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ORIGINAL RESEARCH



Efficacy and safety of bictegravir/emtricitabine/tenofovir alafenamide fumarate for adult patients with human immunodeficiency virus-1 in China: a retrospective real-world cohort study

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ABSTRACT

Background: This study aimed to evaluate the therapeutic effect and tolerance of bictegravir/emtricitabine/tenofovir alafenamide fumarate (BIC/FTC/TAF) use for 24 weeks in anti-retroviral therapy (ART)-naïve patients in China.

Methods: This single-center retrospective cohort study included ART-naïve patients who received BIC/FTC/TAF from July 2021 to April 2022. The proportion of patients with HIV RNA < 50 copies/mL at the end point of 24 weeks (virological suppression rate) was the primary outcome, and the changes in CD4 cell count, CD4/CD8 ratio, weight, blood lipid, and safety were secondary outcomes.

Results: A total of 80 ART-naïve patients were enrolled. The virological suppression rate was 86.3% at 24 weeks. The median CD4 cell count increased from 212 cells/μL (interquartile range [IQR]: 90.3–398.3) at baseline to 348 cells/μL (IQR: 219.8–541.0) at 24 weeks. The median CD4/CD8 ratio increased from 0.25 (IQR: 0.13–0.37) at baseline to 0.40 (IQR: 0.26–0.66) at 24 weeks. During the follow-up of 80 ART-naïve patients using BIC/FTC/TAF, 16 participants had adverse events; however, these events did not lead to drug withdrawal.

Conclusion: This real-world cohort study showed that BIC/FTC/TAF could achieve good immunological and virological responses in ART-naïve patients. In addition, this study also shows good safety.

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1. Introduction

Anti-retroviral therapy (ART) has profoundly affected people living with HIV (PLWH). Acquired Immune Deficiency Syndrome (AIDS) is no longer fatal but a controllable chronic infectious disease [1]. However, continuous ART use can cause ART drug toxicity and other side effects, which pose a greater threat to the health of PLWH than AIDS or other related diseases [2]. Therefore, reducing the side effects of ART drugs while ensuring efficacy is crucial.

Integrase strand transfer inhibitors (INSTIs) are novel drugs that have attracted considerable attention; they have strong antiviral effects, minimal side effects, a high resistance barrier, and few drug-drug interactions (DDI) [3–6]. Bictegravir (BIC) is a novel INSTIs that has been formulated into a single-tablet regimen with emtricitabine (FTC) and tenofovir alafenamide fumarate (TAF). Additionally, it is more effective and safer, has a higher adherence rate, and has fewer DDIs than other INSTIs [7–10]. BIC/FTC/TAF became available in China in January 2020, and China's 2021 edition of the AIDS Diagnosis and Treatment Guidelines immediately recommended it as the first-line treatment for HIV-1 infection [11]. However, few studies have included Chinese individuals with HIV-1 infection. Therefore, this study evaluated the therapeutic effects and tolerance of 24 weeks BIC/FTC/TAF treatment in ART-naïve patients with HIV-1 in China.

2. Patients and methods

2.1. Study design

This single-center, retrospective cohort study was conducted at Guiyang Public Health Clinical Center, one of southwest China's largest infectious disease hospitals, responsible for treating 20% of patients with AIDS in the Guizhou province and 80% in Guiyang City. ART-naïve participants who started ART at Guiyang Public Health Clinical Center between July 2021 and April 2022 were included; follow-up continued until October 2022. The inclusion criteria included the following: 1) age >18 years old; 2) positive for HIV-1 antibodies by immunoblotting; 3) ART-naïve; and 4) the ART regimen included BIC/FTC/TAF. The exclusion

criteria were: 1) pregnancy; 2) loss of follow-up or death; 3) missing HIV viral load, CD4 count, CD4/CD8 ratio, and blood biochemistry data at baseline or 24 ± 4 weeks.

The primary outcome was the virological suppression rate, determined based on the proportion of patients with < 50 copies/mL HIV RNA after 24 weeks of BIC/FTC/TAF use. The secondary outcomes were the CD4 cell count, the CD4/CD8 ratio, safety (i.e. adverse events), weight, and blood lipid levels after 24 weeks of treatment.

2.2. Data collection and laboratory inspection

The demographic baseline characteristics and HIV-related information were obtained from the China AIDS Prevention and Control Database and the hospital case system. Age, sex, height, weight, CD4+T cell count, HIV RNA levels, HIV-1 diagnosis time, ART start date, and the ALT, AST, blood lipid, and creatinine concentrations were obtained from the hospital's Laboratory Information System/Hospital Information System. The reasons for BIC/FTC/TAF selection and termination were also extracted from the medical records system.

2.3. Statistical analyses

Excel was used to input data, and SPSS version 23.0 software (SPSS Inc., Chicago, IL, U.S.A.) was used for the statistical analysis. Based on the data distribution type, baseline data are expressed as means ± standard deviation (SD) or medians with interquartile ranges (IQRs). Continuous data were analyzed using a *t*- or Wilcoxon rank sum test based on the distribution. All statistical tests were bilateral, and a *P*-value of < 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

Between July 2021 and April 2022, 92 patients received BIC/FTC/TAF, but five participants discontinued treatment due to economic difficulties, two were lost during follow-up, and one died from unrelated causes. Additionally, two participants had no baseline data, and another two had no 24-week data. These participants (*N* = 12) were excluded, and 80 were included in the analyses (Figure 1.).

Table 1 summarizes the baseline characteristics of the study participants. Most participants were men (72.5%), and the median age at baseline was 40.0 (IQR: 28.0, 54.0) years.

Heterosexual transmission was the dominant risk factor (63.7%). The viral load was higher than 500,000 copies/mL in 20% of participants, the median CD4+T cell count was 212 (IQR: 90.3–398.3) cells/μL, and 36.3% of cases were complicated by opportunistic infections. The most common reasons for using BIC/FTC/TAF were convenience medication (58.9%), fewer DDIs (13.3%), and fewer side effects (10.8%).

3.2. Virologic responses

The 24-week virological suppression rate was 86.3% (69/80); Figure 2. details the baseline CD4 cell counts and HIV RNA loads at baseline and subsequent virological suppression rates. For participants with 50–100,000 copies/mL at baseline, the 24-week virological suppression rates was 93.5%. The rates for those with 100,001–500,000 copies/mL and > 500,000 copies/mL were 88.9% and 62.5%, respectively (Figure 2.a). The virological suppression rates also varied after 24 weeks based on the baseline CD4 cell counts. For participants with CD4 ≤ 200 at baseline, the 24-week virological suppression rates was 84.6%. The rates for those with CD4 > 200 cells/μL was 87.8% (Figure 2.b). Table 2 presents the viral loads of 11 participants with virological non-suppression. Of these 11 participants, six had a baseline HIV RNA of > 500,000 copies/mL, and the follow-up HIV RNA results showed that all of them achieved virological suppression. In the other five cases, the baseline was HIV RNA < 500,000 copies/mL, four cases achieved virological suppression during follow-up, and the other case was considered to have low-level viremia.

3.3. Immunological responses

The median CD4 count increased from 212 (IQR: 90.3–398.3) at baseline to 348 (IQR: 219.8–541.0) at 24 weeks. The median CD4/CD8 ratio also increased from 0.25 (IQR: 0.13–0.37) at baseline to 0.40 (IQR: 0.26–0.66) at 24 weeks. For participants

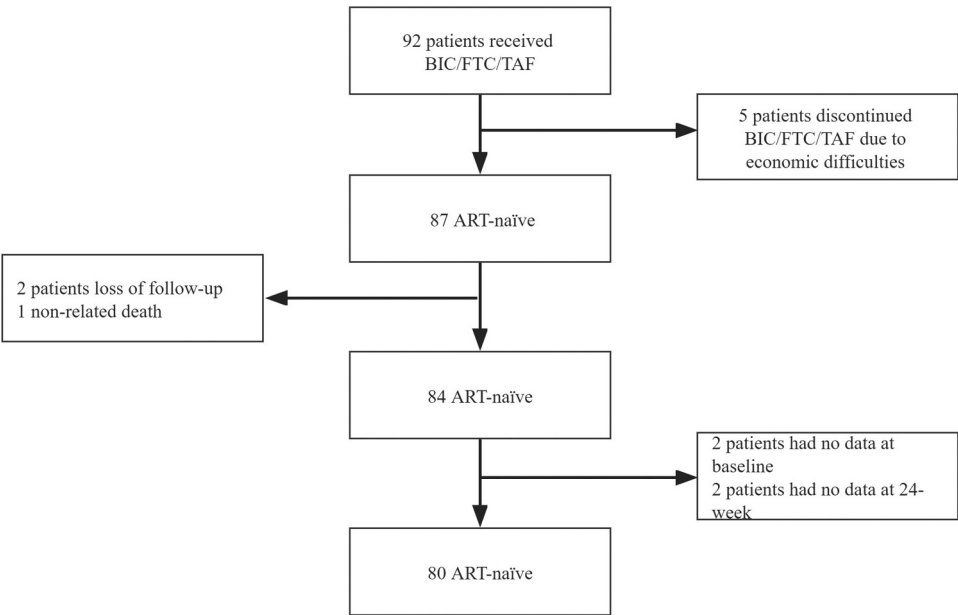


Figure 1. Flowchart of participant inclusion in the study.

Table 1. Baseline characteristics of the included patients.

Characteristics	ART-naïve patients (N = 80)
Sex, male, No (%)	58 (72.5)
Age, median (IQR)	40 (28–54)
HIV-1 risk factors, No. (%)	
MSM	28 (35)
Heterosexual	51 (63.7)
Bisexual	1 (1.3)
Marriage, No. (%)	
Single	31 (38.8)
Married	39 (48.7)
Divorced or widowed	10 (12.5)
Baseline HIV-1 RNA, copies/mL, No. (%)	
50–100,000	46 (57.5)
100,001–500,000	18 (22.5)
>500,000	16 (20)
Baseline CD4 count, cells/ μ L, No. (%)	
<200	39 (48.7)
$\geq$ 200	41 (51.3)
Baseline CD4 count, cells/ μ L, median (IQR)	212 (90.3–398.3)
Weight (kg), median (IQR)	57.8 (53.8,65)
Body mass index, kg/m ²	
<18.5	12 (15)
18.5–23.9	52 (65)
24–27.9	13 (16.3)
$\geq$ 28	3 (3.7)
BIC/FTC/TAF usage, weeks, median (IQR)	41.5 (34.1–48.1)
Time from confirmed HIV-1 to starting BIC/FTC/TAF, days, median (IQR)	11 (6–23)
Complication, No. (%)	
Opportunistic infection	29 (36.3)
Cardiovascular disease	9 (11.3)
Syphilis	8 (10)
Diabetes	3 (3.7)
HBV	8 (10)
HCV	1 (1.3)

Abbreviations: ART, anti-retroviral therapy; BIC/FTC/TAF, bicitgravir/emtricitabine/tenofovir alafenamide fumarate; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HIV-1, Human immunodeficiency virus-1; IQR, Interquartile range; MSM, Men who have sex with men.

with CD4 $\leq$ 200 at baseline, the median CD4 count increased from 82 (IQR: 29.5–141) at baseline to 225 (IQR: 119.5–293) at 24 weeks, and the median CD4/CD8 ratio increased from 0.13 (IQR: 0.08–0.22) at baseline to 0.28 (IQR: 0.18–0.4) at 24 weeks. For participants with CD4 > 200 at baseline, the median CD4 count increased from 397 (IQR: 291–484) at baseline to 488 (IQR: 409–663) at 24 weeks, and the median CD4/CD8 ratio increased from 0.34 (IQR: 0.25–0.49) at baseline to 0.64 (IQR: 0.4–0.79) at 24 weeks (Table 3).

3.4. Laboratory indexes

Table 4 details the laboratory indexes at baseline and 24 weeks. The total bilirubin, triglyceride, and blood amylase levels did not differ between baseline and week 24 ($P > 0.05$). However, the body weight (57.8 vs. 60.5, kg, $P = 0.004$) and body mass index (21.5 vs. 22.6, kg/m², $P = 0.007$) significantly increased from the baseline to week 24. In contrast, the aspartate aminotransferase (AST) (28.5 vs. 23.0, U/L, $P = 0.009$) and alanine aminotransferase (ALT) (23.5 vs. 19.0, U/L, $P = 0.005$) levels significantly decreased from the baseline to week 24, but no significant difference was observed in the hepatitis B virus (HBV) -positive subgroup. Renal function also decreased from baseline to week 24, evidenced by significant decreases in creatinine levels (66.7 vs. 82.6, μ mol/L, $P = 0.008$) and the Chronic Kidney Disease Epidemiology Collaboration value calculated from the serum creatinine concentration

(CKD-EPI SCR; 103.9 vs. 82.7, mL/min, $P = 0.002$). Finally, total cholesterol, high-density lipoprotein, and low-density lipoprotein levels significantly increased, and the blood glucose level decreased from baseline to week 24 ($P < 0.05$).

3.5. Adverse events

Sixteen participants experienced adverse events during the follow-up period but did not stop taking the medication. The most common adverse events were skin rash (7.5%), skin pruritus (5.0%), and digestive tract reactions (2.5%). During the follow-up period, two participants were hospitalized, one had suppurative tonsillitis, and one had a neck mass.

4. Discussion

This study is the first to evaluate the short-term efficacy and safety of BIC/FTC/TAF treatment in ART-naïve Chinese patients with HIV-1 infection. The virological suppression rate was 86.3% after 24 weeks.

A high viral load at baseline leads to delayed virus suppression and increased chances of virology failure [12,13]. We observed the same trend in this study. The subgroup analyses demonstrated that the higher the baseline viral load, the lower the 24-week virological suppression rate, but with extended follow-up time, patients with high baseline viral load could also achieve virological suppression, which was consistent

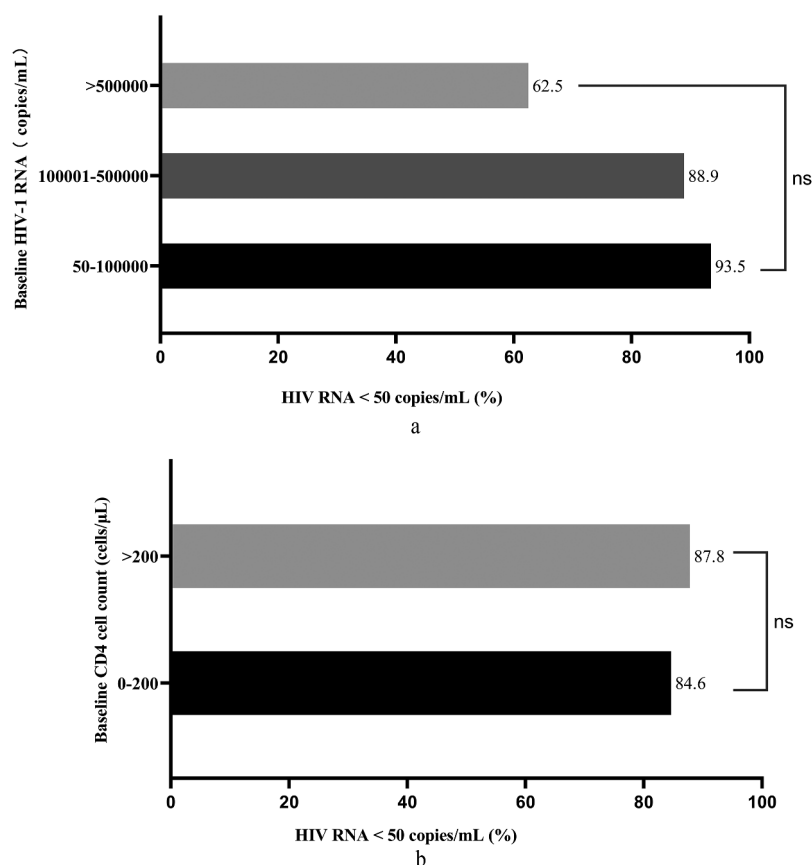


Figure 2. Virological suppression at 24 weeks. (a) Virological suppression rates of different baseline viral loads at 24 weeks. (b) Virological suppression rates of different baseline CD4 count at 24 weeks.

with the 5-year data of GS-US-380-1489 and GS-US-380-1490 [14]. However, the baseline CD4 cell count did not affect the virological suppression rates after 24 weeks, suggesting that BIC/FTC/TAF can achieve the same curative effect in patients with advanced AIDS, which is crucial for southwest China, where late detection is common. Similarly, patients with different baseline characteristics can achieve similar curative effects, indicating that BIC/FTC/TAF therapy can be started quickly, positively affecting the long-term prognosis of those infected with HIV-1 and speeding virological suppression, thus controlling the risk of HIV transmission [15–17]. Among those patients with a normal CD4 count and better treatment, a low CD4/CD8 ratio was an independent risk factor for serious non-AIDS events and mortality. In addition, a low CD4/CD8 ratio during ART suggests persistent immune dysfunction and inflammation. Therefore, simultaneously monitoring the CD4 count and CD4/CD8 ratio could comprehensively reflect the immune status of the body [18]. Significant immunological changes were observed after 24 weeks of BIC/FTC/TAF treatment; the CD4 count increased significantly, as did the CD4/CD8 ratio, consistent with other studies [7–10,19].

Moreover, in the present study, the creatinine levels increased, and the CKD-EPI Scr value decreased (but remained within a normal range) compared with the baseline values after 24 weeks of treatment. BIC could have increased serum creatinine by inhibiting the renal transporter organic cation transporter 2 [20], which may explain this result. However,

creatinine levels at 24 weeks do not accurately reflect the decline in the glomerular filtration rate and renal function. We found no evidence of adverse renal events, and no patient stopped taking the medication because of renal function problems, supporting this conclusion. In addition, we observed that after 24 weeks of BIC/FTC/TAF treatment, liver parameters decreased significantly. No significant changes were observed in the HBV-positive subgroup, while the HBV-negative subgroup showed the same trend as that of the other patients, indicating that the improvement in liver parameters was not driven by HBV treatment. This also confirmed the safety of BIC/FTC/TAF for the liver.

After 24 weeks of BIC/FTC/TAF treatment, compared with the baseline, the body weight increased significantly (57.8 vs. 60.5 kg, $P < 0.01$), comparable to the results of a previous observational study [12]. In the same period, the increase in median body weight in this study exceeded that in GS-US-380-1489 and GS-US-380-1490 [7,8]. In our study, 36.3% of the patients had opportunistic infections at baseline, and were in the late stages of AIDS, which may explain this result. After starting ART, these patients gained considerable weight, indicating health recovery. Other studies have also reported weight gain with BIC/FTC/TAF treatment [12,21], but several factors contribute to the weight increase. For patients with HIV-1, health recovery may cause weight gain owing to the alleviation of HIV-related inflammation and accelerated of catabolism [22]. In addition, ART accelerates the regression of

Table 2. Characteristics of patients with HIV/AIDS with ≥ 50 copies/mL of HIV-1 RNA after 24 weeks.

No.	Age	Sex	Viral load (copies/mL)			Other comments	CD4 count (cells/ μ L)			
			Weeks				Weeks			Missed dose
			B	12	24		B	12	24	
a. Baseline HIV RNA > 500,000 copies/mL										
1	27	M	46,000,000	196	51.4	<50 copies/mL for four consecutive tests from Wk 42 to Wk 84	360	462	651	0
2	33	M	941,000	714	235	<50 copies/mL for two consecutive tests from Wk 51 to Wk 77	267	452	421	0
3	55	F	2,830,000	85.4	93.4	Wk 62: < 50	34	104	221	0
4	53	M	828,000	NA	236	<50 copies/mL for two consecutive tests from Wk 61 to Wk 74	165	311	445	0
5	31	M	806,000	147	55.2	<50 copies/mL for two consecutive tests from Wk 54 to Wk 79	83	138	187	0
6	28	M	1,920,000	118	71.8	<50 copies/mL for two consecutive tests from Wk 41 to Wk 66	82	149	125	0
b. Baseline HIV RNA < 500,000 copies/mL										
7	61	F	429,000	718	160	Wk 64: 120; Wk 77:143	256	366	461	0
8	58	M	30,900	94.8	59	<50 copies/mL for two consecutive tests from Wk 54 to Wk 80	42	248	205	0
9	24	M	174,000	90.6	143	Wk 43: 429; Wk 70: < 50	453	NA	512	0
10	22	M	14,000	0	88	<50 copies/mL for two consecutive tests from Wk 42 to Wk 67	291	NA	601	0
11	28	M	4,3100	20	55.2	<50 copies/mL for two consecutive tests from Wk 39 to Wk 64	5	13	91	0

Abbreviations: AIDS, acquired immunodeficiency syndrome; B, baseline; F, female; HIV-1, human immunodeficiency virus-1; M, male; Wk, weeks.

Table 3. Changes in CD4 cell counts and CD4/CD8 ratio at week 24.

	Baseline*	Week 24*	P-value
ALL:			
CD4 count (cells/ μ L)	212 (90.3–398.3)	348 (219.8–541)	0.000
CD4/CD8	0.25 (0.13–0.37)	0.40 (0.26–0.66)	0.000
Baseline CD4 $\leq$ 200:			
CD4 count (cells/ μ L)	82 (29.5–141)	225 (119.5–293)	0.000
CD4/CD8	0.13 (0.08–0.22)	0.28 (0.18–0.4)	0.000
Baseline CD4 > 200:			
CD4 count (cells/ μ L)	397 (291–484)	488 (409–663)	0.004
CD4/CD8	0.34 (0.25–0.49)	0.64 (0.40–0.79)	0.000

*Data are presented as medians (interquartile ranges).

Table 4. Laboratory index changes during the study period ($N = 80$).

Markers	Baseline*	Week 24*	P-value
Weight (kg)	57.8 (53.8–65.0)	60.5 (55.0–68.4)	0.004
Body mass index (kg/m ²)	21.5 (19.5–23.4)	22.6 (20.6–24.7)	0.007
ALT (U/L)	23.5 (16.8–40.1)	19.0 (14.8–25.0)	0.005
AST (U/L)	28.5 (22.0–39.2)	23.0 (19.0–28.0)	0.009
ALT ^a (U/L)	29.5 (15.5–38.5)	19.0 (14.3–20.5)	0.195
AST ^a (U/L)	37.5 (33.0–55.0)	26.0 (19.5–31.0)	0.078
ALT ^b (U/L)	27.0 (19.0–43.3)	19.0 (15.0–25.5)	0.000
AST ^b (U/L)	29.0 (22.8–40.0)	22.5 (18.0–27.0)	0.000
TBIL (μ mol/L)	10.7 (7.8–15.6)	12.1 (8.8–16.0)	0.08
Scr (μ mol/L)	66.7 (58.2–79.8)	82.6 (71.1–94.4)	0.008
CKD-EPI Scr (mL/min)	103.9 (83.3–120.9)	82.7 (72.3–106.3)	0.002
TG (μ mol/L)	1.5 (1.1–2.3)	1.7 (1.2–2.7)	0.18
TC (μ mol/L)	4.0 (3.3–4.8)	4.5 (3.9–5.0)	0.004
HDL-C (μ mol/L)	0.8 (0.6–1.1)	1.1 (0.9–1.3)	0.005
LDL-C (μ mol/L)	2.2 (1.8–2.8)	2.6 (1.9–3.1)	0.001
Glu (μ mol/L)	5.5 (5.1–6.1)	5.2 (4.9–5.8)	0.03
Serum amylase (U/L)	73.5 (61–82.7)	73 (61.7–88.5)	0.34

*Data are presented as medians (interquartile ranges). ^aHBV-positive participants, $n = 8$; ^bHBV-negative participants, $n = 72$. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CD, cluster of differentiation; CKD-EPI Scr, Chronic Kidney Disease Epidemiology Collaboration value calculated based on the serum creatinine concentration; Glu, glucose (blood); HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Scr, serum creatinine; TBIL, total bilirubin; TC, total cholesterol; TG, triglyceride.

opportunistic infections and gastrointestinal dysfunction, improving appetite and nutrient absorption. Bodyweight changes are also related to sex, race, CD4 count, disease load, and lifestyle, amongst other factors [23–25]. Alternatively, clinicians should pay more attention to blood lipid levels since dyslipidemia is an independent risk factor for the occurrence and development of cardiovascular diseases

[26]. Our research showed that after 24 weeks of treatment, total cholesterol and high- and low- density lipoprotein levels increased significantly, but were still within normal range. The 5-year data of BIC/FTC/TAF use also showed that the blood lipids of patients fluctuate slightly after 5 years of treatment [27]; therefore, we surmised that BIC/FTC/TAF has little influence on blood lipids.

In the present study, no patients discontinued treatment because of adverse events, and most patients had very good tolerance. The most common adverse event was skin rash (7.5%), skin pruritus (5.0%), and digestive tract reactions (2.5%), consistent with Chang et al. [12] and Hayes et al. [28]. During the follow-up period, two patients had severe adverse reactions requiring hospitalization, but they were not drug related.

This study has several limitations. First, this was a single-center retrospective study, and the results may be biased. Second, the observation period was very short; thus, long-term observation periods with more patients are needed. Third, it was impossible to evaluate adverse events in detail.

5. Conclusions

BIC/FTC/TAF achieved good immunological and virological responses in Chinese ART-naïve patients with HIV-1 infection. In addition, no patient discontinued treatment owing to adverse drug reactions. BIC/FTC/TAF only slightly affected weight, blood lipid levels, and liver and kidney function, demonstrating its safety.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

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Ethics statement

The Ethics Committee of Guiyang Public Health Clinical Center (202226) approved this study. The informed consent requirement was waived since the study was retrospective. This study complied with the Declaration of Helsinki.

Data availability statement

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

Author contribution statement

Hai Long had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Lin Gan and Xiaoxin Xie were involved in the study concepts and design. All authors (Lin Gan, Xiaoxin Xie, Yanhua Fu, Yebing Song, Chunli Song, Tingting Ren, and Hai Long) were involved in data

acquisition, analysis, and interpretation. Lin Gan and Hai Long supervised the analysis and were involved in the drafting of the manuscript. All authors read, critically revised and approved the manuscript.

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