

Clinical Efficacy and Safety of Centrally Procured Generic Tenofovir Alafenamide Fumarate: A Real-World Study

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ABSTRACT

Objectives: This real-world study aimed to compare the early efficacy and safety of original versus generic Tenofovir Alafenamide Fumarate (TAF) in treating patients with Chronic Hepatitis B (CHB). **Materials and Methods:** Clinical data and laboratory parameters of patients who initiated TAF therapy for the first time at our institution from May 2020 to September 2025 were retrospectively analyzed. Patients were categorized into the original and generic groups. Of 986 patients initially screened, 299 met the eligibility criteria and 264 were included after 1:3 propensity score matching; balance was assessed by Standardized Mean Differences (SMD). Because two assay platforms with different limits of quantification were in use, virological response was uniformly defined as HBV DNA <100 IU/mL for all patients. Efficacy indicators, including Hepatitis B Virus (HBV) DNA negativity rate, Alanine Aminotransferase (ALT) normalization rate, and changes in renal function and lipid profiles, were compared between the two patient groups at 48 weeks of treatment. Risk differences with 95% Confidence Intervals (CI) are reported for all binary endpoints. **Results:** This study enrolled 264 patients, comprising 66 and 198 in the original and generic groups, respectively. After 48 weeks of treatment, the HBV DNA negativity rates were 92.42% and 89.90% (risk difference 2.53%, 95% CI -5.11% to 10.17%) in the original and generic groups, respectively, whereas the ALT normalization rates were 86.36% and 82.83% (risk difference 3.54%, 95% CI -6.27% to 13.34%), respectively, with no statistically significant differences between the two groups ($p>0.05$). Among patients with detectable HBV DNA at baseline, virological suppression at week 48 was achieved in 16/21 (76.19%) and 53/71 (74.65%) of patients, respectively (risk difference 1.54%, 95% CI -19.30% to 22.38%). The incidence of abnormal estimated glomerular filtration rate was 27.27% and 29.29% in the original and generic groups, respectively. No statistically significant differences between the two groups were observed in the changes in serum lipid parameters (e.g., total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol) and incidence of lipid abnormalities ($p>0.05$). **Conclusion:** No significant differences between original and generic TAF were identified in terms of virological response, biochemical improvement, or safety profile after 48 weeks of treatment for CHB. These findings indicate that the two formulations are comparable in early efficacy and safety. As the confidence intervals for the primary endpoints lie within $\pm 10.2\%$, the findings are consistent with non-inferiority at a 10% margin, although no equivalence margin was pre-specified. Longer-term studies are required before conclusions can be drawn regarding sustained outcomes.

Keywords: Chronic hepatitis B, Generic drugs, Real-world study, Tenofovir alafenamide fumarate.

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INTRODUCTION

Chronic Hepatitis B (CHB) is an infectious disease induced by long-term Hepatitis B Virus (HBV) infection.¹ Epidemiological surveys report a 5.6% HBV infection rate in China,² imposing a substantial public health burden. Antiviral intervention occupies

a core position in the clinical management of CHB, and the rational selection and efficacy evaluation of antiviral agents facilitate the optimization of individualized treatment regimens for patients with CHB. As a prodrug of tenofovir, Tenofovir Alafenamide Fumarate (TAF) converts into biologically active tenofovir diphosphate in target cells to exert antiviral activity.³ The phosphonamidate structural configuration of TAF improves molecular stability in plasma.⁴ Long-term clinical application of TAF achieves potent antiviral effects at a low dosage with favorable metabolic tolerance while sustaining steady bone mineral density and renal function levels,^{5,6} thereby providing an optimized therapeutic option for patients with CHB.



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Original formulations of TAF were officially introduced in the Chinese market in 2019, and generic preparations were included in the seventh round of national volume-based centralized procurement, which markedly reduced the economic burden on patients and achieved effective savings in medical insurance funds. A host of relevant studies have developed systematic evaluation frameworks for generic drugs in terms of pharmaceutical equivalence, bioequivalence, and therapeutic equivalence, with empirical validation acquired across multiple dosage forms and therapeutic areas.⁷ However, pharmaceutical equivalence cannot fully guarantee bioequivalence, nor can bioequivalence completely ensure consistent therapeutic efficacy.⁸ Clinical practitioners generally lack sufficient understanding of generic medications and bioequivalence trials, whereas a considerable proportion hold negative perceptions regarding the curative effect, quality, safety profile, and adverse reaction risks of generic agents.⁹ Real-world evidence reflects drug performance under routine clinical practice and provides dynamic and multidimensional reference for regulatory decision-making, thereby rendering post-marketing real-world research on generic drugs, including biosimilars, irreplaceable value in verifying their safety, clinical effectiveness, and cost-benefit profiles.¹⁰

The current clinical landscape in China lacks in-depth exploration concerning therapeutic equivalence associated with generic TAF preparations. Based on large-sample real-world data, this retrospective cohort study applies Propensity Score Matching (PSM) to compare clinical efficacy and safety profiles between original TAF and volume-based procurement-sourced generic TAF, while conducting exploratory analysis on therapeutic outcomes within the subgroup of patients with positive Hepatitis B e Antigen (HBeAg) with high viral load. Relevant findings aim to supply evidence-based support for national volume-based procurement policies, deliver references to guide clinical medication decision-making, and promote rational clinical application of generic drugs.

MATERIALS AND METHODS

Clinical data

Complete medical records were retrospectively collected from the hospital information system for patients receiving original TAF or volume-based procurement generic TAF from May 2020 to September 2025. Extracted information covered the following items: (1) baseline demographic characteristics, including patient registration number, name, gender, age, visit date, and disease diagnosis; (2) hepatitis B history, prior medication exposure, and comorbid conditions; (3) laboratory parameters involving HBV DNA load (IU/mL), alanine aminotransferase (ALT, U/L), serum creatinine (Cr, $\mu\text{mol/L}$), and estimated glomerular filtration rate (eGFR, $\text{mL}\cdot\text{min}^{-1}\cdot 1.73\text{m}^{-2}$) and lipid profiles, including Total Cholesterol (CH), Triglycerides (TG), High-Density Lipoprotein Cholesterol (HDL-C) and Low-Density Lipoprotein Cholesterol

(LDL-C) at baseline (0 week), 24 weeks, and 48 week after treatment; (4) documented adverse event records. All enrolled participants were assigned to the original drug group and the generic drug group according to medication regimens. This study obtained ethical approval from the Hospital Ethics Committee (approval No. 2026 Lun Jian Shen Zi 02). The present study has been registered in the Medical Research Registration and Filing Information System (registration No. MR-36-26-017668). Safety data were obtained from two sources. Objective laboratory parameters (serum creatinine, eGFR and the lipid profile) were extracted systematically from the hospital laboratory information system at each scheduled time point. Clinical adverse events were retrieved from inpatient and outpatient medical records and therefore depend on passive documentation during routine care. Informed consent was waived by the Ethics Committee owing to the retrospective design.

Inclusion and Exclusion Criteria

Inclusion criteria were (1) aged no less than 18 years without gender restriction, (2) CHB diagnosis according to the diagnostic criteria specified in the Guidelines for the Prevention and Treatment of Chronic Hepatitis B (2022 Edition), (3) initiation of antiviral therapy with TAF for the first time, regardless of prior exposure to other anti-HBV agents, and (4) regular follow-up records and a treatment course of no fewer than 48 weeks.

Exclusion criteria were (1) concurrent infection with human immunodeficiency virus, hepatitis A virus, hepatitis C virus, hepatitis D virus, or hepatitis E virus, as well as complicated alcoholic liver disease, autoimmune hepatitis, drug-induced liver injury, and other liver disorders; (2) diagnosis with primary liver cancer, accompanied by other malignant tumors, with a history of malignancy or organ transplantation; and (3) lacking laboratory and clinical data at key observation time points.

Drug Information

Gilead Sciences Inc. manufactured the original TAF, with the brand name Vemlidy and import drug registration certificate No. H20180060 at a specification of 25 mg per tablet. Anhui Anke Hengyi Pharmaceutical Co., Ltd., produced the generic preparation, holding the national drug approval number H20213589 with an identical specification of 25 mg per tablet. This generic product has passed the national consistency assessment and successfully won the bid in the seventh batch of national volume-based procurement in 2022.

Detection Methods

The COBAS TaqMan fully automated medical Polymerase Chain Reaction (PCR) analytical system and the cobas AmpiPrep automatic nucleic acid extraction and purification instrument, manufactured by Roche Molecular Systems, Inc., were adopted for HBV DNA quantification via high-sensitivity PCR fluorescence assay with matched HBV nucleic acid detection reagents, with a

Lower Limit of Quantification (LLOQ) of 20 IU/mL. The Swift96 automatic nucleic acid extractor (Da and Gene Co., Ltd., of Sun Yat-sen University) and the SLAN-96S fully automated medical PCR analytical system (Shanghai Hongshi Medical Technology Co., Ltd.) were applied alongside the corresponding HBV nucleic acid detection kit adopting the PCR fluorescence probe method, with an LLOQ of 100 IU/mL. Because the two platforms differ in their limits of quantification, virological response was defined uniformly as HBV DNA <100 IU/mL for all patients, irrespective of the platform used, so that the endpoint is identically defined in both groups; a sensitivity analysis applying platform-specific limits is presented in Table S2. The AutoLumo A2000 Plus fully automated chemiluminescence analyzer (Zhengzhou Autobio Diagnostics Co., Ltd.) and supporting reagents were used to detect serum HBV serological markers. HBsAg seroconversion was defined as loss of HBsAg (<0.05 IU/mL) together with the appearance of anti-HBs; HBeAg seroconversion was defined as loss of HBeAg (<0.1 IU/mL) together with the appearance of anti-HBe. Loss of the antigen alone, without antibody appearance, was recorded separately as antigen clearance and is not reported as seroconversion. The upper limits of the normal reference range were set at 40 U/L for ALT and 97 $\mu\text{mol/L}$ for Cr. eGFR ($\text{mL}\cdot\text{min}^{-1}\cdot 1.73\text{ m}^{-2}$) was taken as the value reported by the hospital laboratory information system, calculated from serum creatinine. An abnormal eGFR was defined as a value below 90 $\text{mL}\cdot\text{min}^{-1}\cdot 1.73\text{ m}^{-2}$ (KDIGO GFR category G2 or higher).

Evaluation Indicators

Efficacy indicators

Primary efficacy endpoints included changes in HBV DNA levels and the corresponding seronegative conversion rate at 48 weeks of treatment. Secondary indicators were alterations in ALT levels and the ALT normalization rate at 48 weeks. Additional efficacy parameters covered the dynamic changes of HBsAg and HBeAg levels as well as their serological conversion rates at 48 weeks.

Safety indicators

The primary safety endpoint included the incidence of abnormal eGFR at 48 weeks of treatment. Secondary safety indicators were the incidence of dyslipidemia and the occurrence rate of other adverse reactions. Lipid abnormality was defined according to the reference ranges of our laboratory: total cholesterol >5.17 mmol/L, triglycerides >2.3 mmol/L, LDL-C >3.37 mmol/L, and HDL-C <1.04 mmol/L (i.e. for HDL-C, a decrease below the lower reference limit constituted the abnormality). Only new-onset abnormalities—that is, a parameter within the reference range at baseline that became abnormal at week 48—were counted, and the denominator for each parameter was the number of patients with paired baseline and week-48 measurements for that parameter.

Statistical Methods

PSM was performed using R 4.3.0 software to mitigate the interference of baseline confounding factors. The propensity score was estimated by logistic regression with treatment group as the dependent variable. Covariates were pre-specified as baseline factors plausibly influencing either formulation choice or treatment outcome: age, sex, prior antiviral treatment experience, baseline HBV DNA, baseline ALT, HBeAg status, HBsAg status, presence of cirrhosis, and renal function (serum creatinine and eGFR). Matching was performed by nearest-neighbour matching without replacement at a 1:3 ratio, using a caliper of 0.2 times the standard deviation of the logit of the propensity score. Balance after matching was assessed using Standardized Mean Differences (SMD) rather than significance testing, since *p*-values conflate imbalance with sample size; an absolute SMD below 0.10 was regarded as good balance and below 0.25 as acceptable (Rubin's criterion). Full results are given in Table S1 and Figure S1. Statistical Package for the Social Sciences version 26.0 software was used for statistical processing. Normally distributed measurement data were expressed as mean $\pm$ standard deviation and compared using the *t*-test. Non-normally distributed measurement data were presented as median (P25, P75), using the Wilcoxon rank-sum test or paired Wilcoxon rank-sum test for intergroup comparison. Categorical data were described using case numbers and percentages, with the chi-square test applied for statistical inference; Fisher's exact test was used whenever any expected cell count was below 5. Risk differences with 95% confidence intervals are reported for all binary endpoints. This study defined lipid parameters as secondary safety observational indicators. Lipid data were available for 183 of 264 patients (69.3%) at week 48. Patients with and without available lipid data differed in age (median 47 vs 43 years, *p*=0.023), presence of cirrhosis (*p*=0.002) and prior treatment experience (*p*=0.022); the data are therefore not missing completely at random. The proportion of patients with available lipid data was, however, similar in the two groups (45/66, 68.2% vs 138/198, 69.7%; *p*=0.817), so the missingness is unlikely to bias the between-group comparison. Lipid outcomes were analysed as complete cases, and the number of evaluable patients is reported for every lipid comparison in Table 4. The analyses of primary efficacy and safety endpoints included all enrolled participants. A *p*-value of less than 0.05 indicated statistically significant differences. Details of the missingness assessment are given in Table S3.

RESULTS

Baseline Patient Characteristic

The primary outcome in this study includes the 48-week HBV DNA negative conversion rate. A total of 986 patients receiving TAF during the study period were initially screened. Application of the inclusion and exclusion criteria left 299 eligible patients. After 1:3 propensity score matching, 264 patients entered the

final analysis, comprising 66 in the original drug group and 198 in the generic drug group. The remaining 35 eligible patients were not matched within the caliper. The screening query was not stratified by formulation at the time of extraction, so the 299 eligible patients are reported as a single total and the unmatched patients as a combined figure. Because every retained patient in the original drug group was matched to exactly three controls ($66 \times 3 = 198$), the unmatched patients are expected to derive predominantly from the generic drug group. The patient flow is shown in Figure 1. After matching, 7 of 11 covariates achieved an absolute SMD below 0.10. Slight residual imbalance persisted for age (SMD 0.215), elevated baseline ALT (-0.212), HBeAg positivity (0.194) and baseline eGFR (-0.160), all below the 0.25 threshold; the directions of these residual differences were not systematically favourable to either group, since patients in the original drug group were older, more frequently HBeAg-positive and had lower baseline eGFR, whereas elevated baseline ALT was less frequent in that group. Table 1 shows detailed data. Full balance results are presented in Table S1 and Figure S1.

Efficacy

Efficacy comparison in the overall population

At the treatment endpoint, no statistically significant differences were observed between the two groups in terms of HBV DNA seronegative conversion rate, ALT normalization rate, HBsAg seroconversion rate, and HBeAg serological conversion rate (all $p > 0.05$). No significant intergroup differences were observed in quantitative indicators, including the reduction in HBV DNA

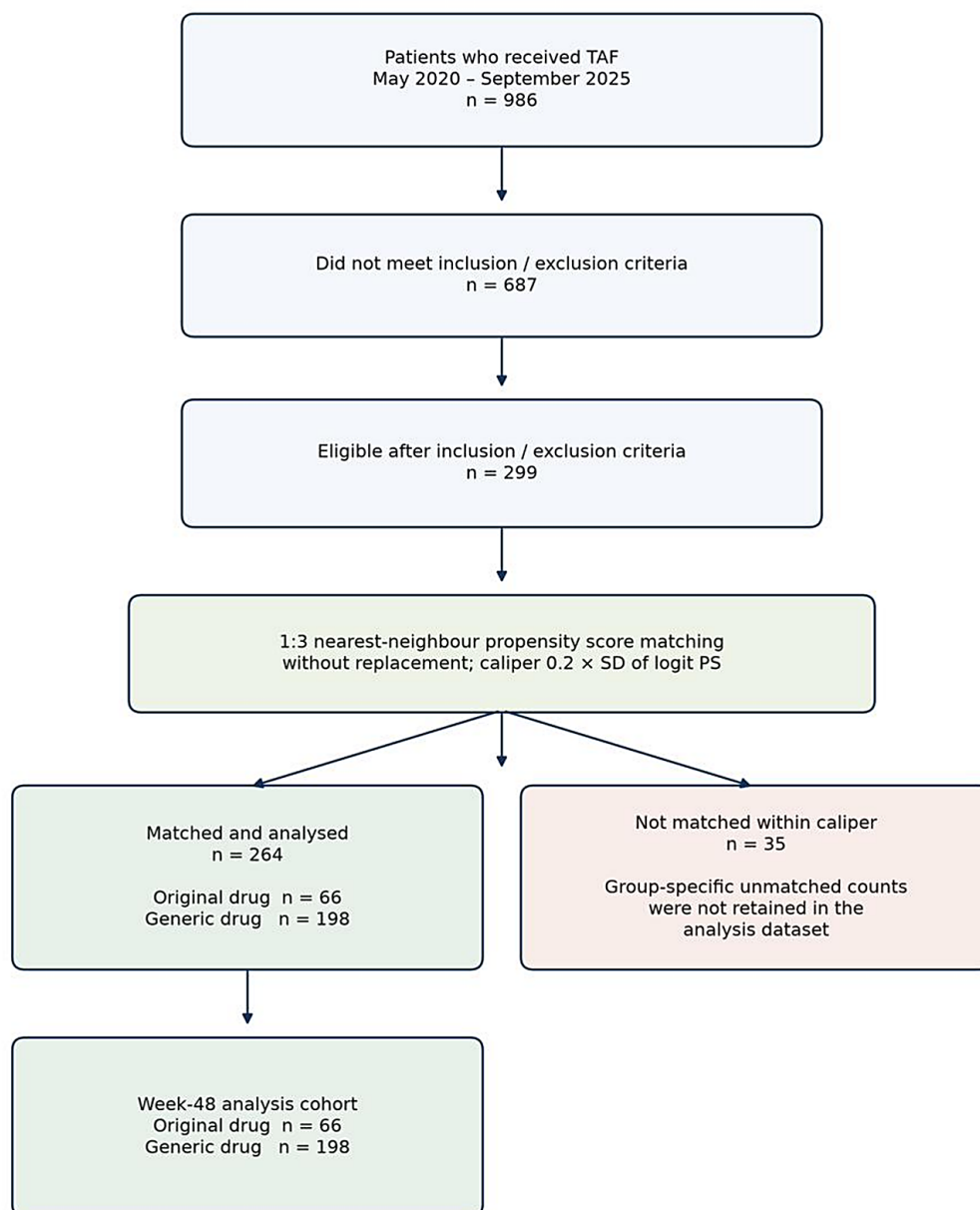
$\log_{10}$ copies and ALT levels (all $p > 0.05$). Table 2 presents the detailed efficacy outcomes (Tables S1-S3).

At 24 and 48 weeks of treatment, the proportions of patients with undetectable HBV DNA were 86.36% and 92.42% in the original drug group and 79.29% and 89.90% in the generic drug group, respectively, with no significant differences between the two groups ($p = 0.204$ and $p = 0.544$; risk difference at week 48 2.53%, 95% CI -5.11% to 10.17%). Restricting the analysis to the 21 and 71 patients with detectable HBV DNA at baseline, virological suppression at week 48 was achieved in 16 (76.19%) and 53 (74.65%) patients, respectively (risk difference 1.54%, 95% CI -19.30% to 22.38%; $p = 0.886$). The proportions of patients with ALT within the normal range were 84.85% and 86.36% in the original drug group and 83.84% and 82.83% in the generic drug group, with no statistically significant intergroup differences ($p = 0.846$ and $p = 0.501$). Among the 11 and 50 patients with elevated ALT at baseline, ALT normalization at week 48 was achieved in 9 (81.82%) and 29 (58.00%) patients, respectively (risk difference 23.82%, 95% CI -2.77% to 50.40%; Fisher's exact $p = 0.182$); this exploratory comparison did not reach statistical significance and is limited by the small number of evaluable patients in the original drug group. It is retained as an exploratory finding only and is not used to infer a between-formulation difference in biochemical response.

At 24 and 48 weeks of treatment, no marked declines were observed in HBV DNA, ALT, or HBsAg levels, and no significant intergroup differences were observed in the median reductions

Table 1: Comparison of baseline characteristics between the original drug group and the generic drug group.

Variables	Original drug group	Generic drug group	Statistical value	p-value
Gender [n (%)]				
Male	44	128	0.089	0.765
Female	22	70		
Age (years)	48.2	45.7	1.533	0.126
Treatment-naïve patients [n (%)]	28 (42.42)	75 (37.88)		
Treatment-experienced patients [n (%)]	38 (57.58)	123 (62.12)	0.430	0.512
HBV DNA ($\log_{10}$ IU/mL)	1.7 (1.7, 2.53)	1.7 (1.7, 2.98)	-1.245	0.213
HBV DNA positive [n (%)]	21 (31.82)	71 (35.86)	0.356	0.551
ALT U/L	24.6 (17.63, 38.1)	26.65 (18.45, 40.65)	-1.124	0.261
Elevated ALT [n (%)]	11 (16.67)	50 (25.25)	2.277	0.131
HBsAg IU/mL	826.1 (91.9, 1600)	1112.2 (187.0, 1600)	-1.877	0.061
HBsAg positive [n (%)]	65 (98.48)	196 (98.98)	0.112	0.737
HBeAg IU/mL	0.10 (0.01, 4.81)	0.08 (0.01, 3.56)	-0.853	0.394
HBeAg positive [n (%)]	39 (59.09)	98 (49.49)	1.826	0.177
Cr μ mol/L	70.65 (60.33, 82.58)	70.9 (57.6, 82.43)	-0.520	0.603
EGFR mL·min ⁻¹ ·1.73m ⁻²	103.41 (85.55, 113.79)	104.09 (88.19, 116.73)	-0.421	0.674
Abnormal eGFR [n (%)]	19 (28.79)	49 (24.75)	0.423	0.516
Concurrent liver cirrhosis [n (%)]	15 (22.73)	42 (21.21)	0.067	0.796



Formulation split of the 299 eligible patients before matching was not retained in the analysis dataset.

Figure 1: Patient flow diagram of 986 patients who received TAF during the study period, 299 met the eligibility criteria and 264 entered the 1:3 propensity-score-matched analysis (66 original drug, 198 generic drug). Thirty-five eligible patients were not matched within the caliper. The screening query was not stratified by formulation at extraction, so the 299 eligible patients are shown as a single total and the 35 unmatched patients as a combined Figure.

of these indicators (all $p > 0.05$). The reduction in HBeAg levels in the original drug group was significantly greater than that in the generic drug group at 24 weeks ($p = 0.006$); however, this difference was no longer statistically significant at 48 weeks ($p = 0.106$).

At 24 and 48 weeks of treatment, 2 and 3 patients in the original drug group achieved HBsAg seroconversion, with HBeAg seroconversion rates of 10.26% (4/39) and 12.82% (5/39),

respectively. In the generic drug group, 1 and 2 patients achieved HBsAg seroconversion, with HBeAg seroconversion rates of 4.08% (4/98) and 8.16% (8/98), respectively. No statistically significant differences were detected between the two groups in these serological indicators (all $p > 0.05$). When the endpoint was instead defined as loss of HBeAg alone, without requiring anti-HBe appearance, the week-48 rates were 25.64% (10/39) and 12.24% (12/98) ($p = 0.054$).

Efficacy comparison in the subgroup of patients with positive HBeAg with high baseline viral load

Among the 264 enrolled patients, 17 with HBeAg positivity and High Baseline Viral Load (HBV DNA $\geq 1 \times 10^6$ IU/mL) were screened out, including 5 in the original drug group and 12 in the generic drug group. Table 3 shows the efficacy outcomes of this subgroup at 48 weeks of treatment. Given the very small subgroup size, this analysis is exploratory and hypothesis-generating only.

The proportions of patients with undetectable HBV DNA were 60.00% (3/5) and 41.67% (5/12) in the original and generic drug groups, respectively (risk difference 18.3%, 95% CI -32.9% to 69.5%; Fisher's exact $p=0.620$). ALT was within the normal range in 100.00% (5/5) and 83.33% (10/12) of patients, respectively (Fisher's exact $p=1.000$). HBeAg seroconversion occurred in 20.00% (1/5) and 8.33% (1/12), respectively (Fisher's exact $p=0.515$). The confidence intervals for all three comparisons are so wide as to exclude no clinically meaningful difference, and no inference of either equivalence or difference should be drawn from them.

Regarding the magnitude of reductions in virological and biochemical indicators, the median HBV DNA log₁₀ reduction

was 4.36 and 5.46, and the median ALT reduction was 47.90 and 60.60 in the original and generic drug groups, respectively. No statistically significant differences were observed between the two groups ($p=0.399$ and $p=0.752$, respectively). Table 3 presents detailed results.

Safety

At 48 weeks of treatment, the incidence of renal function abnormalities was 27.27% and 29.29% in the original and generic drug groups, respectively. The difference between the two groups was not statistically significant (risk difference -2.02%, 95% CI -14.50% to 10.46%; $p=0.754$). At the treatment endpoint, comparison of lipid profiles between the two groups demonstrated that CH, HDL-C, and LDL-C levels slightly increased in both groups, whereas TG levels marginally decreased in the generic drug group. The median values of all lipid parameters remained within the normal reference range, with no significant differences in absolute levels or changes from baseline between the two groups (all $p>0.05$). The incidences of new-onset lipid abnormalities, calculated among patients with paired baseline and week-48 measurements, were as follows in the original and generic drug groups respectively: 23.68% (9/38) vs 19.47% (22/113) for TC,

Table 2: Comparison of efficacy between the original drug group and the generic drug group at 24 and 48 weeks.

Indicator	Time point	Original drug group (n = 66)	Generic drug group (n = 198)	Value	p-value	Risk difference (95% CI), %
HBV DNA reduction log ₁₀	24 weeks	0 (0, 0.64)	0 (0, 1.04)	-0.517	0.605	—
	48 weeks	0 (0, 0.72)	0 (0, 1.22)	-0.113	0.910	—
HBV DNA seronegative conversion [n (%)]	24 weeks	57 (86.36)	157 (79.29)	1.612	0.204	+7.07 (-2.95 to 17.09)
	48 weeks	61 (92.42)	178 (89.90)	0.368	0.544	+2.53 (-5.11 to 10.17)
ALT reduction	24 weeks	0.1 (-4.35, 5.78)	1.4 (-4.55, 10.43)	-0.841	0.400	—
	48 weeks	1.05 (-6.43, 5.78)	-0.05 (-7.20, 9.13)	-0.011	0.991	—
ALT normalization [n (%)]	24 weeks	56 (84.85)	166 (83.84)	0.038	0.846	+1.01 (-9.05 to 11.07)
	48 weeks	57 (86.36)	164 (82.83)	0.454	0.501	+3.54 (-6.27 to 13.34)
(HBsAg) reduction (log ₁₀ IU/mL)	24 weeks	0.03 (-0.05, 0.22)	0 (0, 0.136)	-0.841	0.400	—
	48 weeks	0 (-0.05, 0.40)	0.05 (0, 0.29)	-0.739	0.460	—
HBsAg seroconversion [n (%)]	24 weeks	2/65 (3.08)	1/196 (0.51)	Fisher	0.154	+2.57 (-1.75 to 6.88)
	48 weeks	3/65 (4.62)	2/196 (1.02)	Fisher	0.101	+3.59 (-1.70 to 8.89)
(HBeAg) reduction (log ₁₀ IU/mL)	24 weeks	0.04 (0, 0.31)	0 (0, 0.11)	-2.763	0.006	—
	48 weeks	0.11 (0, 0.57)	0 (0, 0.26)	-1.617	0.106	—
HBeAg serological conversion [n (%)]	24 weeks	4/39 (10.26)	4/98 (4.08)	Fisher	0.224	+6.17 (-4.12 to 16.47)
	48 weeks	5/39 (12.82)	8/98 (8.16)	Fisher	0.518	+4.66 (-7.15 to 16.47)

Table 3: Comparison of therapeutic efficacy in the HBeAg-positive subgroup with high viral load.

Indicator	Original drug group	Generic drug group	Value	p-value
HBV DNA seronegative conversion [n (%)]	3 (60.00)	5 (41.67)	Fisher	0.620
ALT normalization [n (%)]	5 (100.00)	10 (83.33)	Fisher	1.000
HBeAg seroconversion [n (%)]	1 (20.00)	1 (8.33)	Fisher	0.515
HBV DNA reduction log10	4.36 (4.21, 5.30)	5.46 (4.30, 5.91)	-0.844	0.399
ALT reduction	47.90(-4.05, 590.2)	60.60 (11.18, 160.95)	-0.316	0.752

Note: The sample size of this subgroup is relatively small, and the results are from an exploratory analysis, which are only for trend reference.

13.16% (5/38) vs 7.08% (8/113) for TG, 10.53% (4/38) vs 6.54% (7/107) for HDL-C, and 10.53% (4/38) vs 10.28% (11/107) for LDL-C. None of these differences reached statistical significance (all $p > 0.05$). No other adverse events were reported in either group during the treatment period (Table 4).

DISCUSSION

Effective and safe antiviral therapy is the cornerstone of long-term management of CHB. It can not only effectively delay disease progression but also yield favorable tolerability.¹¹ TAF has become a first-line Nucleotide Analog (NA) in clinical practice due to its superior renal and bone safety profile as well as potent inhibitory effect on HBV replication. With the full implementation of generic consistency evaluation and national volume-based procurement policies, the clinical utility of generic TAF has become increasingly widespread with prominent cost-effectiveness advantages. Whether generic TAF is completely equivalent to the original branded drug in terms of efficacy and safety under real-world clinical settings constitutes the core objective of the present study. The current findings revealed that generic TAF achieved comparable efficacy and safety to the branded counterpart after 48 weeks of treatment in patients with CHB, which was consistent with previous findings reported by Zhang Wen *et al.* regarding imported and domestic TAF.¹²

No obvious reductions were found in quantitative HBsAg and HBeAg levels between the two groups. Oral NAs mainly suppress HBV DNA synthesis by targeting the reverse transcription step of the HBV replication cycle, while exerting no direct elimination effect on intracellular covalently closed circular DNA and pre-synthesized viral antigens, including HBsAg and HBeAg. This mechanism leads to an extremely slow decline of serum HBsAg and HBeAg levels, and longer follow-up duration may be required to achieve meaningful serological benefits.¹³ The consistent declining trends of HBsAg and HBeAg in both groups further indicated that branded and generic TAF exerted equivalent effects on serological markers without obvious intergroup divergence.

This study further focused on the special subgroup of patients with positive HBeAg with high baseline viral load. This population demonstrates significant clinical heterogeneity in liver fibrosis, immune status, and treatment response and is generally regarded

as a difficult-to-treat subgroup in antiviral management.^{14,15} Subgroup analysis revealed no statistically significant differences between the branded group and the generic group in terms of HBV DNA seronegative conversion, ALT normalization, HBeAg seroconversion, and magnitude of changes in various indicators at 48 weeks. Both groups presented consistent efficacy trends without contradictory or divergent results, indicating internal stability and reliability of the findings. In this study, only one clinically key subgroup was predefined without further multiple subgroup stratification and repeated statistical testing. Such design effectively avoided false-positive risks caused by multiple comparisons and improved the robustness of subgroup results.¹⁶ These exploratory findings still provide valuable evidence for TAF medication selection in HBeAg-positive patients with high viral load despite being limited by the relatively small sample size and statistical power.¹⁷⁻²⁰

Our findings are consistent with the limited body of comparative evidence on generic nucleos(t)ide analogues in chronic hepatitis B. In a prospective study of 40 patients with prior antiviral resistance who switched from brand-name to generic entecavir 1 mg, non-inferiority in maintaining undetectable HBV DNA was demonstrated against a pre-specified 10% margin, with a 95% confidence interval of -2.80% to 8.20%,²¹ the width of that interval is closely comparable to the -5.11% to 10.17% observed for the primary virological endpoint in the present study, despite the different populations and study designs. A multicentre cohort study conducted in China likewise reported comparable virological response and treatment adherence between generic and brand-name entecavir.²² Beyond hepatology, real-world evaluations of the national volume-based procurement programme in other therapeutic areas have consistently documented substantial reductions in expenditure and improvements in affordability following generic substitution.^{23,24} What that literature has largely not addressed, however, is whether the substituted products deliver equivalent clinical outcomes in routine care; the generic consistency evaluation on which procurement eligibility rests is based on pharmaceutical and bioequivalence testing rather than on therapeutic equivalence established in patients.²⁴ The present study contributes real-world clinical outcome data for one such centrally procured product, and to our knowledge is among the first to do so for generic TAF in chronic hepatitis B.

Table 4: Comparison of safety between the original drug group and the generic drug group after 48 weeks of treatment.

Indicator	Original drug group	Generic drug group	Value	p-value
Cr ($\mu\text{mol/L}$)	73.08	73.09	-0.005	0.996
eGFR ($\text{mL}\cdot\text{min}^{-1}\cdot 1.73\text{m}^{-2}$)	103.13	101.95	0.339	0.735
Abnormal eGFR [<i>n</i> (%)]	18 (27.27)	58 (29.29)	0.099	0.754
CH (mmol/L)	4.88 (4.32, 5.51)	4.80 (4.22, 5.53)	-0.520	0.603
Change in total cholesterol (ΔCH , mmol/L)	0.26 (-0.22, 0.61)	0.31 (-0.16, 0.92)	-1.061	0.289
Abnormal total cholesterol [<i>n</i> (%)]	9/38 (23.68)	22/113 (19.47)	0.310	0.578
TG (mmol/L)	1.56 (0.88, 1.94)	1.06(0.79, 1.81)	-1.480	0.139
Change in triglycerides (ΔTG , mmol/L)	0.06 (-0.6, 0.75)	-0.03(-0.27, 0.33)	-1.452	0.147
Abnormal triglycerides [<i>n</i> (%)]	5/38 (13.16)	8/113 (7.08)	Fisher	0.314
HDL-C (mmol/L)	1.25 (0.98, 1.53)	1.36 (1.14, 1.56)	-1.210	0.227
Change in HDL-C ($\Delta\text{HDL-C}$, mmol/L)	0.01 (-0.16, 0.18)	0.03 (-0.17, 0.26)	-0.802	0.423
Abnormal HDL-C [<i>n</i> (%)]	4/38 (10.53)	7/107 (6.54)	Fisher	0.479
LDL-C (mmol/L)	2.72 (2.35, 3.21)	2.72 (2.17, 3.34)	-0.486	0.627
Change in LDL-C ($\Delta\text{LDL-C}$, mmol/L)	0.04 (-0.64, 0.31)	0.07 (-0.29, 0.53)	-1.544	0.123
Abnormal LDL-C [<i>n</i> (%)]	4/38 (10.53)	11/107 (10.28)	0.002	1.000

Note: Only new-onset abnormalities were included in the incidence calculation; a decrease alone in HDL-C was defined as an abnormality.¹⁹

Among treatment-experienced patients, 2 patients in the original drug group had previously received the centrally procured generic formulation, and 13 patients in the generic drug group had previously received the original formulation. In addition, 2 patients in the original drug group changed to the generic formulation during follow-up; in accordance with the initial prescription these patients were retained in the original drug group. A sensitivity analysis excluding these two patients ($n=262$) yielded materially unchanged results and is reported in the Limitations. They represent 2 of 66 patients (3.0%) in the original drug group. This treatment switching is acknowledged as a source of exposure misclassification in the Limitations. Because of the small numbers involved, no formal comparison was made between switchers and non-switchers, and no inference regarding relative efficacy is drawn from these patients.

Regarding safety, no serious adverse events occurred during the treatment period in either group. The incidence rates of renal function abnormalities and dyslipidemia were comparable between the two groups, with no statistical difference. These findings indicated that both branded and generic TAF demonstrated favorable tolerability regarding renal safety and lipid metabolic impacts with comparable safety profiles.^{17,18} Previous studies have raised potential concerns about the unfavorable effect of TAF on lipid metabolism,¹⁹ whereas other studies argued that TAF does not increase the risk of atherosclerotic cardiovascular disease. The present study showed that TAF exerted no significant influence on lipid parameters, which was in accordance with the results reported by Song Yuxuan *et al.*²⁰ Moreover, generic TAF demonstrated non-inferior safety to the branded drug, delivering

a favorable risk-benefit profile in real-world clinical practice and satisfying the safety requirements for long-term antiviral therapy.

The principal clinical implication of these findings is economic. Before the seventh round of national volume-based procurement, TAF was priced at approximately RMB 398 per bottle of 30 tablets, equivalent to an annual treatment cost of about RMB 4,776 for a patient taking one 25 mg tablet daily. Following the inclusion of TAF in the seventh procurement round in 2022, winning bid prices ranged from approximately RMB 0.32 to RMB 0.94 per tablet, with the lowest-priced products supplied at RMB 9.68 per bottle of 30 tablets—an annual cost of approximately RMB 116 per patient. Municipal healthcare security authorities have reported reductions of 96% to 98% in the unit price of TAF following implementation, corresponding to savings of approximately RMB 4,660 per patient per year.^{25,26} Because chronic hepatitis B requires indefinite antiviral therapy, and because premature discontinuation is associated with virological relapse and hepatic decompensation, drug cost is not solely a question of affordability but a determinant of long-term adherence and therefore of clinical outcome. A price reduction of this magnitude removes a substantial barrier to sustained treatment, particularly for patients without comprehensive insurance coverage and for those in economically less developed regions. Evidence that the centrally procured generic formulation achieves comparable early virological and biochemical control, and a comparable renal and lipid safety profile, is a necessary precondition for translating this price reduction into a genuine clinical and public health benefit rather than a purely budgetary one.

This study has several limitations to be acknowledged. First, this was a single-center real-world retrospective cohort study; the

designation “real-world” reflects the source of the data rather than the number of participating centres, but single-centre derivation nonetheless limits generalizability. The sample size of the branded group was relatively small due to economic accessibility and clinical availability. PSM was applied to balance baseline confounding factors, and balance was verified by standardized mean differences; slight residual imbalance nevertheless persisted for age and baseline ALT (both SMD $\approx$ 0.21), and unmeasured confounding cannot be excluded. Second, two HBV DNA platforms with different limits of quantification (<20 vs <100 IU/mL) were in use, and the high-sensitivity platform was used more often in the original drug group (18.2% vs 7.6%, $p=0.014$). Because a more sensitive assay detects low-level viraemia that a less sensitive assay reports as undetectable, this imbalance would tend to underestimate the rate of undetectable HBV DNA in the original drug group, and therefore works against rather than in favour of the observed comparability. Virological response was accordingly defined uniformly as <100 IU/mL for all patients; in a sensitivity analysis, classification by platform-specific limits changed the outcome in fewer than 2% of patients at either time point and altered no conclusion. Third, the follow-up period was limited to 48 weeks, so that long-term clinical endpoints including HBsAg clearance, progression of cirrhosis and the occurrence of hepatocellular carcinoma could not be assessed. Fourth, the safety assessment was restricted in scope: bone mineral density and markers of bone metabolism were not evaluated, nor were markers of renal tubular function, although bone and renal safety are the principal advantages claimed for TAF over tenofovir disoproxil fumarate. Fifth, only one predefined key subgroup (HBeAg-positive with high viral load) was analysed, and with 5 and 12 patients it is severely underpowered; its confidence intervals exclude no clinically meaningful difference and its findings are hypothesis-generating only. Sixth, underreporting of adverse events was possible given the passive recording system in this retrospective analysis, and the safety assessment therefore rests principally on objective laboratory endpoints. Seventh, the two formulations were available in different calendar periods—the original from 2019 and the centrally procured generic following national volume-based procurement in 2022—so the two groups are not fully contemporaneous, and secular changes in clinical practice and laboratory platforms may contribute to residual confounding. Eighth, two patients in the original drug group changed to the generic formulation during follow-up and were retained in that group according to the initial prescription, constituting 3.0% (2/66) of that group. A sensitivity analysis excluding these two patients ($n=262$) yielded materially unchanged results: at week 48 the risk difference for undetectable HBV DNA was 2.29% (95% CI -5.51% to 10.09%) versus 2.53% (95% CI -5.11% to 10.17%) in the primary analysis, that for ALT within the normal range was 4.67% (95% CI -4.98% to 14.33%) versus 3.54% (95% CI -6.27% to 13.34%), and that for abnormal

eGFR was -1.17% (95% CI -13.88% to 11.54%) versus -2.02% (95% CI -14.50% to 10.46%); no conclusion was altered. Ninth, the screening extraction was not stratified by formulation, so the 299 eligible patients are reported as a single total and the 35 unmatched patients as a combined Figure in Figure 1; in addition, the retained analysis dataset comprises the matched cohort only, so Figure S1 presents post-matching standardized mean differences without a pre-matching comparator. Therefore, high-quality multicenter, large-sample, and randomized controlled trials with prolonged follow-up duration, expanded subgroup stratification and wider generic varieties are warranted in the future.

CONCLUSION

In conclusion, PSM analysis revealed that generic TAF was comparable to branded TAF after 48 weeks of treatment in patients with CHB in primary efficacy endpoints, including HBV DNA suppression, ALT normalization, and HBeAg seroconversion. The confidence intervals for the primary endpoints lie within $\pm 10.2\%$, which is consistent with non-inferiority at a 10% margin, although no equivalence margin was pre-specified and formal equivalence was therefore not tested. For safety outcomes, the two groups demonstrated similar profiles in renal function and lipid metabolism, and no serious adverse events were recorded in either group. Findings in the HBeAg-positive high-viral-load subgroup were exploratory and, given the very small sample, permit no inference. These early results support the use of centrally procured generic TAF in the clinical management of CHB, while longer-term and multicentre studies remain necessary to confirm sustained efficacy and safety.

ABBREVIATIONS

ALT: Alanine Aminotransferase; **TC:** Total Cholesterol; **CHB:** Chronic Hepatitis B; **Cr:** Serum Creatinine; **DNA:** Deoxyribonucleic Acid; **eGFR:** Estimated Glomerular Filtration Rate; **HBeAg:** Hepatitis B e Antigen; **HBsAg:** Hepatitis B Surface Antigen; **HBV:** Hepatitis B Virus; **HDL-C:** High-Density Lipoprotein Cholesterol; **HIV:** Human Immunodeficiency Virus; **IU:** International Unit; **LDL-C:** Low-Density Lipoprotein Cholesterol; **log₁₀:** Base-10 Logarithm; **NA:** Nucleos(t)ide Analogue; **PCR:** Polymerase Chain Reaction; **PSM:** Propensity Score Matching; **RNA:** Ribonucleic Acid; **TAF:** Tenofovir Alafenamide Fumarate; **TG:** Triglycerides;

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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ETHICAL STATEMENT AND INFORMED CONSENT

This study obtained ethical approval from the Hospital Ethics Committee (approval No. 2026 Lun Jian Shen Zi 02). The present study has been registered in the Medical Research Registration and Filing Information System (registration No. MR-36-26-017668).

AUTHORS CONTRIBUTION

Guoqin Zhu: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Project administration, Supervision, Funding acquisition, Writing-original draft, Writing-review & editing. **Longchuan Zhu:** Investigation, Patient recruitment, Clinical data collection, Validation, Writing-review & editing. **Dan He:** Data curation, Formal analysis, Visualization, Validation, Writing-review & editing. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

SUMMARY

This real-world retrospective study compared the clinical efficacy and safety of original and centrally procured generic Tenofovir Alafenamide Fumarate (TAF) in patients with chronic hepatitis B after 48 weeks of treatment. Following 1:3 propensity score matching, 264 patients were analyzed. Generic TAF demonstrated comparable virological suppression, alanine aminotransferase normalization, serological responses, renal safety, lipid profile changes, and adverse event rates to the original formulation. Similar therapeutic trends were also observed in HBeAg-positive patients with high baseline viral load. These findings support the clinical equivalence of generic TAF, validating its use as a safe, effective, and cost-efficient first-line antiviral therapy for chronic hepatitis B.

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Table S1: Covariate balance after 1:3 propensity score matching.

Covariate	Type	Original drug group (n=66)	Generic drug group (n=198)	SMD	Balance
Age (years)	Continuous	48.18±11.95	45.69±11.30	0.215	Acceptable
Male sex	Binary	66.67%	64.65%	0.043	Good
Baseline ALT (U/L)	Continuous	46.59±102.93	47.27±155.54	-0.005	Good
Elevated baseline ALT	Binary	16.67%	25.25%	-0.212	Acceptable
Baseline HBV DNA positive	Binary	31.82%	35.86%	-0.085	Good
HBeAg positive	Binary	59.09%	49.49%	0.194	Acceptable
HBsAg positive	Binary	98.48%	98.99%	-0.045	Good
Cirrhosis	Binary	22.73%	21.21%	0.037	Good
Prior antiviral treatment	Binary	57.58%	62.12%	-0.093	Good
Baseline creatinine (μmol/L)	Continuous	73.93±20.45	73.82±45.02	0.003	Good
Baseline eGFR	Continuous	101.85±24.48	105.96±26.76	-0.160	Acceptable

SMD, standardized mean difference. Continuous variables are presented as mean±standard deviation and binary variables as percentages. Balance was classified as good ($|\text{SMD}| < 0.10$) or acceptable ($0.10 \leq |\text{SMD}| < 0.25$, Rubin's criterion). Seven of eleven covariates achieved $|\text{SMD}| < 0.10$. The four covariates with slight residual imbalance were not systematically favourable to either group: patients in the original drug group were older, more frequently HBeAg-positive and had lower baseline Egfr-all associated with a poorer treatment response-whereas elevated baseline ALT was less frequent in that group. Baseline ALT is markedly right-skewed, so its standardized difference as a continuous variable is attenuated by the inflated pooled standard deviation; the dichotomised variable is the more informative measure.

Table S2: Sensitivity analysis of the definition of virological response according to assay platform.

Time point	Classification criterion	Original drug group	Generic drug group	χ^2	<i>p</i>	Risk difference (95% CI)
Week 24	Platform-specific LLOQ	55/66 (83.33%)	154/198 (77.78%)	0.926	0.336	+5.56% (-5.14 to 16.25)
Week 24	Unified <100 IU/mL	57/66 (86.36%)	157/198 (79.29%)	1.612	0.204	+7.07% (-2.95 to 17.09)
Week 48	Platform-specific LLOQ	60/66 (90.91%)	175/198 (88.38%)	0.323	0.570	+2.53% (-5.72 to 10.77)
Week 48	Unified <100 IU/mL	61/66 (92.42%)	178/198 (89.90%)	0.368	0.544	+2.53% (-5.11 to 10.17)

LLOQ, lower limit of quantification; CI, confidence interval. Two platforms were in use during the study period, with LLOQs of 20 IU/mL (27/264 patients, 10.2%) and 100 IU/mL (237/264, 89.8%). Use of the high-sensitivity platform was more frequent in the original drug group (12/66, 18.2% vs 15/198, 7.6%; $\chi^2=6.065$, $p=0.014$). In the primary analysis, virological response was defined uniformly as HBV DNA <100 IU/mL for all patients. When patients were instead classified according to each platform's own LLOQ, the outcome classification changed in 5 of 264 patients (1.9%) at week 24 (2 original, 3 generic) and in 4 of 264 (1.5%) at week 48 (1 original, 3 generic); no between-group comparison changed in direction or in statistical significance.

Table S3: Assessment of the mechanism of missing lipid data

Characteristic	Lipid data available (n=183)	Lipid data unavailable (n=81)	<i>p</i>
Age, median (years)	47	43	0.023
Cirrhosis	-	-	0.002
Prior antiviral treatment	-	-	0.022
Availability by group	Original 45/66 (68.2%)	Generic 138/198 (69.7%)	0.817

Lipid data were available for 183 of 264 patients (69.3%) at week 48. Patients with and without available lipid data differed in age, presence of cirrhosis and prior treatment experience, indicating that the data were not missing completely at random. The proportion of patients with available lipid data was, however, similar in the two groups ($p=0.817$), so the missingness is unlikely to have biased the between-group comparison, although it limits the generalisability of the absolute incidence figures. Lipid outcomes were analysed as complete cases and are reported as secondary exploratory safety endpoints.

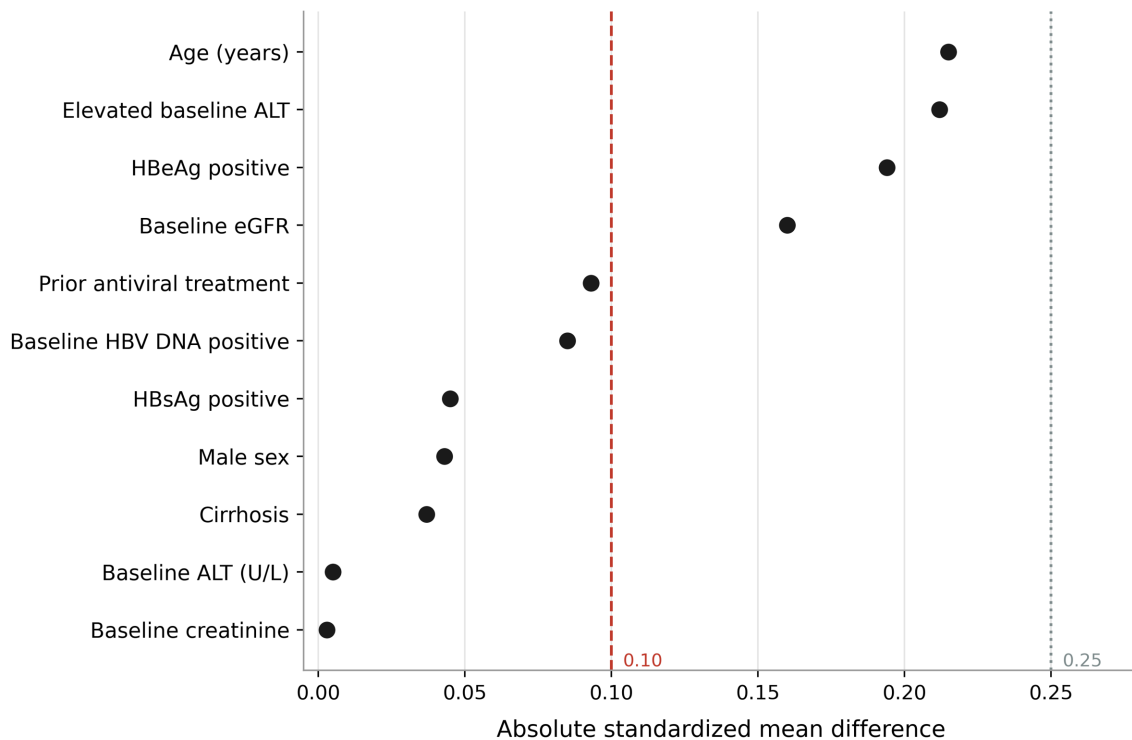


Figure S1: Covariate balance after 1:3 propensity score matching. Absolute standardized mean differences for the eleven covariates included in the propensity score model, after 1:3 nearest-neighbour matching without replacement. The dashed line indicates the threshold of 0.10 and the dotted line the threshold of 0.25 proposed by Rubin. Seven covariates lie below 0.10 and all eleven lie below 0.25. The retained analysis dataset comprises the matched cohort, so post-matching differences are shown without a pre-matching comparator.