroe WK, van der Spek D, Choi HSJ, Patel K, Brakenhoff S, *et al*. Association Between the Presence of Metabolic Comorbidities and Liver-Related Events in Patients With Chronic Hepatitis B. Clin Gastroenterol Hepatol 2023;21(12):3089–3096.e1. DOI: 10.1016/j.cgh.2023.03.024, PMID: 37004973.

[13] Zhang J, Ling N, Lei Y, Peng M, Hu P, Chen M. Multifaceted Interaction Between Hepatitis B Virus Infection and Lipid Metabolism in Hepatocytes: A Potential Target of Antiviral Therapy for Chronic Hepatitis B. Front Microbiol 2021;12:636897. DOI: 10.3389/fmicb.2021.636897, PMID: 33776969.

[14] Wu T, Zheng X, Yang M, Zhao A, Li M, Chen T, *et al*. Serum lipid alterations identified in chronic hepatitis B, hepatitis B virus-associated cirrhosis and carcinoma patients. Sci Rep 2017;7:42710. DOI: 10.1038/srep42710, PMID: 28198443.

[15] Naeem M, Bacon BR, Mistry B, Britton RS, Di Bisceglie AM. Changes in serum lipoprotein profile during interferon therapy in chronic hepatitis C. Am J Gastroenterol 2001;96(8):2468–2472. DOI: 10.1111/j.1572-0241.2001.04055.x, PMID: 11513192.

[16] Wu L, Li Z, Gao N, Deng H, Zhao Q, Hu Z, *et al*. Interferon-α could induce liver steatosis to promote HBsAg loss by increasing triglyceride level. Heliyon 2024;10(12):e32730. DOI: 10.1016/j.heliyon.2024.e32730, PMID: 38975233.

[17] Xu B, Fan A, Qian B, Liang J, Li T, Yin W, *et al*. Effect of pegylated interferon α-2b on low-density lipoprotein in patients with chronic hepatitis B. Front Med (Lausanne) 2026;13:1787001. DOI: 10.3389/fmed.2026.1787001, PMID: 42490957.

[18] Cao X, Hu Q, Xu W, Li Q, Zhang J, Chen L, *et al*. Kinetics changes in total cholesterol predict HBeAg seroconversion in chronic hepatitis B patients treated with pegylated interferon-alfa. J Viral Hepat 2023;30(4):310–318. DOI: 10.1111/jvh.13787, PMID: 36529685.

[19] Song K, Ren L, Qian Y, Wang H, Guo Z, Zhang H, *et al*. Effect of dyslipidemia on HBsAg clearance in nucleos(t)ide analogues-experienced chronic hepatitis B patients treated with peginterferon alfa. BMC Infect Dis 2024;24(1):1273. DOI: 10.1186/s12879-024-10093-w, PMID: 39528941.

[20] Lin S, Huang W, Liao Z, Ma H, Wu W, Lin M, *et al*. Comparison of lipid profile alterations in chronic hepatitis b patients receiving tenofovir alafenamide or tenofovir disoproxil fumarate. Sci Rep 2024;14(1):27369. DOI: 10.1038/s41598-024-78656-0, PMID: 39521860.

[21] Li JJ, Zhao SP, Zhao D, Lu GP, Peng DQ, Liu J, *et al*. 2023 Chinese guideline for lipid management. Front Pharmacol 2023;14:1190934. DOI: 10.3389/fphar.2023.1190934, PMID: 37711173.

[22] Fernández-Miranda C, Castellano G, Guijarro C, Fernández I, Schöebel N, Larumbe S, *et al*. Lipoprotein changes in patients with chronic hepatitis C treated with interferon-alpha. Am J Gastroenterol 1998;93(10):1901–1904. DOI: 10.1111/j.1572-0241.1998.00546.x, PMID: 9772052.

[23] Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, *et al*. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. Lancet 2012;380(9841):572–580. DOI: 10.1016/S0140-6736(12)60312-2, PMID: 22607825.

[24] Niisuke K, Kuklenyik Z, Horvath KV, Gardner MS, Toth CA, Asztalos BF. Composition-function analysis of HDL subpopulations: influence of lipid composition on particle functionality. J Lipid Res 2020;61(3):306–315. DOI: 10.1194/jlr.RA119000258, PMID: 31953305.

[25] Rastogi A, Sakhuja P, Kumar A, Hissar S, Jain A, Gondal R, *et al*. Steatosis in chronic hepatitis B: prevalence and correlation with biochemical, histologic, viral, and metabolic parameters. Indian J Pathol Microbiol 2011;54(3):454–459. DOI: 10.4103/0377-4929.85074, PMID: 21934202.

[26] Zheng RD, Chen JN, Zhuang QY, Lu YH, Chen J, Chen BF. Clinical and virological characteristics of chronic hepatitis B patients with hepatic steatosis. Int J Med Sci 2013;10(5):641–646. DOI: 10.7150/ijms.5649, PMID: 23569427.

[27] Ünver Ulusoy T, Bilek HC, Demirköse H, Keleş A. Evaluation of TyG index and TG/HDL-C ratio in HBeAg negative chronic hepatitis B infected patients. Biomol Biomed 2023;23(1):137–144. DOI: 10.17305/bjbms.2022.7320, PMID: 35765946.

[28] Barnett AG, van der Pols JC, Dobson AJ. Regression to the mean: what it is and how to deal with it. Int J Epidemiol 2005;34(1):215–220. DOI: 10.1093/ije/dyh299, PMID: 15333621.

[29] Cheng PN, Feng IC, Chen JJ, Kuo HT, Lee PL, Yu ML, *et al*. Body weight increase and metabolic derangements after tenofovir disoproxil fumarate switch to tenofovir alafenamide in patients with chronic hepatitis B. Aliment Pharmacol Ther 2024;59(2):230–238. DOI: 10.1111/apt.17765, PMID: 37845815.

[30] Shaheen AA, AlMattooq M, Yazdanfar S, Burak KW, Swain MG, Congly SE, *et al*. Tenofovir disoproxil fumarate significantly decreases serum lipoprotein levels compared with entecavir nucleos(t)ide analogue therapy in chronic hepatitis B carriers. Aliment Pharmacol Ther 2017;46(6):599–604. DOI: 10.1111/apt.14218, PMID: 28707319.

[31] Suzuki K, Suda G, Yamamoto Y, Abiko S, Kinoshita K, Miyamoto S, *et al*. Effect of switching from tenofovir disoproxil fumarate to tenofovir alafenamide on lipid profiles in patients with hepatitis B. PLoS One 2022;17(1):e0261760. DOI: 10.1371/journal.pone.0261760, PMID: 35051189.

[32] Cao F, Fan T, Jiang X, Wang J, Liu Y, Zhu L, *et al*. Effects of tenofovir alafenamide fumarate on serum lipid profiles in patients with

chronic hepatitis B. Virol J 2024;21(1):234. DOI: 10.1186/s12985-024-02515-7, PMID: 39342240.

[33] Singh H, Bharadvaja N. Network pharmacology and computational approach to explore the potential underlying mechanism of Centella asiatica in the treatment of diabetes mellitus. Curr Proteomics 2024; 21(6):911–937. DOI: 10.2174/0115701646364860250102115855.

[34] Zargar AA, Mehta V, Huddar V, Gupta R, Bhandari K, Posa MK, *et al*. Incretin hormones: mechanisms, therapeutic implications, and future directions in glucose regulation and diabetes management. Curr Proteomics 2025;22(2):100014. DOI: 10.1016/j.curpro.2025.100014.

[35] Yue Y, Tao Y, Wang J, Zhao S, Zhao F, Shen L, *et al*. Circulating exosomes studied by label-free proteomics analysis reveal transition signatures from diabetes mellitus to diabetic kidney disease. Curr Proteomics 2024;21(3):187–203. DOI: 10.2174/0115701646309538240805093732.

[36] Hu P, Shang J, Zhang W, Gong G, Li Y, Chen X, *et al*. HBsAg Loss with Peg-interferon Alfa-2a in Hepatitis B Patients with Partial Response to Nucleos(t)ide Analog: New Switch Study. J Clin Transl Hepatol 2018;6(1):25–34. DOI: 10.14218/JCTH.2017.00072, PMID: 29577029.

[37] Yuen MF, Lim SG, Plesniak R, Tsuji K, Janssen HLA, Pojoga C, *et al*. Efficacy and Safety of Bepirovirsen in Chronic Hepatitis B Infection. N Engl J Med 2022;387(21):1957–1968. DOI: 10.1056/NEJMoa2210027, PMID: 36346079.

[38] Lee IC, Yang SS, Lee CJ, Su CW, Wang YJ, Lan KH, *et al*. Incidence and Predictors of HBsAg Loss After Peginterferon Therapy in HBeAg-Negative Chronic Hepatitis B: A Multicenter, Long-term Follow-up Study. J Infect Dis 2018;218(7):1075–1084. DOI: 10.1093/infdis/jiy272, PMID: 29741704.

[39] Lok AS, Zoulim F, Dusheiko G, Chan HLY, Buti M, Ghany MG, *et al*. Durability of Hepatitis B Surface Antigen Loss With Nucleotide Analogue and Peginterferon Therapy in Patients With Chronic Hepatitis B. Hepatol Commun 2020;4(1):8–20. DOI: 10.1002/hep4.1436, PMID: 31909352.