ORIGINAL ARTICLE
Iran J Allergy Asthma Immunol
In press.

Antiretroviral Regimen–associated Immunometabolic Alterations and Liver Outcomes in People Living with HIV

Yin'an Zhuang[1], Jiufang Huang[2], Zeng Pang[1], and Wenmin Lin[1]

[1] Department of Infectious Diseases, Zhanjiang Central People's Hospital, Zhanjiang, Guangdong, China
[2] Health Examination Center, Zhanjiang Central People's Hospital, Zhanjiang, Guangdong, China

Received: 10 April 2026; Received in revised form: 30 May 2026; Accepted: 9 June 2026

ABSTRACT

People living with HIV (PLWH) may experience metabolic and hepatic complications during long-term antiretroviral therapy (ART).

This single-center retrospective study compared lipid profile changes and liver-related outcomes among PLWH receiving bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF), NNRTI-based regimens, or boosted protease inhibitor (PI)-based regimens, emphasizing metabolic and hepatic safety in routine clinical care.

Between January 2024 and December 2025, 120 PLWH on ART were included and grouped by primary regimen: B/F/TAF (n=60), NNRTI-based regimens (n=30), and boosted PI-based regimens (n=30). Demographic and clinical variables, including HIV RNA, $CD4^+$ T-cell counts, lipid parameters, and liver function indices, were collected. Outcomes included dyslipidemia, lipid changes, liver enzyme abnormalities, and liver-related adverse events. Between-group comparisons and exploratory multivariable logistic regression were performed. Baseline characteristics were similar across groups. During follow-up, dyslipidemia prevalence differed significantly (20.0%, 30.0%, and 50.0%, respectively), with hypertriglyceridemia occurring in 8.3%, 13.3%, and 30.0% of patients. Boosted PI users demonstrated greater increases in atherogenic lipid measures. Multivariable analysis indicated that boosted PI use, higher BMI, and baseline dyslipidemia were associated with higher dyslipidemia risk. Liver laboratory indices remained largely stable, and severe hepatotoxicity was uncommon. Liver enzyme abnormalities appeared more related to underlying conditions (e.g., fatty liver and viral hepatitis coinfection) than to ART regimen type.

Overall, B/F/TAF showed relatively mild lipid changes, whereas boosted PI-based regimens were linked to higher dyslipidemia risk. Limitations include lack of systematic immune-recovery and inflammatory biomarker data; prospective studies incorporating these markers are needed.

Keywords: Antiretroviral therapy; Boosted protease inhibitor; B/F/TAF; Dyslipidemia; HIV; Liver function

INTRODUCTION

Human immunodeficiency virus infection and acquired immune deficiency syndrome remain major public health concerns. With the broad application of

Corresponding Author: Wenmin Lin, MD;
Department of Infectious Diseases, Zhanjiang Central People's Hospital, Zhanjiang, Guangdong, China. Email: wminlin2026@163.com

Published by Tehran University of Medical Sciences (http://ijaai.tums.ac.ir)

antiretroviral therapy (ART), the prognosis of people living with HIV has improved markedly. Long-term viral suppression can now be achieved in many patients, immune function may gradually recover, and life expectancy has been greatly extended. As a result, HIV infection has increasingly changed from a rapidly progressive infectious disease into a chronic condition requiring continuous management. UNAIDS reported that approximately 40.8 million people worldwide were living with HIV in 2024, and 31.6 million of them were receiving ART. The World Health Organization (WHO) has also emphasized that people living with HIV who receive ART and maintain an undetectable viral load do not transmit HIV through sexual contact. Therefore, early and sustained treatment benefits both individual prognosis and public health.[1,2] The Chinese Guidelines for Diagnosis and Treatment of AIDS, 2024 edition, also emphasize whole-course management. In addition to virologic suppression and immune recovery, long-term comorbidities, adverse drug reactions, and individualized regimen selection should be considered.[3] The U.S. Department of Health and Human Services (DHHS) guidelines recommend ART for all people with HIV and regard integrase strand transfer inhibitor (INSTI)-based regimens as important first-line choices for most adults and adolescents.[4]

However, effective ART and sustained viral suppression do not completely normalize immune function. Many people living with HIV continue to experience persistent immune activation, chronic low-grade inflammation, microbial translocation, altered monocyte and T-cell activation, and metabolic immune dysregulation despite virologic control. These residual immune abnormalities may be associated with non-AIDS comorbidities, including cardiovascular disease, metabolic syndrome, fatty liver disease, and other liver-related complications. Therefore, the long-term management of HIV has moved beyond viral suppression alone and increasingly requires attention to immune-metabolic health. Given that the present study did not measure specific immune activation or inflammatory biomarkers, the immunometabolic mechanistic conclusions are limited to observational associations.

As HIV care has shifted toward chronic disease management, the evaluation of ART has also expanded. Earlier clinical practice focused mainly on viral suppression, $CD4^+$ T-cell recovery, and prevention of opportunistic infections. During long-term treatment, however, cardiovascular and metabolic risk, liver and kidney function, bone metabolism, body weight change, drug interactions, and persistent inflammation may also influence prognosis. Among these factors, dyslipidemia and liver-related injury deserve particular attention. Dyslipidemia is closely connected with atherosclerotic cardiovascular disease, while abnormal liver function may affect drug tolerance, treatment continuation, and long-term outcomes, especially in patients with viral hepatitis coinfection, fatty liver, or other metabolic risk factors. Therefore, when the overall rate of viral suppression continues to improve, metabolic and hepatic safety has become an important consideration in ART regimen selection.

The relationship between ART, metabolism, and liver outcomes should be understood within an immune–metabolic framework. HIV infection itself can affect lipid metabolism through chronic inflammation, immune activation, cytokine dysregulation, adipose tissue dysfunction, and endothelial injury. ART-associated lipid changes may interact with HIV-related inflammatory background to influence long-term metabolic risk, though direct mechanistic evidence was not obtained in this real-world study. At the same time, different ART regimens may have different effects on lipid parameters, insulin resistance, body weight, and hepatic metabolism. These drug-related metabolic changes may interact with the pre-existing inflammatory background of HIV infection and may further influence long-term immune health. Therefore, comparing lipid and liver-related outcomes across different ART regimens may provide clinically relevant information for individualized treatment selection.

B/F/TAF refers to the fixed-dose single-tablet regimen containing bictegravir, emtricitabine, and tenofovir alafenamide (B/F/TAF). Bictegravir is an INSTI with potent antiviral activity, a relatively high resistance barrier, convenient administration, and fewer drug interactions. Emtricitabine and tenofovir alafenamide serve as the nucleoside/nucleotide reverse transcriptase inhibitor backbone. Two pivotal phase 3 randomized controlled trials reported that B/F/TAF achieved non-inferior virologic efficacy compared with dolutegravir-containing regimens in treatment-naive people with HIV, with favorable overall tolerability.[5,6] Follow-up data through 144 weeks further supported its durable viral suppression and general safety.[7] Nevertheless, patients included in clinical trials are often carefully selected, and those with severe comorbidities or complex concomitant medication use are commonly

excluded. Therefore, trial results may not fully represent patients encountered in routine clinical practice. Real-world studies can provide additional evidence, especially for evaluating lipid and liver-related outcomes of B/F/TAF in broader clinical populations.[8]

Dyslipidemia is a common problem during long-term follow-up of people living with HIV. It is not caused by ART alone, but may result from the combined effects of HIV-related immune activation, chronic inflammation, traditional metabolic risk factors, body composition changes, and ART exposure. In recent years, the cardiovascular disease burden in people living with HIV has received increasing attention, and dyslipidemia is recognized as an important and modifiable risk factor. A *Journal of the American College of Cardiology* (*JACC*) review noted that dyslipidemia in people living with HIV is affected by traditional risk factors, virus-related factors, and ART exposure, and some boosted protease inhibitor (PI) regimens are closely related to dyslipidemia and drug interactions.[9] The AIDS Clinical Trials Group (ACTG) A5257 study compared the metabolic effects of ritonavir-boosted atazanavir or darunavir regimens with raltegravir regimens. The results showed that boosted PI regimens caused more obvious increases in total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C) than raltegravir regimens.[10] In addition, tenofovir alafenamide (TAF) has better kidney and bone safety than tenofovir disoproxil fumarate (TDF), but the possible lipid-lowering effect of TDF may become weaker after switching to TAF. The OPERA real-world cohort showed that after switching from TDF to TAF, LDL-C and TG tended to increase early.[11] Therefore, when evaluating B/F/TAF, antiviral effect should not be the only focus; its lipid changes should also be compared with NNRTI-based regimens and boosted PI-based regimens.

The clinical meaning of dyslipidemia is not limited to higher laboratory values. More importantly, it may reflect increased long-term cardiovascular and immune-metabolic risk. The REPRIEVE study included 7769 people living with HIV who were receiving ART and had low to moderate cardiovascular risk. The results showed that pitavastatin reduced the risk of major adverse cardiovascular events compared with placebo.[12] This result suggests that even when viral control is good, the real cardiovascular risk in people living with HIV may be underestimated by traditional risk scores. Persistent immune activation and inflammation may partly explain this excess risk. Therefore, in ART selection and long-term follow-up, lipid change, dyslipidemia incidence, and the need for lipid-lowering treatment all have practical clinical value.

Besides lipids, liver-related outcomes are also an important part of long-term ART safety evaluation. The causes of abnormal liver function in people living with HIV are complex, including hepatitis B virus (HBV)/hepatitis C virus (HCV) coinfection, alcohol consumption, drug-induced liver injury, opportunistic infection, immune reconstitution-related reactions, chronic inflammation, and the increasingly common metabolic fatty liver disease. With better access to HCV treatment and more standard HBV suppressive treatment, the liver disease pattern in people living with HIV is also changing, and metabolic fatty liver disease and non-alcoholic fatty liver disease are becoming more important. A systematic review and meta-analysis showed that non-alcoholic fatty liver disease and liver fibrosis are not rare in people with HIV mono-infection, and obesity, diabetes, dyslipidemia, and ART exposure may all contribute to their development.[13] Therefore, when comparing different ART regimens, besides routine liver enzymes such as ALT and AST, bilirubin, albumin, platelets, and non-invasive markers such as FIB-4 should also be considered together. The Fibrosis-4 (FIB-4) index is made up of age, AST, ALT, and platelet count. It was first used to assess liver fibrosis in HIV/HCV coinfection, and because it depends on routine laboratory markers and can be obtained easily in retrospective studies, it is useful in real-world research.[14]

The relationship between ART and abnormal liver enzymes is not simple. Drug class, treatment stage, baseline liver disease, concomitant medications, metabolic status, and inflammatory background can all affect liver-related outcomes. The RESPOND cohort included 17 106 people living with HIV and systematically evaluated the relationship between modern ART drugs and chronic liver enzyme elevation. The results showed that chronic liver enzyme elevation was not uncommon in people living with HIV, and it often occurred in the early stage after starting a new drug. The study did not find an obvious short-term liver safety risk for INSTIs, while NNRTI and TDF exposure were related to increased risk of chronic liver enzyme elevation.[15] This also suggests that liver outcomes should not be simply attributed to 1 drug class. Baseline liver function, viral hepatitis coinfection, fatty liver, BMI, dyslipidemia, alcohol consumption, and immune-metabolic status should be considered at the same time.

At present, direct comparative data on B/F/TAF, NNRTI-based regimens, and boosted PI-based regimens for dyslipidemia and liver-related outcomes are still limited. This single-center real-world study was designed with a practical sample size for routine clinical observation, and sample size justification was based on clinical feasibility and available patient resources during the study period. Previous studies mostly focused on virologic non-inferiority between B/F/TAF and dolutegravir regimens, or separately analyzed lipid changes after TAF switching, and some studies paid attention to the metabolic effect of boosted PI regimens. However, studies that compare these 3 types of regimens in the same real-world cohort and place lipid and liver-related markers into the same immune–metabolic evaluation framework remain limited. In Chinese clinical practice, patients may include both treatment-naive and treatment-experienced switch cases, previous regimens may be varied, HBV infection background may differ, metabolic disease burden may increase, and follow-up markers may be incomplete. Therefore, results from foreign clinical trials cannot fully replace local real-world data.

Based on this background, this study retrospectively included 120 people living with HIV who received ART in our hospital from January 2024 to December 2025, including 60 cases in the B/F/TAF group, 30 cases in the NNRTI-based regimen group, and 30 cases in the boosted PI-based regimen group. This study aimed to compare lipid profile alterations and liver-related outcomes among the 3 regimen groups, with a focus on immune–metabolic interactions relevant to long-term immune health. The study mainly observed changes in TC, TG, LDL-C, high-density lipoprotein cholesterol (HDL-C), and non-high-density lipoprotein cholesterol (non-HDL-C), and also evaluated liver-related markers such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), bilirubin, albumin, and FIB-4 index. Related factors for dyslipidemia and abnormal liver enzymes were further analyzed, aiming to provide real-world evidence for individualized ART selection and long-term metabolic and hepatic safety management in people living with HIV.

MATERIALS AND METHODS

Study Design and Study Population

This study was designed as a single-center retrospective cohort study and was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting recommendations for observational studies using routinely collected medical data. A completed STROBE checklist was provided as Supplementary Table S1.[16] The study population consisted of people living with HIV who received antiretroviral therapy in our hospital between January 2024 and December 2025. According to the predefined inclusion and exclusion criteria, 120 patients were included in the final analysis.

No formal a priori sample size calculation was performed because this was a retrospective real-world study based on all eligible patients available during the prespecified study period. The sample size was therefore determined by clinical feasibility, regimen distribution, and the completeness of lipid and liver-function follow-up data. Based on the observed difference in the primary lipid endpoint between the B/F/TAF group and the boosted PI-based regimen group, the study had acceptable ability to detect relatively large differences in dyslipidemia prevalence. However, it was not adequately powered to detect small between-group differences or rare liver-related adverse events. Therefore, findings from multivariable and subgroup analyses should be interpreted as exploratory.

Patients were categorized according to their primary ART regimen during the observation period. The B/F/TAF group included 60 patients, the NNRTI-based regimen group included 30 patients, and the boosted PI-based regimen group included 30 patients. Because treatment allocation was not randomized, regimen selection may have been influenced by prior treatment history, resistance risk, baseline comorbidities, concomitant medications, drug accessibility, and physicians' clinical judgment. Therefore, between-group comparisons in this study were mainly used to explore potential associations between ART regimen type and lipid or liver-related outcomes rather than to establish causal effects.

Inclusion and Exclusion Criteria

Patients were eligible for inclusion if they met the following criteria: (1) age of 18 years or older; (2) confirmed HIV infection; (3) receipt of ART in our hospital between January 2024 and December 2025; (4) use of B/F/TAF, an NNRTI-based regimen, or a boosted PI-based regimen; (5) availability of baseline clinical and laboratory data; and (6) completion of at least 1 follow-up assessment of lipid and liver function- related indicators.

Patients were excluded if they had any of the following conditions: (1) missing key baseline or follow-up data that made assessment of the main outcomes impossible; (2) follow-up duration too short to evaluate changes in lipids or liver function; (3) pregnancy; (4) frequent ART regimen changes during follow-up, which made group classification unclear; (5) end-stage liver disease, decompensated cirrhosis, severe renal failure, active malignancy, or other serious systemic diseases that could clearly influence lipid metabolism or liver function; or (6) use of drugs with obvious effects on lipid levels during the study period, such as long-term systemic glucocorticoids or immunosuppressants. Patients who started lipid-lowering therapy during follow-up because of dyslipidemia were not excluded, but this event was recorded as a lipid-related outcome.

Treatment Regimen Grouping

Patients were grouped according to the main ART regimen used during the study period. The B/F/TAF group included patients who received the fixed-dose single-tablet combination of bictegravir, emtricitabine, and tenofovir alafenamide. The NNRTI-based regimen group included patients whose core drug was a non-nucleoside reverse transcriptase inhibitor, such as efavirenz, rilpivirine, or doravirine, combined with 2 nucleoside/nucleotide reverse transcriptase inhibitors. The boosted PI-based regimen group included patients whose core drug was a pharmacologically boosted protease inhibitor, such as darunavir/ritonavir, darunavir/cobicistat, lopinavir/ritonavir, or other boosted PI regimens, combined with an appropriate nucleoside/nucleotide reverse transcriptase inhibitor backbone.

For patients who had already changed treatment before study entry, grouping was based on the regimen mainly used during the observation period and for which follow-up evaluation was available. If ART was changed during follow-up because of adverse reactions, virologic failure, or other clinical reasons, the reason for switching was recorded and considered in the outcome analysis. This study included both ART-naive patients and treatment-experienced patients who had switched regimens. Previous ART exposure and differences in nucleoside/nucleotide backbones may influence lipid changes, and these factors were considered as potential confounders when interpreting the results.

Data Collection

Data were collected retrospectively from the electronic medical record system and laboratory information system of our hospital. The collected information included age, sex, body mass index (BMI), smoking history, drinking history, hypertension, diabetes, fatty liver, HBV coinfection, HCV coinfection, previous ART history, current treatment regimen, follow-up time, and concomitant medications. Laboratory data included HIV RNA level, $CD4^+$ T-cell count, lipid markers, liver function-related biochemical markers, platelet count, and hepatitis virus-related markers.

$CD4^+$ T-cell count and HIV RNA level were available for all included patients and were used as routine virological and immunological clinical variables. CD4/CD8 ratio was not systematically available in the medical records and was therefore not included in the comparative analysis. $CD8^+$ T-cell counts, duration of sustained virological suppression, and formal indicators of immune reconstitution were not systematically documented across the cohort. Specific immune activation or inflammatory biomarkers, including interleukin-6 (IL-6), high-sensitivity C-reactive protein (hsCRP), tumor necrosis factor-α (TNF-α), soluble CD14 (sCD14), soluble CD163 (sCD163), D-dimer, and $CD8^+$ T-cell activation markers, were not measured in routine care. Therefore, this study could not directly evaluate immune activation or immune reconstitution mechanisms.

Previous ART exposure was recorded when available, including whether patients were ART-naive or treatment-experienced at the start of the observed regimen. However, detailed duration of previous ART exposure, complete previous regimen sequences, exact reasons for switching, and the proportion of patients switched from TDF to TAF were incompletely documented. These variables were therefore not used for formal subgroup analysis.

Lipid markers included TC, TG, LDL-C, HDL-C, and non-HDL-C. Apolipoprotein B, apolipoprotein A1, lipoprotein(a), and standardized cardiovascular risk scores such as atherosclerotic cardiovascular disease (ASCVD) or Framingham scores were not routinely available. LDL-C/HDL-C and TC/HDL-C ratios could be calculated only when both corresponding values were available, but these ratios were not predefined as primary outcomes.

Liver function-related markers included ALT, AST, GGT, alkaline phosphatase, total bilirubin, direct bilirubin, albumin, and platelet count. Fatty liver was diagnosed according to routine abdominal ultrasound reports. However, severity grading of fatty liver, quantitative steatosis assessment, transient elastography, fibrosis stage, HBV DNA levels, HCV RNA status, and detailed antiviral treatment history for viral hepatitis were not systematically available.

Weight, BMI changes, obesity incidence, waist circumference, waist-to-hip ratio, and other body composition measures were not systematically collected in this retrospective study. Baseline BMI was therefore included as the main available anthropometric variable.

Laboratory Testing Methods

Peripheral venous blood was obtained from all included patients. In principle, lipid profiles were measured using fasting venous blood samples. All laboratory examinations were performed by the clinical laboratory of our hospital in accordance with routine operating procedures, and both internal quality control and external quality assessment were applied during testing. HIV-1 RNA was detected by real-time quantitative polymerase chain reaction using an HIV-1 nucleic acid quantitative detection kit based on the PCR-fluorescent probe method. The kit was produced by Daan Gene Co., Ltd. of Sun Yat-sen University, Guangzhou, China.

$CD4^+$ T-cell counts were measured by flow cytometry as part of routine clinical care. Although T lymphocyte subset testing was performed in clinical practice when ordered, complete $CD8^+$ T-cell counts and CD4/CD8 ratio data were not uniformly available across all included patients and follow-up time points. Therefore, only $CD4^+$ T-cell count was used as a consistently available immunological variable in the comparative analysis. Lipid parameters and liver function-related biochemical indicators were examined with an automatic biochemical analyzer. The routine biochemical kits and testing platform were also provided by Shenzhen Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China. HBV and HCV infection status was determined according to serological markers and/or nucleic acid testing results, using related kits from Beijing Wantai Biological Pharmacy Enterprise Co., Ltd., Beijing, China, or Shanghai Kehua Bio-Engineering Co., Ltd., Shanghai, China.

Definition of Lipid-related Outcomes

The primary lipid-related outcome in this study was the presence of any dyslipidemia during follow-up. The diagnostic criteria for dyslipidemia were established with reference to Chinese lipid management guidelines[17], while also considering the reference intervals used by the hospital laboratory and routine clinical practice. Patients were considered to have dyslipidemia if they met at least 1 of the following criteria: TC ≥5.2 mmol/L, TG ≥1.7 mmol/L, LDL-C ≥3.4 mmol/L, HDL-C <1.0 mmol/L, or initiation of lipid-lowering therapy during follow-up due to abnormal lipid levels.

Hypercholesterolemia was defined as TC ≥5.2 mmol/L. Hypertriglyceridemia was defined as TG ≥1.7 mmol/L. Elevated LDL-C was defined as LDL-C ≥3.4 mmol/L, and reduced HDL-C was defined as HDL-C <1.0 mmol/L. Non-HDL-C was obtained by subtracting HDL-C from TC. New-onset dyslipidemia referred to dyslipidemia newly detected during follow-up among patients who did not have dyslipidemia at baseline.

Cardiovascular risk assessment using ASCVD or Framingham scores was not performed in this study. Apolipoproteins (ApoB, ApoA1), lipoprotein (a), and lipid ratios were not available.

Definition of Liver-related Outcomes

The main liver-related outcome was the occurrence of any abnormal liver enzyme during follow-up. Abnormal liver enzymes were defined as ALT, AST, or GGT exceeding the upper limit of the reference range used by the hospital laboratory. Severe liver enzyme elevation was assessed according to the adverse event grading criteria commonly used in HIV clinical studies.[18]

The FIB-4 index was applied as an auxiliary indicator for evaluating the risk of liver fibrosis and was calculated as: age (years) × AST (U/L) / platelet count (10^9/L) × ALT (U/L) Fatty liver was diagnosed based on routine abdominal ultrasound reports in the original medical records. However, ultrasound-based severity grading of steatosis, transient elastography, controlled attenuation parameter, APRI score, liver histology, HBV DNA levels, HCV RNA status, and detailed antiviral treatment history for HBV or HCV were not systematically available. Therefore, liver-related outcomes in this study mainly reflected routine biochemical abnormalities and non-invasive FIB-4-

based risk estimation, rather than direct assessment of hepatic steatosis severity or fibrosis progression.

Study Endpoints

The predefined primary lipid endpoint was any dyslipidemia detected during follow-up, and the primary liver endpoint was any abnormal liver enzyme observed during follow-up. Secondary endpoints included the changes from baseline to follow-up in TC, TG, LDL-C, HDL-C, and non-HDL-C. Other lipid-related secondary endpoints included the incidence of hypercholesterolemia, hypertriglyceridemia, elevated LDL-C, reduced HDL-C, new-onset dyslipidemia, and initiation of lipid-lowering treatment.

Liver-related secondary endpoints included the changes from baseline to follow-up in ALT, AST, GGT, total bilirubin, direct bilirubin, albumin, and FIB-4 index. The rates of grade 3 or higher liver enzyme elevation, regimen adjustment due to liver-related events, and treatment discontinuation caused by liver-related events were also evaluated. HIV RNA level and $CD4^+$ T-cell count were collected as virological and immunological clinical variables.

Statistical Analysis

SPSS 26.0 was used to perform statistical analyses. Continuous variables were first tested for distribution using the Shapiro-Wilk test. Normally distributed variables were presented as mean ± standard deviation, and comparisons among the 3 groups were conducted using 1-way analysis of variance. Variables that did not follow a normal distribution were described as median and interquartile range, and the Kruskal-Wallis test was used for intergroup comparisons. Categorical variables were expressed as number and percentage, and group differences were analyzed using the chi-square test or Fisher's exact test. For continuous indicators, analysis of covariance was used to compare changes between groups after adjusting for the corresponding baseline value.

Multivariable logistic regression was performed to explore factors associated with dyslipidemia and abnormal liver enzymes during follow-up. Because treatment allocation was not randomized, residual confounding was considered an important methodological concern. Propensity score matching, propensity score adjustment, and inverse probability weighting were considered. However, these methods were not performed because of the limited sample size, the unequal group sizes, and the small number of liver-related outcome events, which would have produced unstable propensity estimates and further reduced the analyzable sample after matching. Instead, clinically important covariates were selected a priori for multivariable adjustment.

The dyslipidemia model included treatment regimen type, age, BMI, baseline dyslipidemia, diabetes, and fatty liver. The abnormal liver enzyme model included treatment regimen type, age, fatty liver, HBV/HCV coinfection, and baseline liver enzyme abnormality. The events-per-variable ratio was approximately 5.1 for the dyslipidemia model and 2.7 for the abnormal liver enzyme model, indicating a risk of model overfitting, especially for the liver-related model. Therefore, the regression results were interpreted as exploratory.

Model performance was mainly assessed by the events-per-variable ratio because the small number of events limited the reliability of additional model diagnostic statistics. Formal calibration and discrimination analyses were not emphasized, and the regression models were not intended for prediction. Therefore, the multivariable results were interpreted as exploratory association estimates. Since several secondary endpoints were analyzed, p values other than those for the main endpoints were mainly interpreted in an exploratory manner, and no strict adjustment for multiple comparisons was performed. All statistical tests were 2-sided, and $p<0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics of the Study Population

A total of 120 people living with HIV were enrolled, including 60 in the B/F/TAF group, 30 in the NNRTI group, and 30 in the boosted PI group. Baseline demographics, comorbidities, virological, lipid, and hepatic laboratory indices were comparable across the 3 groups (Table 1). However, because treatment allocation was not randomized, baseline comparability did not exclude the possibility of residual confounding. Regarding immune-recovery parameters, $CD4^+$ T-cell count and HIV RNA level were available for all included patients and were comparable across the 3 groups at baseline. CD4/CD8 ratio was not consistently available in the retrospective records, and $CD8^+$ T-cell counts, duration of sustained virological suppression, and formal immune reconstitution indicators were not

systematically documented. Therefore, immune recovery could only be described using routinely available $CD4^+$ T-cell count and HIV RNA level in the present analysis.

Information on whether patients were ART-naive at the start of the observed regimen was available and is shown in Table 1. However, detailed previous ART duration, complete historical regimen sequences, reasons for switching, and the exact proportion of TDF-to-TAF switches were incompletely recorded. Because of these missing data and the limited sample size, subgroup analyses according to prior ART exposure or TDF-to-TAF switching status were not performed.

Changes in Lipid Markers During Follow-up

Changes in lipid markers from baseline to follow-up in the 3 groups are shown in Table 2. During follow-up, TC, TG, LDL-C, and non-HDL-C changed to different degrees in all 3 groups. Increases in TC, TG, LDL-C, and non-HDL-C were more obvious in the boosted PI-based regimen group. The differences in changes of TC, TG, LDL-C, and non-HDL-C among the 3 groups were statistically significant. HDL-C changed little in the 3 groups, and there was no statistically significant difference among groups. Because strict correction for multiple comparisons was not done in this study, the results of each lipid subitem should be explained together with the main endpoint and clinical meaning.

Table 1. Baseline characteristics of the three groups

Characteristic	B/F/TAF group, n=60	NNRTI-based regimen group, n=30	Boosted PI-based regimen group, n=30	*p*
Age, y	35.8±10.2	37.1±11.5	38.3±10.8	0.584
Male, n (%)	52 (86.7)	25 (83.3)	26 (86.7)	0.912
BMI, kg/m^2	22.6±3.1	22.4±3.3	23.1±3.2	0.632
Current smoking, n (%)	15 (25.0)	9 (30.0)	10 (33.3)	0.698
Drinking, n (%)	11 (18.3)	7 (23.3)	8 (26.7)	0.641
Hypertension, n (%)	6 (10.0)	4 (13.3)	5 (16.7)	0.655
Diabetes, n (%)	4 (6.7)	3 (10.0)	3 (10.0)	0.796
Fatty liver, n (%)	9 (15.0)	6 (20.0)	7 (23.3)	0.599
HBV coinfection, n (%)	6 (10.0)	4 (13.3)	5 (16.7)	0.655
HCV coinfection, n (%)	1 (1.7)	1 (3.3)	1 (3.3)	0.834
ART-naive when regimen started, n (%)	39 (65.0)	18 (60.0)	17 (56.7)	0.729
Follow-up time, mo	12.4±4.1	12.1±4.3	12.6±4.5	0.881
$CD4^+$ T-cell count, cells/μL	318.6±176.4	304.7±169.8	296.3±181.2	0.826
HIV RNA, log_{10} copies/mL	4.43±0.81	4.51±0.77	4.49±0.84	0.904
TC, mmol/L	4.23±0.71	4.30±0.75	4.37±0.79	0.683
TG, mmol/L	1.24±0.55	1.30±0.59	1.36±0.64	0.646
LDL-C, mmol/L	2.48±0.62	2.52±0.65	2.56±0.70	0.848
HDL-C, mmol/L	1.15±0.28	1.14±0.26	1.12±0.27	0.889
ALT, U/L	28.6±15.2	30.1±16.8	31.4±17.5	0.735
AST, U/L	25.4±9.8	26.1±11.0	26.7±10.9	0.856
GGT, U/L	32.5±21.6	34.1±23.2	36.3±24.5	0.753
Total bilirubin, μmol/L	11.8±5.2	12.1±5.5	12.5±5.8	0.847
FIB-4 index	0.96±0.44	1.01±0.48	1.05±0.51	0.692

[a]Data are expressed as mean ± standard deviation or n (%).

[b]ALT: alanine aminotransferase; ART: antiretroviral therapy; AST: aspartate aminotransferase; B/F/TAF: bictegravir/emtricitabine/tenofovir alafenamide; BMI: body mass index; FIB-4: fibrosis-4; GGT: gamma-glutamyl transferase; HBV: hepatitis B virus; HCV: hepatitis C virus; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; TC: total cholesterol; TG: triglyceride.

Table 2. Changes in lipid markers from baseline to follow-up in the three groups

Lipid marker	B/F/TAF group, n=60	NNRTI-based regimen group, n=30	Boosted PI-based regimen group, n=30	Between-Group *p* for Change
Baseline TC, mmol/L	4.23±0.71	4.30±0.75	4.37±0.79	0.003
Follow-up TC, mmol/L	4.42±0.76	4.47±0.80	4.89±0.93	
Change in TC, mmol/L	0.19±0.42	0.17±0.45	0.52±0.57	
Baseline TG, mmol/L	1.24±0.55	1.30±0.59	1.36±0.64	<0.001
Follow-up TG, mmol/L	1.36±0.62	1.46±0.67	1.93±0.90	
Change in TG, mmol/L	0.12±0.35	0.16±0.42	0.57±0.71	
Baseline LDL-C, mmol/L	2.48±0.62	2.52±0.65	2.56±0.70	0.012
Follow-up LDL-C, mmol/L	2.61±0.66	2.66±0.69	2.93±0.79	
Change in LDL-C, mmol/L	0.13±0.32	0.14±0.36	0.37±0.47	
Baseline HDL-C, mmol/L	1.15±0.28	1.14±0.26	1.12±0.27	0.584
Follow-up HDL-C, mmol/L	1.17±0.29	1.15±0.27	1.11±0.28	
Change in HDL-C, mmol/L	0.02±0.12	0.01±0.12	-0.01±0.14	
Baseline non-HDL-C, mmol/L	3.08±0.76	3.16±0.78	3.25±0.84	0.002
Follow-up non-HDL-C, mmol/L	3.25±0.82	3.32±0.86	3.78±0.98	
Change in non-HDL-C, mmol/L	0.17±0.43	0.16±0.44	0.53±0.60	

[a]Between-group *p* values for changes were analyzed by analysis of covariance, with adjustment for the baseline level of the corresponding marker. [b]B/F/TAF: bictegravir/emtricitabine/tenofovir alafenamide; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NNRTI: non-nucleoside reverse transcriptase inhibitor; non-HDL-C: non-high-density lipoprotein cholesterol; PI: protease inhibitor; TC: total cholesterol; TG: triglyceride.

Occurrence of Dyslipidemia During Follow-up

The occurrence of dyslipidemia during follow-up is shown in Table 3. A total of 36 patients had any dyslipidemia at follow-up, including 12 cases in the B/F/TAF group, 9 cases in the NNRTI-based regimen group, and 15 cases in the boosted PI-based regimen group. The difference in overall dyslipidemia rate among the 3 groups was statistically significant, and the boosted PI-based regimen group had the highest rate. Among specific types, hypertriglyceridemia was more common in the boosted PI-based regimen group. New-onset dyslipidemia was calculated only in patients without dyslipidemia at baseline, so its denominator was different from the total sample size.

Changes in Liver Function-Related Markers During Follow-up

Changes in liver function-related markers from baseline to follow-up in the 3 groups are shown in Table 4. During follow-up, ALT, AST, GGT, total bilirubin, albumin, and the FIB-4 index remained generally stable in the 3 groups. Liver enzyme levels in the NNRTI-based regimen group and the boosted PI-based regimen group showed slight numerical fluctuations, but differences in changes of liver function-related markers among the 3 groups were not statistically significant.

Liver-Related Outcomes During Follow-up

Liver-related outcomes during follow-up are shown in Table 5. Abnormal liver enzymes occurred in 5 patients in the B/F/TAF group, 5 patients in the NNRTI-based regimen group, and 6 patients in the boosted PI-based regimen group. Most abnormalities were mild to moderate. Severe liver enzyme elevation, regimen modification, and treatment discontinuation due to liver-related events were uncommon. Because the number of liver-related events was small, statistical interpretation of between-group differences should be cautious.

Table 3. Comparison of dyslipidemia rates during follow-up among the three groups

Outcome	B/F/TAF group, n=60	NNRTI-based regimen group, n=30	Boosted PI-based regimen group, n=30	*p*
Any dyslipidemia, n (%)	12 (20.0)	9 (30.0)	15 (50.0)	0.014
Hypercholesterolemia, n (%)	7 (11.7)	5 (16.7)	9 (30.0)	0.097
Hypertriglyceridemia, n (%)	5 (8.3)	4 (13.3)	9 (30.0)	0.024
Elevated LDL-C, n (%)	6 (10.0)	5 (16.7)	8 (26.7)	0.123
Reduced HDL-C, n (%)	4 (6.7)	3 (10.0)	3 (10.0)	0.804
New-onset dyslipidemia, n/N (%)	8/52 (15.4)	6/25 (24.0)	10/24 (41.7)	0.044
Started lipid-lowering treatment, n (%)	3 (5.0)	3 (10.0)	5 (16.7)	0.192

[a]New-onset dyslipidemia was calculated only in patients without dyslipidemia at baseline.
[b]B/F/TAF: bictegravir/emtricitabine/tenofovir alafenamide; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor.

Table 4. Changes in liver function-related markers from baseline to follow-up in the three groups

Liver function marker	B/F/TAF group, n=60	NNRTI-based regimen group, n=30	Boosted PI-based regimen group, n=30	Between-Group *p* for Change
Baseline ALT, U/L	28.6±15.2	30.1±16.8	31.4±17.5	0.714
Follow-up ALT, U/L	29.4±14.9	32.5±18.2	33.9±19.0	
Change in ALT, U/L	0.8±10.4	2.4±12.6	2.5±13.1	
Baseline AST, U/L	25.4±9.8	26.1±11.0	26.7±10.9	0.752
Follow-up AST, U/L	25.9±9.7	27.8±11.7	28.3±12.4	
Change in AST, U/L	0.5±7.6	1.7±8.4	1.6±9.3	
Baseline GGT, U/L	32.5±21.6	34.1±23.2	36.3±24.5	0.186
Follow-up GGT, U/L	34.2±22.4	38.7±25.1	42.6±29.8	
Change in GGT, U/L	1.7±11.2	4.6±13.4	6.3±15.6	
Baseline total bilirubin, μmol/L	11.8±5.2	12.1±5.5	12.5±5.8	0.781
Follow-up total bilirubin, μmol/L	12.0±5.1	12.7±5.8	13.2±6.4	
Change in total bilirubin, μmol/L	0.2±3.0	0.6±3.5	0.7±4.2	
Baseline albumin, g/L	42.5±3.8	42.1±4.1	41.8±4.4	0.913
Follow-up albumin, g/L	42.9±3.6	42.4±4.0	42.0±4.2	
Change in albumin, g/L	0.4±2.1	0.3±2.3	0.2±2.5	
Baseline FIB-4 index	0.96±0.44	1.01±0.48	1.05±0.51	0.394
Follow-up FIB-4 index	0.98±0.46	1.07±0.52	1.12±0.56	
Change in FIB-4	0.02±0.18	0.06±0.21	0.07±0.24	

[a]Between-group *p* values for changes were analyzed by analysis of covariance, with adjustment for the baseline level of the corresponding marker. [b]ALT: alanine aminotransferase; AST: aspartate aminotransferase; B/F/TAF: bictegravir/emtricitabine/tenofovir alafenamide; FIB-4: fibrosis-4; GGT: gamma-glutamyl transferase; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor.

Among patients with abnormal liver enzymes, most events were identified through routine laboratory monitoring rather than through specific hepatic symptoms recorded in the medical records. The abnormalities were mainly mild to moderate elevations of ALT, AST, or GGT. Grade 3 or higher liver enzyme elevation was uncommon, occurring in 1 patient in the NNRTI-based regimen group and 1 patient in the boosted PI-based regimen group. Management strategies included repeat liver function testing, review of concomitant medications, evaluation of viral hepatitis or fatty liver where clinically indicated, and ART regimen modification in selected cases. Three patients underwent regimen change because of liver-related events, and 1 patient in the boosted PI-based regimen group discontinued treatment because of a liver-related event. Available follow-up records suggested stabilization or improvement of liver function after clinical management in most cases.

Causality assessment was limited by the retrospective design. Because several patients had underlying fatty liver, viral hepatitis coinfection, baseline liver enzyme abnormality, or concomitant metabolic risk factors, liver enzyme abnormalities could not be confidently attributed to ART regimen alone. Therefore, liver-related adverse events were interpreted as clinically associated events rather than confirmed drug-induced liver injury.[18]

Analysis of Factors Related to Dyslipidemia and Abnormal Liver Enzymes

Multivariable logistic regression was used to analyze factors related to dyslipidemia and abnormal liver enzymes during follow-up. Considering the limited sample size and number of outcome events, a simple model was used to reduce overfitting. The dyslipidemia model included treatment regimen type, age, BMI, baseline dyslipidemia, diabetes, and fatty liver; the abnormal liver enzyme model included treatment regimen type, age, fatty liver, HBV/HCV coinfection, and baseline liver enzyme abnormality. As shown in Table 6, after adjustment for limited possible confounding factors, compared with the B/F/TAF group, the boosted PI-based regimen was associated with an increased risk of dyslipidemia during follow-up. Higher BMI and baseline dyslipidemia were also associated with an increased risk of dyslipidemia. For liver-related outcomes, treatment regimen type was not statistically associated with abnormal liver enzymes; fatty liver, HBV/HCV coinfection, and baseline liver enzyme abnormality were associated with abnormal liver enzymes during follow-up. Because the number of abnormal liver enzyme events was small, the liver enzyme model results should be viewed as exploratory findings.

Table 5. Comparison of liver-related outcomes during follow-up among the three groups

Outcome	B/F/TAF group, n=60	NNRTI-based regimen group, n=30	Boosted PI-based regimen group, n=30	*p*
Any abnormal liver enzyme, n (%)	5 (8.3)	5 (16.7)	6 (20.0)	0.254
ALT elevation, n (%)	3 (5.0)	4 (13.3)	4 (13.3)	0.286
AST elevation, n (%)	2 (3.3)	3 (10.0)	3 (10.0)	0.343
GGT elevation, n (%)	2 (3.3)	3 (10.0)	4 (13.3)	0.198
Total bilirubin elevation, n (%)	1 (1.7)	1 (3.3)	2 (6.7)	0.460
Grade 3 or higher liver enzyme elevation, n (%)	0 (0.0)	1 (3.3)	1 (3.3)	0.362
Regimen changed because of liver event, n (%)	0 (0.0)	1 (3.3)	2 (6.7)	0.153
Treatment stopped because of liver event, n (%)	0 (0.0)	0 (0.0)	1 (3.3)	0.220

[a]Abnormal liver enzymes were defined as ALT, AST, or GGT above the upper limit of the reference range of our hospital laboratory. [b]Grade 3 or higher liver enzyme elevation was judged according to the preset adverse event grading standard. [c]ALT: alanine aminotransferase; AST: aspartate aminotransferase; B/F/TAF: bictegravir/emtricitabine/tenofovir alafenamide; GGT: gamma-glutamyl transferase; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor.

Table 6. Multivariable logistic regression analysis of factors related to dyslipidemia and abnormal liver enzymes

Variable	Dyslipidemia, OR (95% CI)	*p*	Abnormal liver enzyme, OR (95% CI)	*p*
B/F/TAF group	Reference	—	Reference	—
NNRTI-based regimen group	1.45 (0.49–4.29)	0.501	1.49 (0.39–5.64)	0.556
Boosted PI-based regimen group	2.92 (1.10–7.78)	0.032	1.65 (0.47–5.80)	0.433
Age, per 1-y increase	1.02 (0.98–1.06)	0.317	1.01 (0.96–1.06)	0.741
BMI, per 1 kg/m^2 increase	1.18 (1.01–1.37)	0.036	—	—
Baseline dyslipidemia	3.40 (1.22–9.45)	0.019	—	—
Diabetes	1.71 (0.41–7.13)	0.459	—	—
Fatty liver	1.86 (0.67–5.15)	0.232	3.25 (1.01–10.51)	0.048
HBV/HCV coinfection	—	—	3.71 (1.06–13.00)	0.040
Baseline liver enzyme abnormality	—	—	4.29 (1.18–15.60)	0.027

[a]The dyslipidemia model was adjusted for treatment regimen type, age, BMI, baseline dyslipidemia, diabetes, and fatty liver.
[b]The abnormal liver enzyme model was adjusted for treatment regimen type, age, fatty liver, HBV/HCV coinfection, and baseline liver enzyme abnormality. [c]Because the sample size and number of events were limited, the model results were mainly used for exploratory interpretation. [d]B/F/TAF: bictegravir/emtricitabine/tenofovir alafenamide; BMI: body mass index; CI: confidence interval; HBV: hepatitis B virus; HCV: hepatitis C virus; NNRTI: non-nucleoside reverse transcriptase inhibitor; OR: odds ratio; PI: protease inhibitor.

For the multivariable models, the number of outcome events was limited. The dyslipidemia model included 36 events and approximately 7 model parameters, with an events-per-variable ratio of about 5.1. The abnormal liver enzyme model included 16 events and approximately 6 model parameters, with an events-per-variable ratio of about 2.7. These values were below the commonly preferred threshold for stable multivariable modeling, particularly for the liver-related model. Therefore, the odds ratios should be interpreted as exploratory estimates. The findings support the observed association between boosted PI-based regimens and dyslipidemia, but they do not establish causal effects or robust prediction models.

DISCUSSION

In this real-world retrospective cohort of 120 people living with HIV, we compared lipid profile changes and liver-related outcomes among patients receiving B/F/TAF, NNRTI-based regimens, or boosted PI-based regimens. The main finding was that boosted PI-based regimens were associated with a higher prevalence of dyslipidemia, particularly hypertriglyceridemia, and greater increases in atherogenic lipid parameters, including TC, TG, LDL-C, and non-HDL-C. In contrast, lipid changes in the B/F/TAF group were relatively mild. Liver-related laboratory indices remained largely stable across groups, and severe hepatotoxicity was uncommon. These findings suggest that ART regimen selection may differentially influence metabolic outcomes in people living with HIV, while liver enzyme abnormalities appear to be more strongly affected by baseline hepatic and metabolic conditions than by regimen type alone.

From the results of this study, ART regimens should not be evaluated solely on the basis of virologic suppression. For people with HIV who need long-term treatment, metabolic and hepatic safety also influence long-term management. B/F/TAF, a common INSTI single-tablet combination in clinical practice, offers convenient dosing, stable viral suppression, and good overall tolerability. Previous real-world studies also showed that B/F/TAF has good overall safety in clinical practice, but its metabolic and liver performance can still be affected by patients' baseline characteristics, previous ART exposure, and comorbidities.[19] In this study, the B/F/TAF group showed mild lipid increases; compared with the boosted PI-based regimen group, increases in TG, LDL-C, and non-HDL-C were smaller, and the

dyslipidemia rate was lower. These findings are best interpreted as indicating that, in this study sample and follow-up period, lipid changes associated with B/F/TAF were relatively mild rather than demonstrating a lipid-lowering or clearly protective effect.

It should also be noted that TAF in B/F/TAF cannot simply be seen as metabolically neutral. Previous studies found that after switching from TDF to TAF, some patients may have increases in LDL-C and TG, possibly because the potential lipid-lowering effect of TDF disappears. Besides the OPERA cohort, some real-world studies of switching to B/F/TAF also suggested that weight, lipid, and glucose metabolism markers may change with previous medication and baseline metabolic status.[20] Therefore, lipid changes observed during B/F/TAF treatment cannot be attributed only to bictegravir, and the role of the TAF backbone and previous TDF exposure should not be ignored. In this study, the mild lipid increase in the B/F/TAF group is not inconsistent with previous TAF-related studies. In clinical work, patients who already have dyslipidemia at baseline, higher BMI, fatty liver, or previous switching from TDF to TAF still need regular lipid monitoring.

In this study, the boosted PI-based regimen group had a higher risk of dyslipidemia, especially shown as TG increase and a higher overall dyslipidemia proportion, which was generally consistent with previous studies. Earlier studies suggested that PI drugs and their pharmacokinetic boosters may take part in dyslipidemia by affecting adipocyte differentiation, insulin sensitivity, lipid transport, and liver lipid synthesis.[9,10] At the same time, ritonavir or cobicistat, as boosters, may increase drug interaction through Cytochrome P450 3A (CYP3A)-related pathways, and then further affect metabolic status. However, dyslipidemia in people with HIV is often affected by many factors, including chronic inflammation, immune activation, lifestyle, age, BMI, diabetes, and previous treatment history.[21] Therefore, the results of this study should be understood as an association between boosted PI-based regimens and increased risk of dyslipidemia, and should not be simply interpreted as a direct causal effect of a single drug.

In this study, the dyslipidemia risk of NNRTI-based regimens was between B/F/TAF and boosted PI-based regimens, but multivariable analysis did not show a statistically significant difference compared with B/F/TAF. This finding also highlights that NNRTIs do not have uniform metabolic effects. Efavirenz, rilpivirine, and doravirine differ in their effects on lipids, central nervous system adverse reactions, and drug interactions. The DRIVE-AHEAD study showed that the doravirine/lamivudine/TDF regimen had noninferior antiviral efficacy compared with the efavirenz/emtricitabine/TDF regimen, and had smaller effects on LDL-C and non-HDL-C.[22] The DRIVE-SHIFT study also suggested that treatment-experienced patients with viral suppression could maintain suppression after switching to doravirine/lamivudine/TDF, and showed good long-term tolerance.[23] Therefore, if the NNRTI group includes heterogeneous regimens, analyzing it as a single group may dilute differences between specific drugs. For a retrospective study with limited sample size, this grouping is practical, but future larger studies still need further stratification by specific NNRTI drugs.

From a clinical management perspective, dyslipidemia is not an isolated laboratory problem, but an entry point for long-term cardiovascular risk management in people with HIV. As ART becomes more effective and people with HIV live longer, cardiovascular disease increasingly influences long-term prognosis. The REPRIEVE study included people with HIV receiving ART and with traditional cardiovascular risk at low to moderate level, and showed that pitavastatin significantly reduced the risk of major adverse cardiovascular events.[12] The updated European AIDS Clinical Society (EACS) guidelines also further stressed the importance of cardiovascular and metabolic health management in people with HIV.[24] This study did not observe hard endpoints such as cardiovascular events, and the follow-up period was insufficient to assess long-term cardiovascular outcomes, but lipid changes, dyslipidemia rate, and start of lipid-lowering treatment can be used as early risk recognition markers. For patients using boosted PI-based regimens, with baseline dyslipidemia, or with higher BMI, lipid monitoring, lifestyle intervention, and cardiovascular risk assessment should be initiated earlier in clinical practice.

However, cardiovascular risk assessment in the present study remained limited. ASCVD, Framingham, or other validated cardiovascular risk scores were not calculated because complete information required for these tools was not consistently available in the retrospective records. Therefore, dyslipidemia in this study should be interpreted as an intermediate metabolic outcome rather than a direct measure of cardiovascular

risk. The results suggest the need for earlier risk recognition, but they cannot determine whether the observed lipid changes translated into actual cardiovascular events during follow-up. Future prospective studies should combine lipid trajectories with standardized cardiovascular risk assessment, inflammatory biomarkers, and cardiovascular outcomes.

Another issue is that contemporary ART regimens may influence body weight and adiposity, which may further affect lipid metabolism and liver-related outcomes. In the present study, baseline BMI was available and was included in the dyslipidemia model, but longitudinal weight change, BMI change, obesity incidence, waist circumference, and body composition measures were not systematically recorded. Therefore, the observed lipid changes could not be separated from possible changes in body weight or fat distribution. In addition, advanced lipid markers such as ApoB, ApoA1, lipoprotein(a), LDL-C/HDL-C ratio, and TC/HDL-C ratio were not routinely measured or were not predefined endpoints. These markers may better reflect atherogenic lipid burden and cardiovascular risk than conventional lipid parameters alone. Their absence limited the depth of cardiovascular-metabolic risk assessment in this cohort.

For liver-related outcomes, this study found that ALT, AST, GGT, bilirubin, albumin, and FIB-4 index were generally stable in the 3 groups, and severe liver enzyme elevation and treatment stopping because of liver events were uncommon. This suggests that during the follow-up time of this study, the 3 types of regimens did not show obvious differences in routine liver function safety. However, this conclusion should be understood carefully. First, the sample size of this study was 120 cases, and severe liver adverse events were rare by nature, so the statistical power was not enough to find rare but important liver toxicity events. Second, routine liver function markers mainly reflect liver cell injury or cholestasis, and cannot fully represent liver steatosis, inflammatory activity, or fibrosis progression. The RESPOND cohort showed that chronic liver enzyme elevation is not uncommon in people with HIV, and its occurrence may be related to ART exposure, previous drugs, hepatitis virus infection, and metabolic factors, while modern INSTIs did not show an obvious short-term liver safety signal.[15] Therefore, this study is more suitable to show that no obvious difference was seen among the 3 types of regimens in short-term routine liver function markers, and it should not be further inferred that 1 regimen has clear liver-protective effect.

Multivariable analysis showed that fatty liver, HBV/HCV coinfection, and baseline liver enzyme abnormality were associated with abnormal liver enzymes during follow-up, whereas ART regimen type was not independently associated with this outcome. This finding has clinical relevance. Abnormal liver enzymes in people with HIV often reflect multiple factors, including underlying liver disease, viral hepatitis, metabolic abnormalities, alcohol use, concomitant medications, and ART. In recent years, as survival time of people with HIV becomes longer, metabolic fatty liver disease has become more important in the HIV population. A systematic review and meta-analysis showed that non-alcoholic fatty liver disease, steatohepatitis, and liver fibrosis are not rare in people with HIV mono-infection, and obesity, diabetes, dyslipidemia, and ART exposure may all contribute to their development.[13] Other studies suggested that non-invasive markers such as FIB-4 can be used for initial risk stratification of liver fibrosis in HIV-related populations, but the results should be interpreted in the clinical context.[25] Therefore, when abnormal liver enzymes are found in clinical practice, they should not first be simply attributed to the ART regimen, and fatty liver, HBV/HCV coinfection, drinking, metabolic syndrome, and previous liver function abnormality should be evaluated systematically.

We also considered subgroup analysis according to viral hepatitis status because HBV and HCV coinfection may substantially influence liver enzyme abnormalities and fibrosis risk. However, the number of patients with viral hepatitis coinfection was small, especially for HCV coinfection, and the number of liver-related events was limited. Formal subgroup analysis or interaction testing by HBV/HCV status would therefore be statistically unstable and could lead to misleading estimates. Instead, HBV/HCV coinfection was included as a covariate in the exploratory liver enzyme regression model. The observed association between HBV/HCV coinfection and abnormal liver enzymes supports the clinical importance of underlying liver disease, but this result requires confirmation in larger cohorts with HBV DNA, HCV RNA, antiviral treatment history, liver imaging, and fibrosis assessment.

This study included the FIB-4 index in liver-related evaluation, as a supplement to routine liver function markers. FIB-4 is calculated from age, AST, ALT, and platelet count, and it was first used to evaluate the risk of significant liver fibrosis in HIV/HCV coinfection.[14]

Its advantage is that it depends on routine laboratory markers and is easy to obtain in retrospective studies and real-world data. However, FIB-4 cannot replace liver elastography, controlled attenuation parameter, magnetic resonance imaging proton density fat fraction (MRI-PDFF), or liver histopathology, and it can be affected by age, platelet count, and short-term liver enzyme fluctuation. In some HIV/HBV or HIV/HCV related cohorts, FIB-4 is more suitable as a screening and risk stratification tool, rather than being used alone to confirm fibrosis progression.[26] Therefore, FIB-4 results in this study should be considered an initial risk assessment, not a definite judgment of liver fibrosis progression. In the future, if liver imaging or elastography markers can be combined, it will be more helpful for evaluating long-term effects of different ART regimens on structural liver changes.

In addition, the characterization of baseline liver disease was incomplete in this retrospective cohort. Fatty liver was identified according to routine abdominal ultrasound reports, but the severity of steatosis was not graded in a standardized way. Fibrosis stage, transient elastography, controlled attenuation parameter, HBV DNA levels, HCV RNA status, and detailed antiviral treatment history for viral hepatitis were not systematically available. These missing data may have affected the interpretation of liver-related outcomes, because liver enzyme abnormalities in people living with HIV may be influenced by viral hepatitis activity, metabolic fatty liver disease, alcohol exposure, concomitant medications, and previous liver injury. Therefore, the liver-related findings of this study should be understood as routine biochemical safety observations rather than a full assessment of liver disease progression.

A feature of this study is that dyslipidemia and liver-related outcomes were evaluated in the same real-world cohort. Previous studies often evaluated ART safety in separate domains such as lipids, liver function, kidney function, bone metabolism, or weight change, but clinical decisions often need to balance several risks. For example, TAF may have kidney and bone safety advantages compared with TDF, but some patients may have higher lipids; boosted PI regimens have a higher resistance barrier and still have value in patients with complex previous treatment or resistance risk, but metabolic risk and drug interaction need close attention; NNRTI regimens have extensive clinical use, but specific drugs differ clearly. Therefore, ART regimen selection cannot be optimized on the basis of a single dimension and requires consideration of virologic status, resistance risk, previous treatment history, kidney function, bone metabolism, lipid level, baseline liver status, and concomitant medications. This study provides a framework for evaluating metabolic and liver outcomes side by side, rather than simply judging whether 1 regimen is better.

This study has several limitations. First, given its retrospective and non-randomized design, selection bias, information bias, and residual confounding could not be fully avoided. ART regimen selection may have been affected by prior treatment history, resistance risk, comorbidities, economic factors, drug availability, and physician preference. Propensity score-based analyses were not performed because of the limited sample size, unequal group sizes, and small number of liver-related events, and therefore the observed associations should not be interpreted as causal effects. Second, the sample size of 120 participants was determined by the number of eligible patients with available follow-up data during the study period, rather than by a formal a priori sample size calculation. The study had limited power to detect small differences and rare liver-related adverse events. Third, the multivariable models were constrained by the number of outcome events, especially for abnormal liver enzymes, and the low events-per-variable ratio reduced model stability. Fourth, immune-recovery assessment was incomplete. $CD4^+$ T-cell count and HIV RNA were available, but CD4/CD8 ratio, $CD8^+$ T-cell count, duration of sustained virological suppression, formal immune reconstitution indicators, and immune activation or inflammatory biomarkers were not systematically collected. Therefore, mechanistic interpretation regarding immune activation, inflammation, or immune-metabolic pathways remains limited. Fifth, the cohort included both ART-naive and treatment-experienced patients, but detailed previous ART duration, complete prior regimen sequence, reasons for switching, and TDF-to-TAF switching history were incompletely documented. These missing data may have influenced lipid trajectories and limited subgroup analysis. Sixth, characterization of liver disease was limited. Fatty liver was based on routine ultrasound records, but steatosis severity, fibrosis stage, transient elastography, controlled attenuation parameter, HBV DNA levels, HCV RNA status, and antiviral treatment history for viral hepatitis were not systematically available. Subgroup analysis according to

viral hepatitis status was also limited by the small number of coinfected patients and liver-related events. Seventh, cardiovascular risk assessment was incomplete. ASCVD, Framingham, or other validated cardiovascular risk scores were not calculated, and hard cardiovascular outcomes were not evaluated. Eighth, weight change, BMI change, obesity incidence, central adiposity, and body composition data were not systematically collected, which limited interpretation of metabolic changes. Finally, advanced lipid markers, including ApoB, ApoA1, lipoprotein(a), and lipid ratios, were not routinely available. Future prospective studies with larger sample sizes, standardized immune and metabolic assessments, detailed ART exposure history, and quantitative liver and cardiovascular evaluation are needed.

Despite these limitations, this study has certain clinical value. First, it focused on 3 ART regimen types commonly used in real-world practice, which makes the findings relevant to routine clinical care. Second, the study did not simply describe B/F/TAF as completely safe, but compared its relative metabolic and liver-related performance with NNRTI-based and boosted PI-based regimens while acknowledging the possibility of mild lipid changes. This interpretation is closer to actual clinical practice. Third, the analysis included lipid changes, dyslipidemia incidence, liver enzyme abnormalities, FIB-4 index, and regimen changes, providing a relatively comprehensive safety assessment. Finally, the multivariable analysis suggested that dyslipidemia and liver enzyme abnormalities were not determined by ART regimen alone, but were influenced by drug exposure, baseline metabolic status, and underlying liver disease together. This finding is meaningful for individualized long-term management of people living with HIV.

This single-center retrospective cohort study compared lipid profile changes and liver-related outcomes among people living with HIV receiving B/F/TAF, NNRTI-based regimens, or boosted PI-based regimens. The results showed that B/F/TAF was associated with relatively mild lipid changes and more favorable lipid profiles, whereas boosted PI-based regimens were associated with a higher risk of dyslipidemia, particularly hypertriglyceridemia and increases in atherogenic lipid parameters. Liver-related laboratory indices remained generally stable across groups with rare severe hepatotoxicity, and liver enzyme abnormalities were more closely associated with baseline hepatic and metabolic factors (including fatty liver and viral hepatitis coinfection) than with ART regimen type.

These findings highlight the importance of integrating metabolic and hepatic safety into ART selection and long-term management strategies for people living with HIV requiring lifelong treatment. Regular lipid monitoring and liver function assessment are essential. Future prospective studies incorporating immune activation and inflammatory biomarkers are warranted to further clarify the mechanisms linking ART exposure, metabolic alterations, and liver-related outcomes.

STATEMENT OF ETHICS

This retrospective cohort study was approved by the Institutional Review Board of Zhanjiang Central People's Hospital (ZX-20230222-01). The requirement for informed consent was waived because of the retrospective nature of the study and the use of deidentified clinical records.

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

None.

DATA AVAILABILITY

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

AI ASSISTANCE DISCLOSURE

Not applicable.

REFERENCES

1. Sax PE, Pozniak A, Montes ML, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre,

phase 3, non-inferiority trial. Lancet. 2017;390(10107):2073-2082. doi:10.1016/S0140-6736(17)32340-1

2. Deeks ED. Bictegravir/Emtricitabine/Tenofovir Alafenamide: A Review in HIV-1 Infection. Drugs. 2018;78(17):1817-1828. doi:10.1007/s40265-018-1010-7.
3. Smith RA, Raugi DN, Wu VH, et al. Comparison of the Antiviral Activity of Bictegravir against HIV-1 and HIV-2 Isolates and Integrase Inhibitor-Resistant HIV-2 Mutants. Antimicrob Agents Chemother. 2019;63(5):e00014-19. Published 2019 Apr 25. doi:10.1128/AAC.00014-19
4. Beavers C, Pau AK, Glidden D, Hyle E, Kuriakose S, Martin SS, et al. Statin Therapy as Primary Prevention for Persons With HIV: A Synopsis of Recommendations From the U.S. Department of Health and Human Services Antiretroviral Treatment Guidelines Panel. Ann Intern Med. 2025;178(6):847-57.
5. Gallant J, Lazzarin A, Mills A, Orkin C, Podzamczer D, Tebas P, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. Lancet. 2017;390(10107):2063-72.
6. Sax PE, Pozniak A, Montes ML, Koenig E, DeJesus E, Stellbrink HJ, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. Lancet. 2017;390(10107):2073-82.
7. Orkin C, DeJesus E, Sax PE, Arribas JR, Gupta SK, Martorell C, et al. Fixed-dose combination bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir-containing regimens for initial treatment of HIV-1 infection: week 144 results from two randomised, double-blind, multicentre, phase 3, non-inferiority trials. Lancet HIV. 2020;7(6):e389-e400.
8. Squillace N, Ricci E, Maggi P, Taramasso L, Menzaghi B, De Socio GV, et al. Real-life safety of Emtricitabine/Tenofovir Alafenamide/Bictegravir. PLoS One. 2023;18(8):e0289132.
9. Kalra DK, Vorla M, Michos ED, Agarwala A, Virani S, Duell PB, et al. Dyslipidemia in Human Immunodeficiency Virus Disease: JACC Review Topic of the Week. J Am Coll Cardiol. 2023;82(2):171-81.
10. Ofotokun I, Na LH, Landovitz RJ, Ribaudo HJ, McComsey GA, Godfrey C, et al. Comparison of the metabolic effects of ritonavir-boosted darunavir or atazanavir versus raltegravir, and the impact of ritonavir plasma exposure: ACTG 5257. Clin Infect Dis. 2015;60(12):1842-51.
11. Mallon PWG, Brunet L, Fusco JS, Prajapati G, Beyer A, Fusco GP, et al. Lipid Changes After Switch From TDF to TAF in the OPERA Cohort: LDL Cholesterol and Triglycerides. Open Forum Infect Dis. 2021;9(1):ofab621.
12. Grinspoon SK, Fitch KV, Zanni MV, Fichtenbaum CJ, Umbleja T, Aberg JA, et al. Pitavastatin to Prevent Cardiovascular Disease in HIV Infection. N Engl J Med. 2023;389(8):687-99.
13. Kalligeros M, Vassilopoulos A, Shehadeh F, Vassilopoulos S, Lazaridou I, Mylonakis E, et al. Prevalence and Characteristics of Nonalcoholic Fatty Liver Disease and Fibrosis in People Living With HIV Monoinfection: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2023;21(7):1708-22.
14. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006;43(6):1317-25.
15. Roen AO, Peters L, Wandeler G, van der Valk M, Zangerle R, Günthard HF, et al. Chronic Liver Enzyme Elevation and Use of Contemporary ARVs Among People With HIV. Open Forum Infect Dis. 2024;11(6):ofae308.
16. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007;147(8):573-7.
17. Joint Committee on the Chinese Guidelines for Lipid Management. Chinese guideline for lipid management (primary care version 2024)]. Zhonghua Xin Xue Guan Bing Za Zhi. 2024;52(4):330-7.
18. Moro RN, Johnson JL, Martinson N, et al. Differences in Neutrophil Counts Between African and Non-African Countries in 2 International Clinical Trials. J Infect Dis. 2025;232(5):1128-1138. doi:10.1093/infdis/jiaf291
19. Deeks ED. Bictegravir/Emtricitabine/Tenofovir Alafenamide: A Review in HIV-1 Infection. Drugs. 2018;78(17):1817-28.
20. Hsu JY, Sun HY, Chen LY, Chang SY, Chuang YC, Huang YS, et al. Weight and metabolic changes among

virally suppressed people with HIV who switched to co-formulated bictegravir/emtricitabine/tenofovir alafenamide. J Glob Antimicrob Resist. 2024;36:426-35

21. Feinstein MJ, Hsue PY, Benjamin LA, Bloomfield GS, Currier JS, Freiberg MS, et al. Characteristics, Prevention, and Management of Cardiovascular Disease in People Living With HIV: A Scientific Statement From the American Heart Association. Circulation. 2019;140(2):e98-e124.
22. Orkin C, Squires KE, Molina JM, Sax PE, Wong WW, Sussmann O, et al. Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate is Non-inferior to Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate in Treatment-naive Adults With Human Immunodeficiency Virus-1 Infection: Week 48 Results of the DRIVE-AHEAD Trial. Clin Infect Dis. 2019;68(4):535-44.
23. Johnson M, Kumar P, Molina JM, Rizzardini G, Cahn P, Bickel M, et al. Switching to Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (DOR/3TC/TDF) Maintains HIV-1 Virologic Suppression Through 48 Weeks: Results of the DRIVE-SHIFT Trial. J Acquir Immune Defic Syndr. 2019;81(4):463-72.
24. Ambrosioni J, Levi LI, Alagaratnam J, Sempere A, Mastrangelo A, Paioni P, et al. Major revision version 13.0 of the European AIDS Clinical Society guidelines 2025. HIV Med. 2026;27(1):18-32.
25. Blackard JT, Welge JA, Taylor LE, Mayer KH, Klein RS, Celentano DD, et al. HIV mono-infection is associated with FIB-4 - A noninvasive index of liver fibrosis - in women. Clin Infect Dis. 2011;52(5):674-80.
26. Resino S, Micheloud D, Miralles P, Bellón JM, Vargas A, Catalán P, et al. Diagnosis of advanced fibrosis in HIV and hepatitis C virus-coinfected patients via a new noninvasive index: the HGM-3 index. HIV Med. 2010;11(1):64-73.